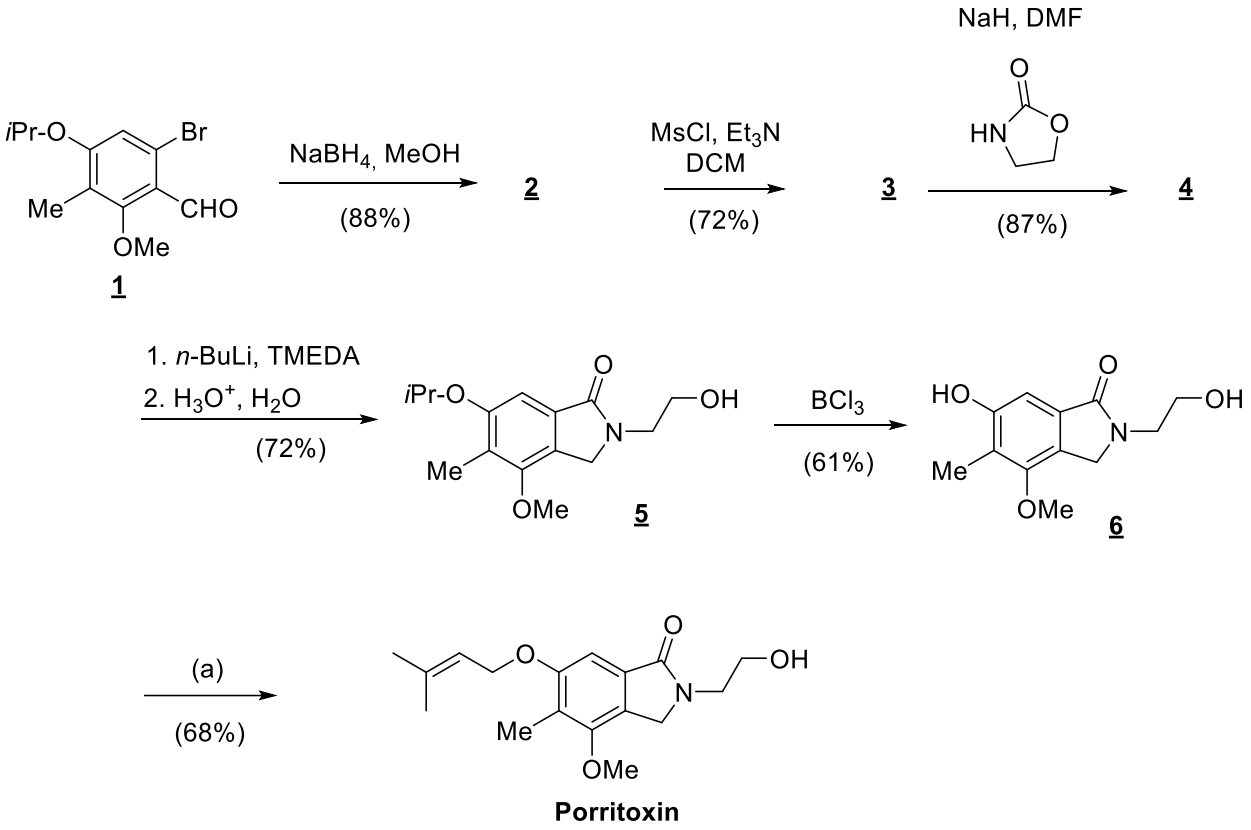
Synthesis of Porritoxin

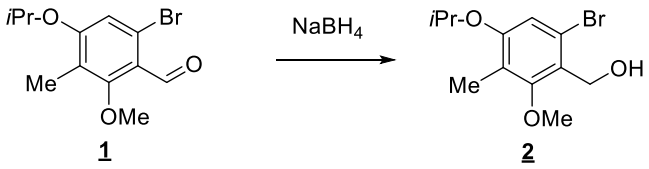
Porritoxin is a phytotoxin derived from a fungus *Aternaria porri*.



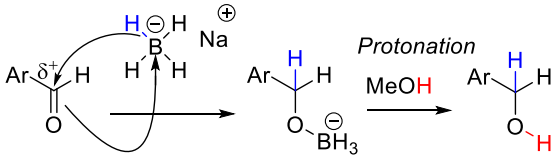
Porritoxin

1. What are the structures of compounds 2, 3 and 4?

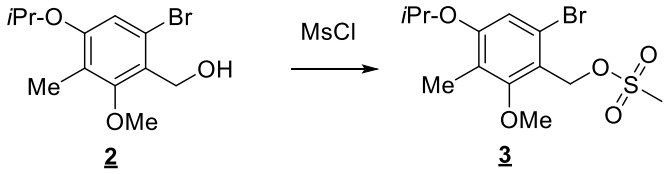
$NaBH_4$ is a smooth reductant which selectively reduces aldehyde and ketone (not ester). So here $NaBH_4$ reduces the aldehyde function of compound **1** to give the alcohol derivative **2**.



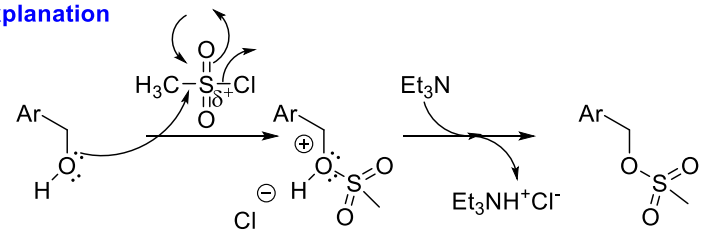
Explanation *equivalent of* $H^{\ominus}$



Alcohol of compound **2** is nucleophilic and attacks mesyl chloride (MsCl = $MeSO_2$-Cl). The interest is to transform the nucleophilic alcohol into a very good leaving group -OMs (sulfonate).

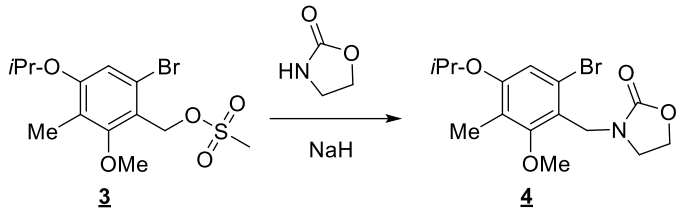


Explanation

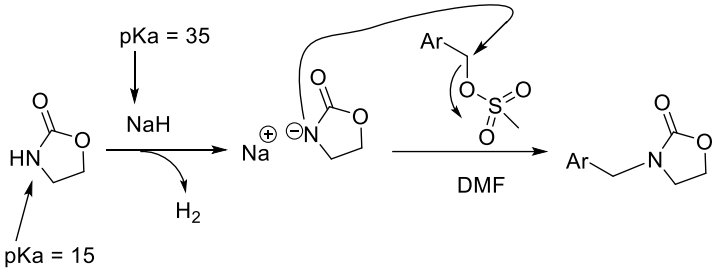


2. Propose a mechanism explaining the formation of 4.

NaH is a strong base able to remove the proton of the carbamate function (NH-CO-O). NH acidity is decreased because of conjugation with C=O group. The formed anion N^- is highly nucleophilic and can do a nucleophilic substitution on C-OMs (the carbon is electrophilic and OMs is an excellent leaving group).

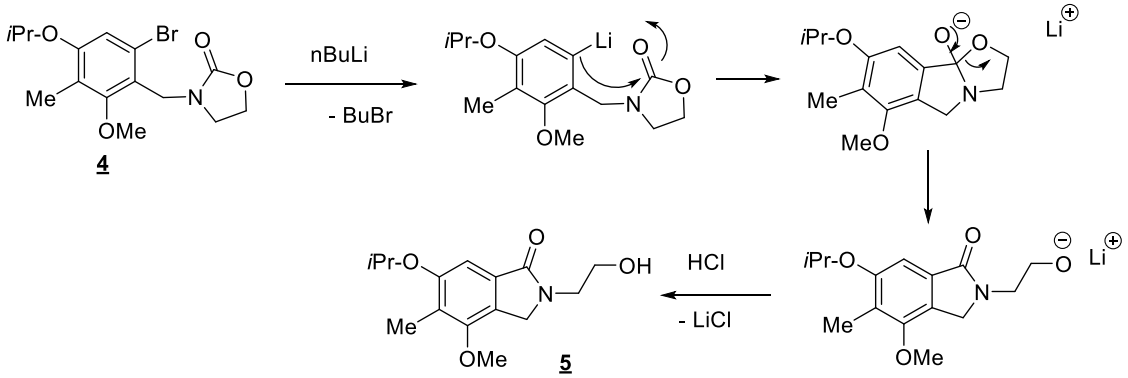


Mechanism



3. What is the first step of transformation of compound 4 into compound 5. Propose a mechanism explaining the transformation of this intermediate into compound 5.

The first step is an exchange between Bromine and lithium. In this intermediate, the carbon bearing the Lithium is an excellent nucleophile and can add onto the C=O bond (the C of the C=O bond is a good electrophile). Then there is a departure of the Alkoxide (the structure is too constraint). Last step is an acid base reaction to lead to compound **5**.

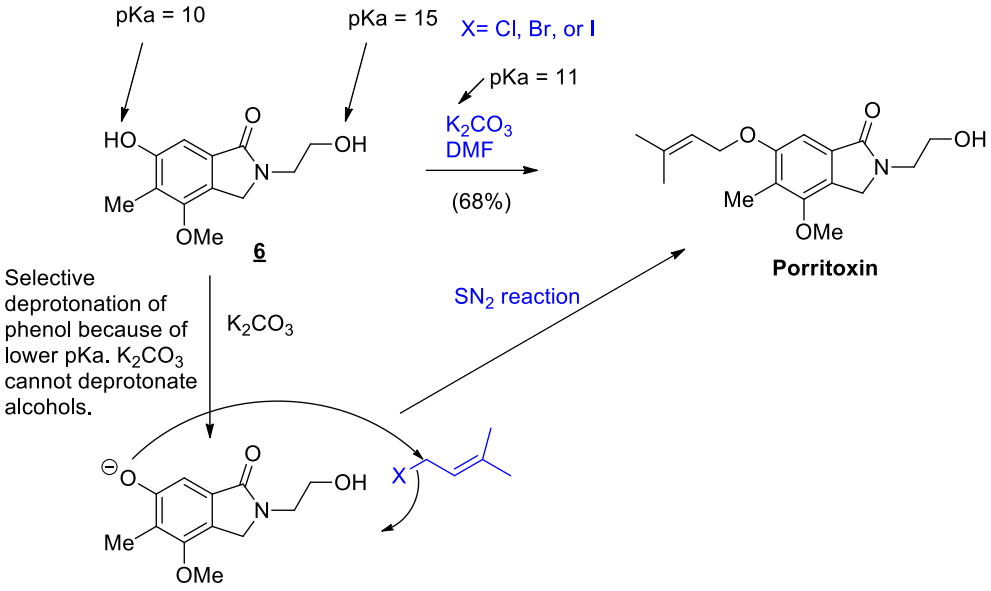


4. By comparing compounds 5 and 6, find the role of BCl_3. Propose an explanation of the enhanced reactivity of isopropyl ether vs methyl ether toward BCl_3 reagent.

BCl_3 acts as a deprotecting agent. The isopropyl ether is less hindered than the methyl one because around isopropyl ether there are a hydrogen and a methyl group while around the methyl ether there are a methyl group and a cycle. Another explanation is that the O of isopropyl ether has an enhanced nucleophilicity (due to donating inductive effects of the three carbon of the isopropyl group) compared to the O of the methyl ether (only one carbon with a donating inductive effect).

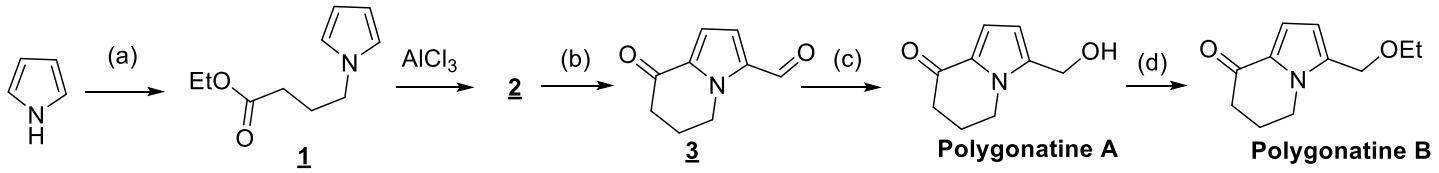
5. Find the conditions (a) allowing access to porritoxin from intermediate 6. What type of mechanism is involved in this reaction? Explain why the reaction can be regioselective here.

K_2CO_3 is a smooth base (pKa= 11), which deprotonates the most acidic hydrogen of the phenol function (pKa 10) and not the hydrogen of the alcohol function (pKa 16). The phenolate, which is nucleophilic, makes then a nucleophilic substitution on the C-Cl bond (the carbon is electrophilic, and the chlorine is a good leaving group).



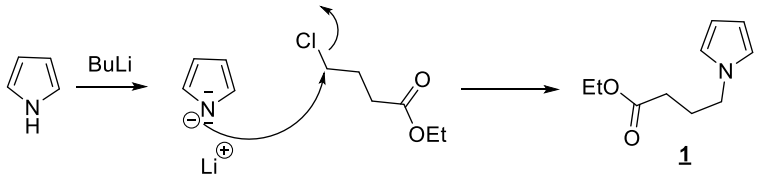
Synthesis of Polygonatines A and B

Polygonatines A and **B** are metabolites found in the rhizomes of *Polygonatum sibiricum*.



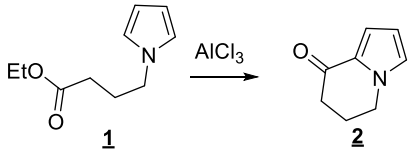
1. **Which reactant (a) can be used to transform pyrrole into compound 1?.**

You can use a strong base like BuLi to deprotonate the NH of the pyrrole. The anion formed is highly nucleophilic and can substitute the chlorine atom of the halogenated compound including the side chain.



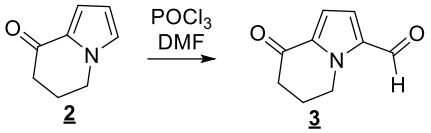
2. **What is the structure of compound 2? What is the type of reaction starting from compound 1 which led to compound 2? Could you explain the regioselectivity of the reaction?**

Ester can react with pyrrole by an acylation reaction like acyl chlorides or anhydrides. $AlCl_3$ is a Lewis acid necessary to activate the reaction. In this case the ester and the pyrrole are in the same molecule so it leads to a cyclic structure (you can notice this ring in compound **3**). Noteworthy, acylation is an aromatic electrophilic substitution, so favored on pyrroles in the alpha position.



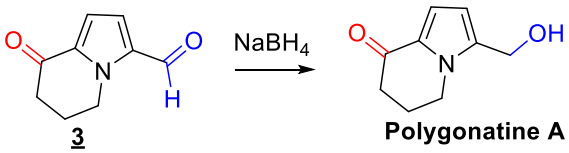
3. Which reactant can be used in step (b) to transform compound 2 into compound 3? What is the name of the reaction? Could you explain the regioselectivity of the reaction?

On pyrrole, you can add aldehyde function thanks to the Vilsmeier Hack reaction. The reactants used are $POCl_3$ and DMF. This reaction is also an aromatic electrophilic substitution, favored on pyrroles in the alpha position.



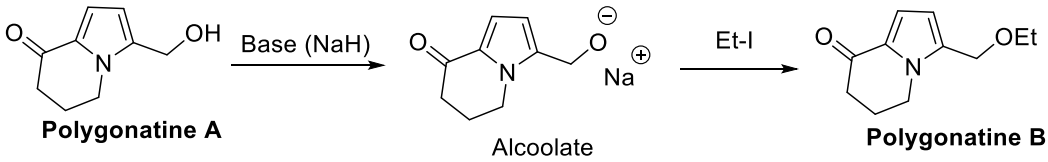
4. Propose conditions (c) to obtain Polygonatine A. How could you explain the regioselectivity of the reaction?

In this reaction, we want to transform an aldehyde function (-CHO in blue) into an alcohol function (CH_2OH). This reaction is a reduction. We can use a smooth reductant like $NaBH_4$. In compound **3** there is also a ketone function (in red). The reaction can be regioselective on the aldehyde function which is in general more reactive than the ketone function.



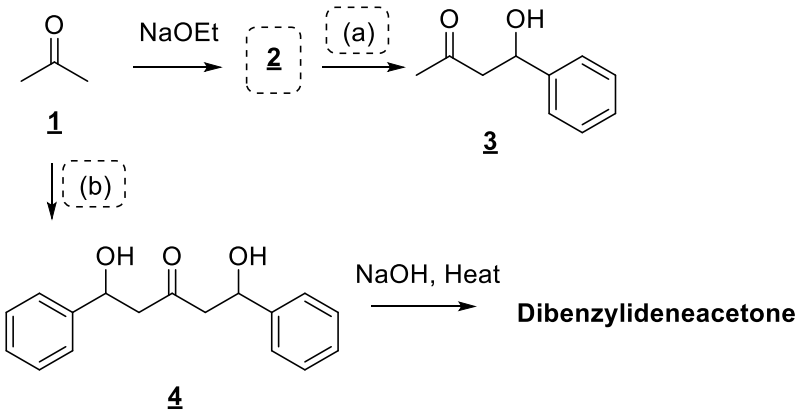
5. Propose conditions (d) to obtain Polygonatine B.

First we must transform the alcohol into alkoxide by using a strong base (the classical one in this case is NaH). Then we can make a nucleophilic substitution with iodoethane (EtI).



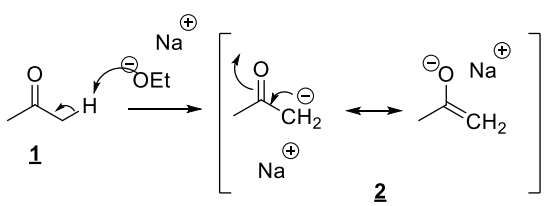
Synthesis of Dibenzylideneacetone

Dibenylideneacetone is a product present in sunscreen.



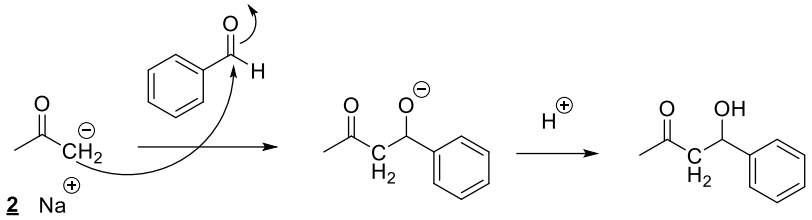
1. What is the structure of intermediate 2? What is the role of NaOEt?

NaOEt is a base which deprotonates the proton in the alpha position referred to the carbonyl in acetone **1**. The resulting salt is in equilibrium between two mesomeric form stabilizing this intermediate.



2. Propose reagent (a) to transform compound 1 into derivative 2. What is the name of the reaction?

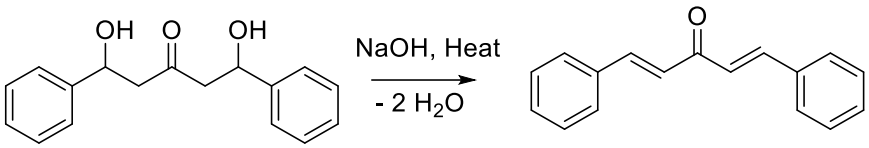
Compound **2** is a nucleophile which can add onto the electrophilic carbon of an aldehyde to lead to an alcohol function of compound **3**. This reaction is called an aldolisation.



3. By comparing compound 3 and 4, deduce the conditions (b) necessary to obtain compound 4.
In compound **4** there are two reactions of aldolization on both sides of the acetone **1**. So we must used at least 2 equivalent of NaOEt and two equivalents of v=benzaldehyde to obtain compound **4**.

4. Give the structure of Dibenzylideneacetone. What is the name of the transformation?

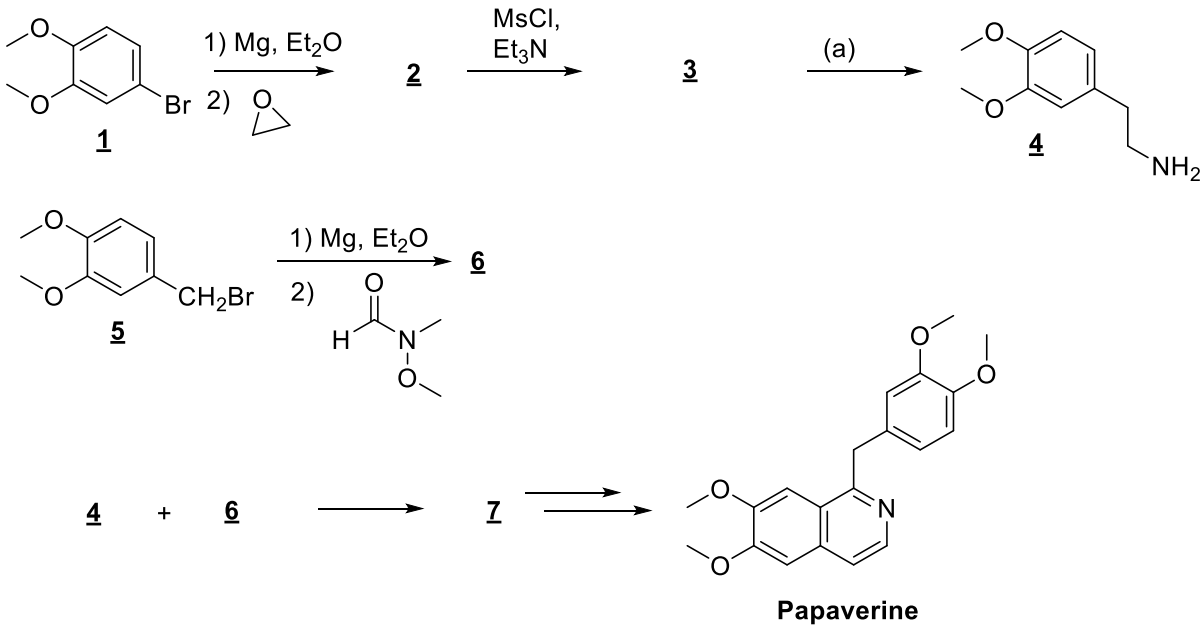
In basic medium upon heating, there is a double dehydration also called crotonisation which leads to **dibenzylideneacetone.**



4 **Dibenzylideneacetone**

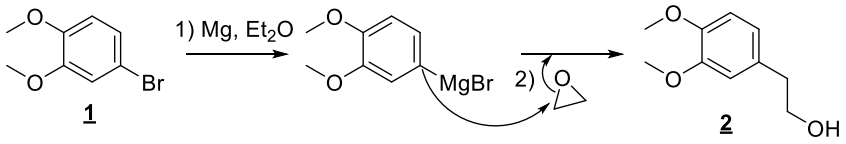
Synthesis of Papaverine

Papaverine is an opium alkaloid antispasmodic used primarily in the treatment of visceral spasm.

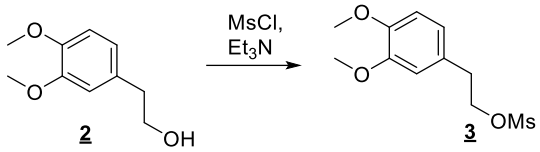


1. Find structures for compounds 2, 3 and 6. What is the interest of using a Weinreb amide in the synthesis of compound 6?

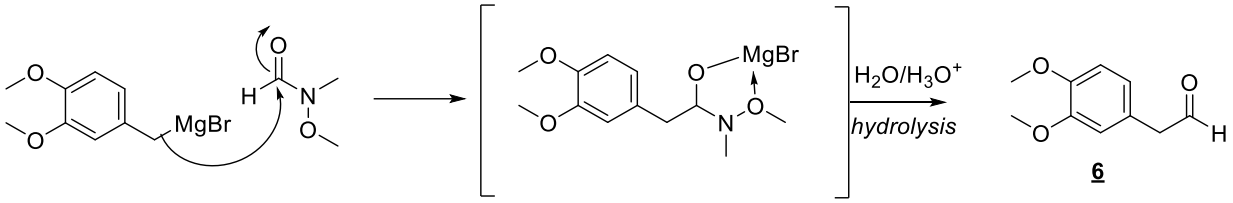
Magnesium inserts in the C-Br bond of compound **1**. The carbon becomes nucleophilic in the C-MgBr bond. It can also make a nucleophilic substitution on the electrophilic carbon of the epoxide to lead to compound **2**.



Alcohol of compound **2** is nucleophilic and attacks mesyl chloride (MsCl = $MeSO_2$-Cl). The interest is to transform the nucleophilic alcohol into a very good leaving group -OMs (sulfonate).

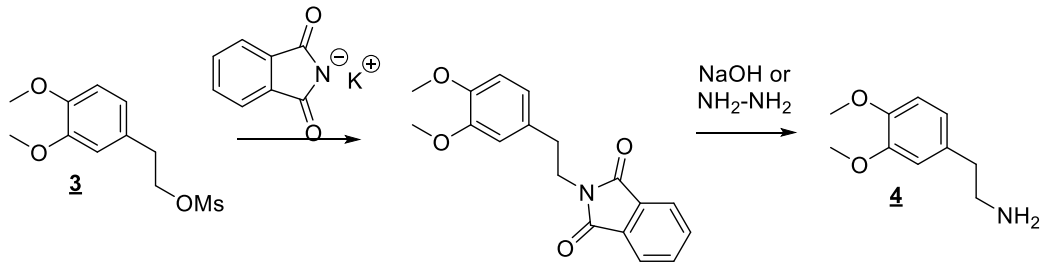


The same type of organomagnesium intermediate can add on a Weinreb amide to give an intermediate, which is stabilized by the internal chelation of OMe to magnesium. The intermediate doesn't generate the aldehyde *in situ* and so no further addition of the organomagnesium is allowed. The aldehyde is generated by hydrolysis of the medium.

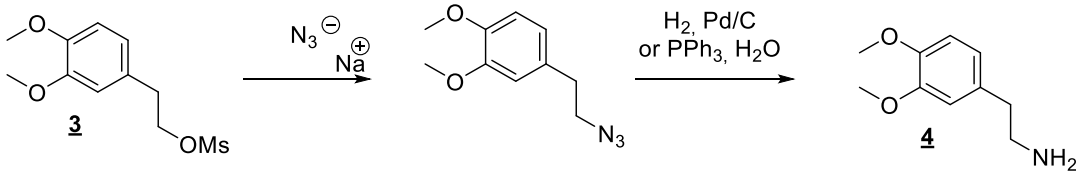


2. Propose a 2 steps route for the synthesis of 4 from 3: conditions (a).

A first possibility is the nucleophilic substitution of the Mesyl group, an excellent leaving group, by a phatlimide salt, a good nucleophile. Then the phtalimide part is removed either by basic conditions (NaOH) or with hydrazine (NH_2NH_2) to give the amine group in compound **4**. This strategy is called Gabriel synthesis.

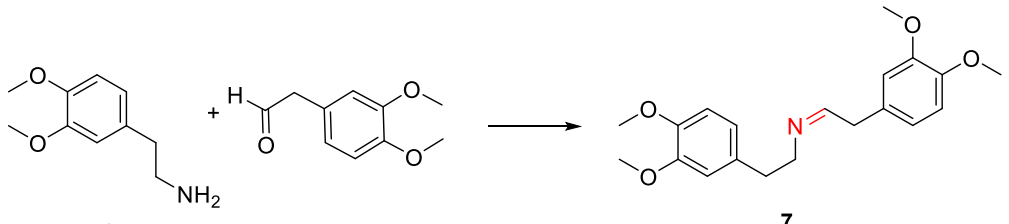


An alternative is the nucleophilic substitution of the mesyl group by another nitrogen nucleophile, sodium azide. Then the azido function is reduced into the amine function (C-O/C-N bonds slide 8).

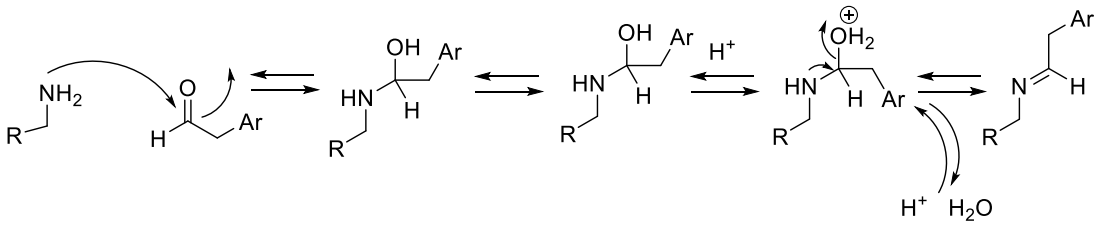


1. What is the structure of compound 7, obtained by reaction of compounds 4 and 6?

The reaction between an amine and an aldehyde leads to an imine function (in red in compound **7**). The reaction is an equilibrium which goes from one side to another, depending on the amount of reagents. Removing water for example drives the reaction to the imine formation.

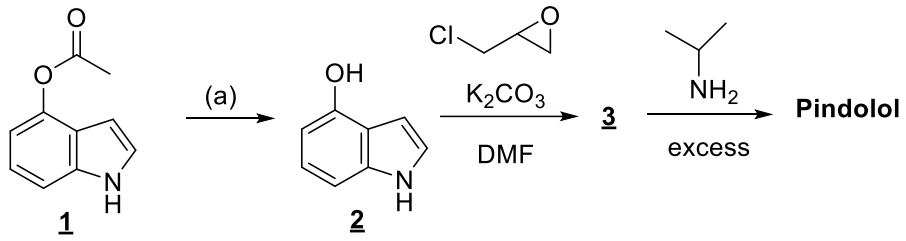


4 **6** **7**



Synthesis of Pindolol

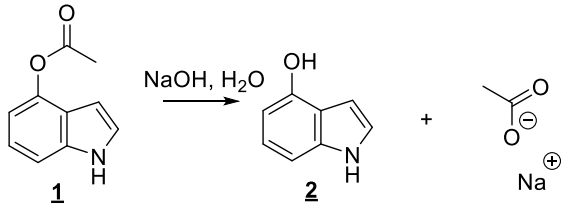
Pindolol is a nonselective beta adrenergic receptor blocker that is widely used for the therapy of hypertension and angina pectoris.



1 **2**

1. Propose conditions to obtain compound 2 from starting material 1.

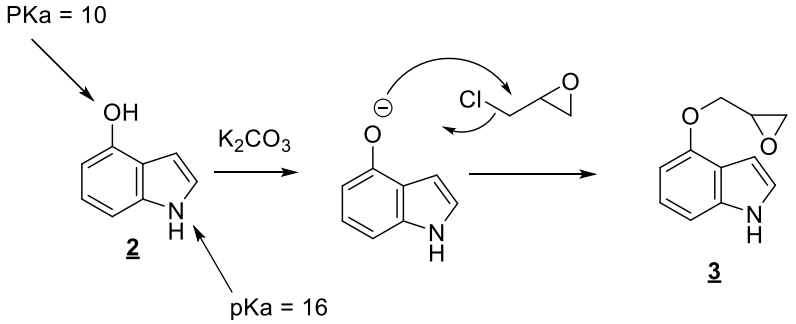
Here you transform an ester into an alcohol with concomitant formation a carboxylic acid/carboxylate. This transformation is a hydrolysis of the ester function. In basic conditions (NaOH, H_2O) this hydrolysis is called saponification.



1 **2**

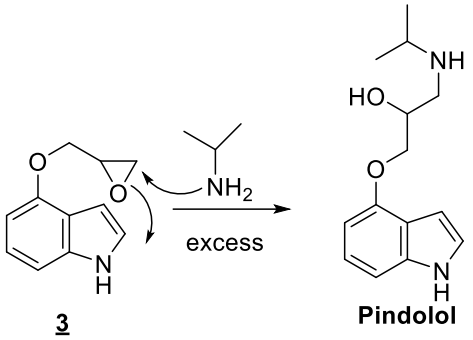
2. Propose the structures of product 3 and Pindolol.

The hydrogen of the phenol is more acidic than the hydrogen of indole (pKa 10 versus pKa 16) and therefore is trapped by the base K_2CO_3. So you have a very nucleophilic phenolate, which can make a nucleophilic substitution of the chlorine atom.



2 **3**

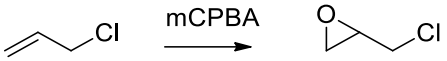
Then the amine (nucleophilic) can attack the epoxide function (the two carbons of epoxide are electrophilic) and open it. The reaction takes place on the less hindered carbon of the epoxide.



3 Pindolol

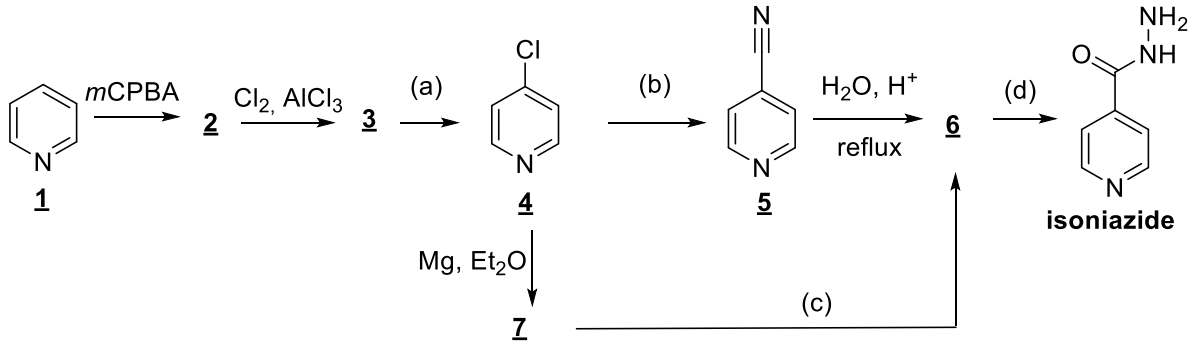
3. Propose a method to prepare epichlorhydrin, the reagent used in the reaction from intermediate 2 to product 3.

A classical method to prepare epoxide is to oxidize an alkene function with an oxidant like *m*CPBA.



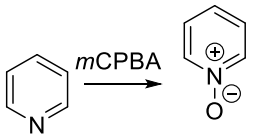
Synthesis of isoniazid

Isoniazid is an antibiotic used for the treatment of tuberculosis.

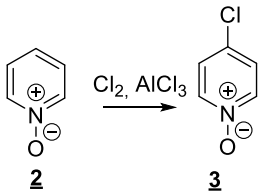


1. What are the structures of compounds 2 and 3?

*m*CPBA is an oxidant. It will transform pyridine into pyridine-*N*-oxide.

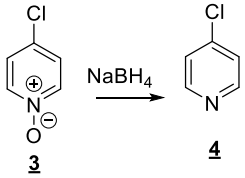


When you use chlorine Cl_2 on an aromatic ring, you always have the replacement of an hydrogen by a chlorine atom (Aromatic electrophilic substitution). In the case of pyridine-*N*-oxide, the reaction takes place on the *para* position.

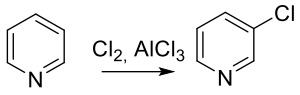


2. Which reactant (a) can be used to transform compound 3 into 4-chloropyridine 4? Which compound(s) will be obtained when using Cl_2, $AlCl_3$ directly with pyridine 1?

To go back to the pyridine function starting from a pyridine-*N*-oxide, you need to make a reduction. A classical reductant for this transformation is $NaBH_4$.



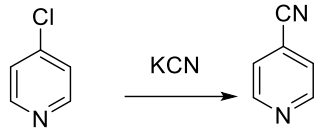
In the case of pyridine, the aromatic electrophilic substitution by chlorine takes place on the *meta* position.



1

3. Propose conditions (b) allowing transformation of intermediate 4 into product 5.

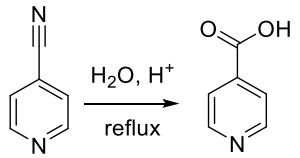
You can add cyanide potassium which is a good nucleophile so you can make an aromatic nucleophilic substitution of the Cl leaving group by the Cyanide. This reaction is favored on pyridine which is en electron deficient ring.



4 5

4. What is the structure of compound 6?

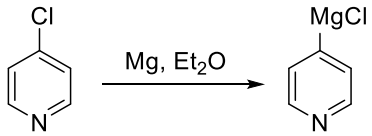
Nitrile function (CN) treated by acidic conditions is hydrolyzed into a carboxylic function.



5 6

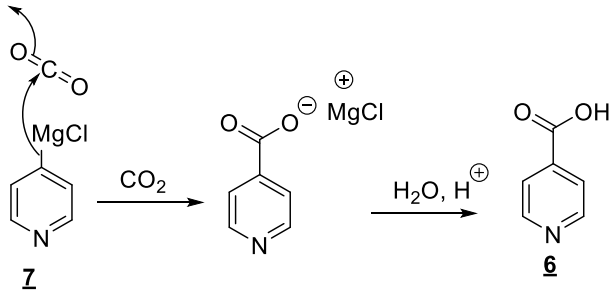
5. Compound 6 could be obtained by another method. What is the structure of intermediate 7 and what is the reactant (c) needed to transform derivative 7 into compound 6?

Magnesium is able to insert into C-Cl and C-Br bond. The carbon is electrophilic in the C-Cl bond and becomes nucleophilic in the C-MgCl bond.



4 7

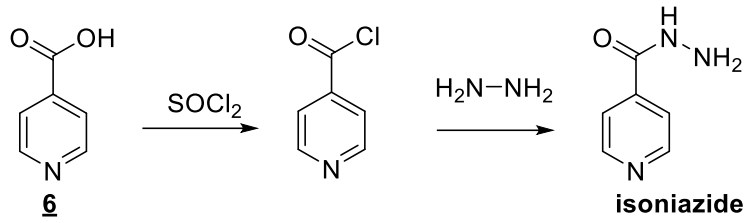
The reactant used to transform compound **7** into carboxylic acid **6** is CO_2 (the carbon of CO_2 is electrophilic). You produce a carboxylate function. When you add acidic water, you protonate the carboxylate to give the carboxylic acid.



7 6

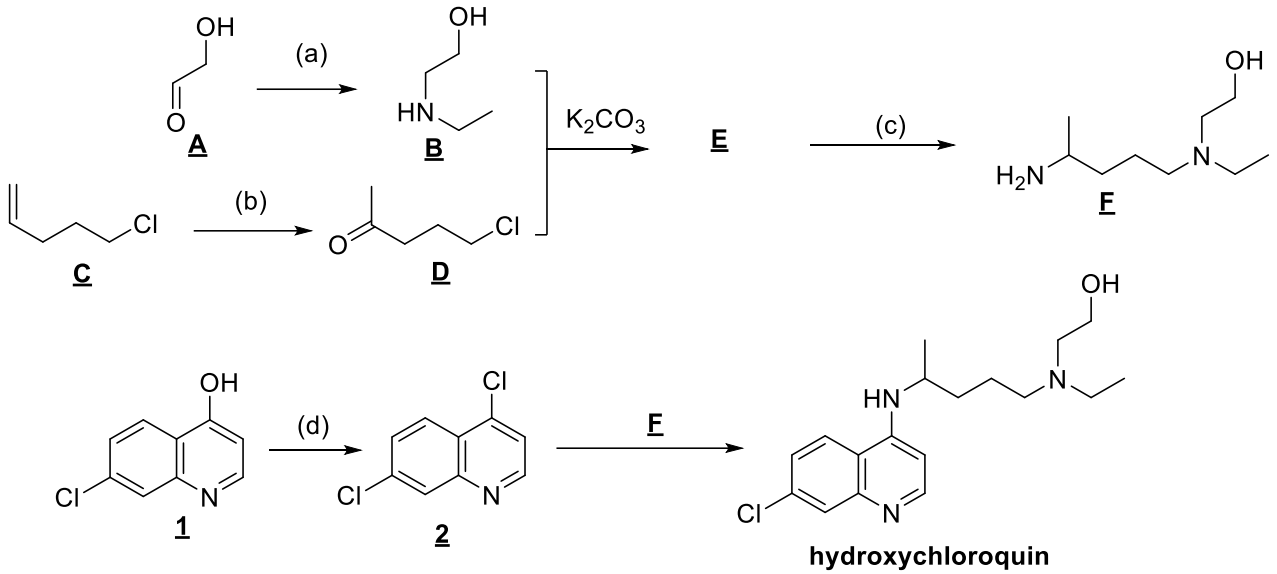
6. Propose conditions (d) allowing transformation of intermediate 6 into isoniazide.

Carboxylic acid can be transformed into “amide” function by reacting with the “amine” derivative. But it’s necessary to activate first the carboxylic acid –COOH into an acyl chloride –COCl by using thionyl chloride ($SOCl_2$).



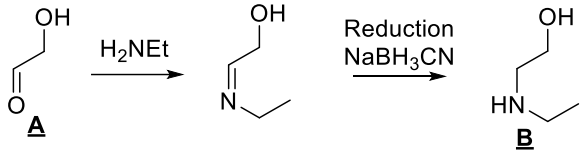
Synthesis of hydroxychloroquin

Hydroxychloroquin is a medication used to treat malaria, rheumatoid arthritis and lupus. It has also been studied to prevent and treat COVID-19, but clinical trials proved its inefficiency.



1. Propose a method (a) to access B from glycoladelhyde A.

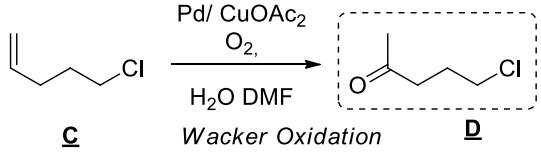
The most direct route to transform an aldehyde into an amine is a reductive amination. It is divided into two reactions:
- first the formation of an imine formed by reaction of the aldehyde with an amine, here H_2NEt.
- then the reduction of the imine function with smooth reductant, selective of the imine function, here $NaBH_3CN$.



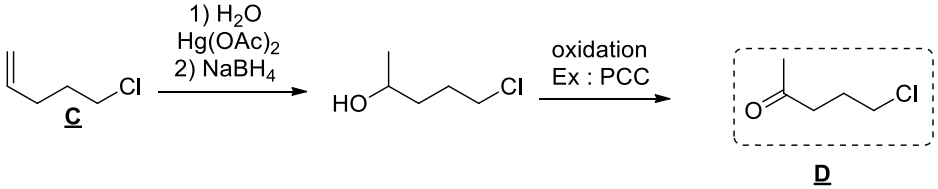
2. Give 2 routes for (b) (3 steps max.) to access D from C.

Three routes are possible to transform compound **C** into compound **D**:

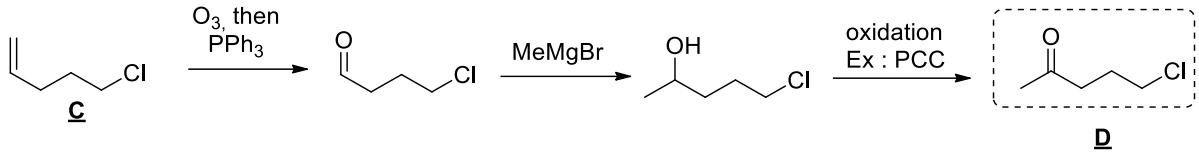
- The Wacker oxidation in one step.



- Hydratation of the alkene function to give an alcohol intermediate, followed by its oxidation into a ketone function.

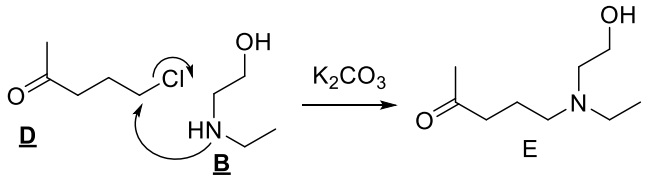


- Ozonolysis of the alkene function which led to an aldehyde. Then addition of MeMgBr (to add the missing CH_3 group) which led to an alcohol (the same than after hydration of the alkene). And finally oxidation of the alcohol into the ketone function.



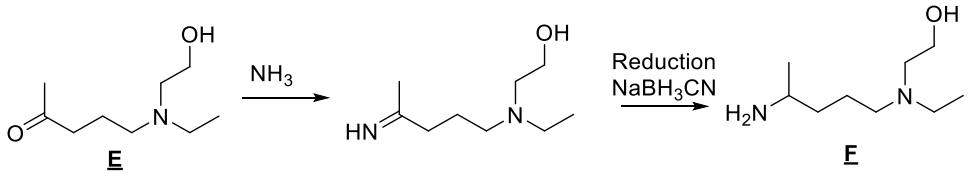
3. Give structure of E. Explain the reactivity of amino group towards hydroxyl group.

Here we have the nucleophilic substitution of the chlorine atom (the C linked to the chlorine is electrophilic) by the amine (amine is the nucleophile). Amine is more reactive than free alcohol. Alcohol needs deprotonation to react in alkylation and K_2CO_3 is not basic enough to deprotonate the alcohol. Role of K_2CO_3 is to scavenge HCl in reaction mixture, else all amine function will trap HCl, leading to an unreactive salt ammonium salt. The lone pair of nitrogen would no longer exist for nucleophilic reaction].



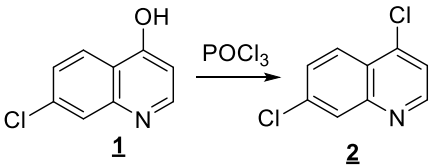
4. Propose conditions (c) to obtain F starting from intermediate E.

It is the same problem than in question 1. Reductive amination is the best route to transform a ketone into an amine. The amine is here ammonia NH_3 and the reductant is $NaBH_3CN$.



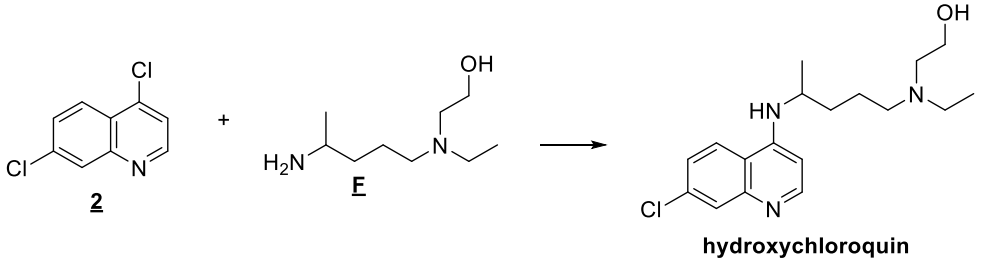
5. Which reactant (d) can be used to transform reagent 1 into compound 2?

You can transform the OH function of quinolone in the same way than OH function of pyridone. The reactant is $POCl_3$ (phosphorous oxychloride)



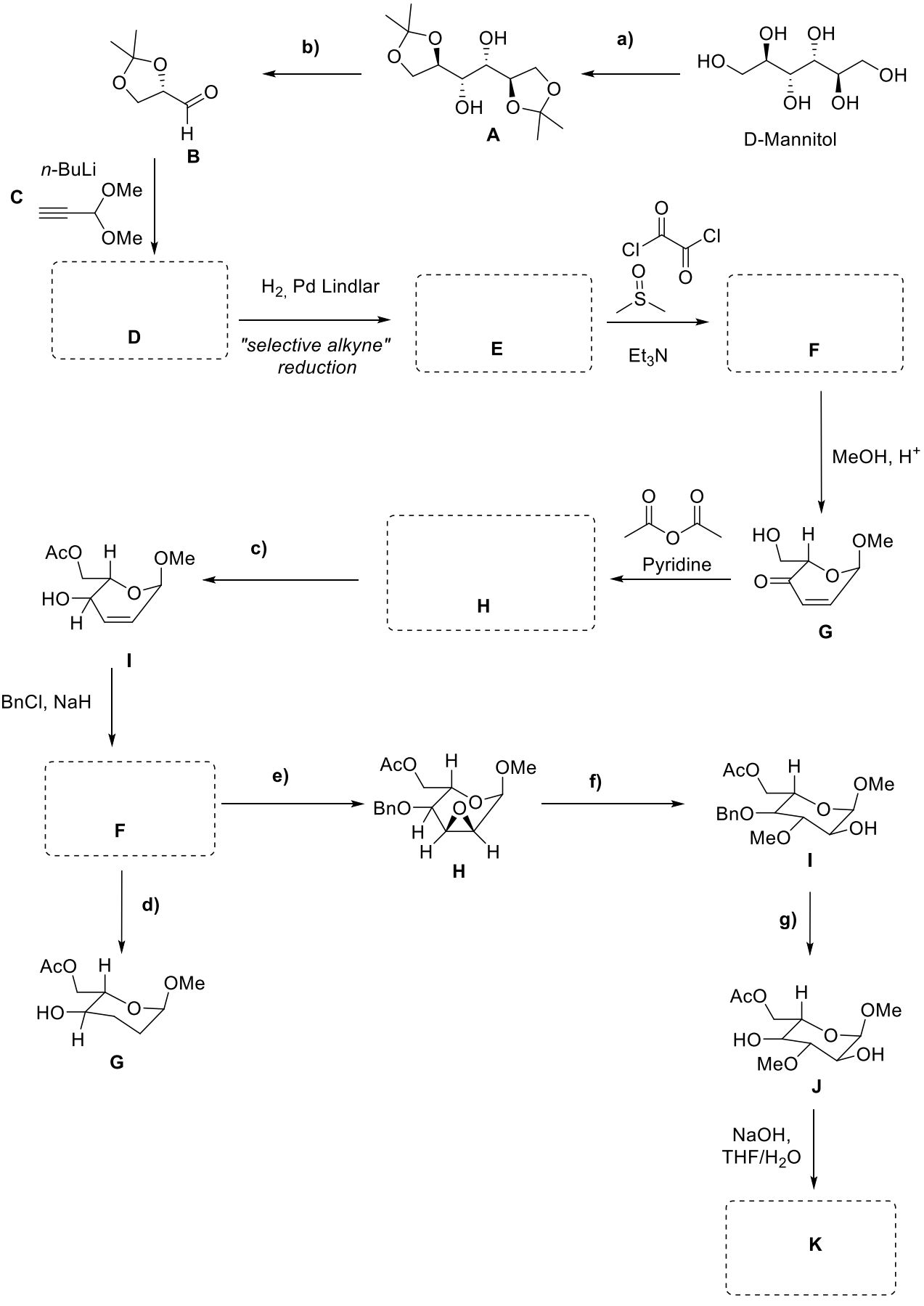
6. What is the type of reaction between 2 and F which led to hydroxychloroquin? How could you explain the regioselectivity of the reaction?

In this step, we replace a chlorine atom by an amino function. It is an aromatic nucleophilic substitution. The reaction takes place only on the pyridine ring because it is an electron poor ring compared to the benzene ring.

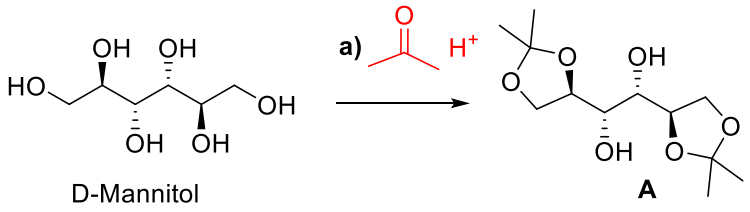


Synthesis of L-Glucose derivatives

L-glucose is not available easily from the "Chiral Pool" in contrast to the natural D-isomer. The synthesis of L-Glucose derivatives is sometimes needed for incorporation into oligosaccharides. Synthetic access is presented below.



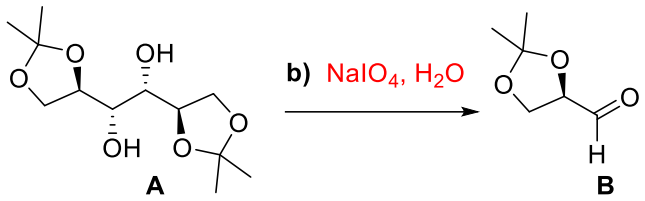
1. **Give conditions a). Explain the regioselectivity of the protection. What is the class of protecting group?**



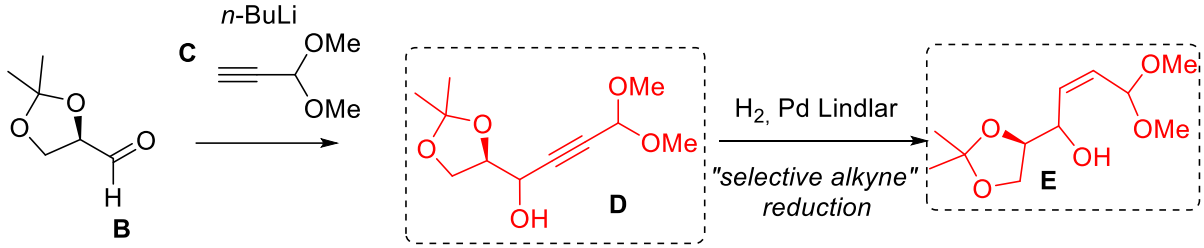
The primary positions are less hindered thus more reactive compared to the internal position where the diol is remaining.

The protecting group is a ketal function

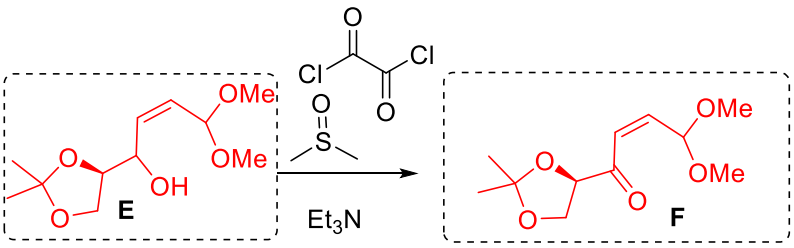
2. **Give conditions b).**



3. **Give product D and product E. Product E is obtained after a "selective alkyne hydrogenation".**

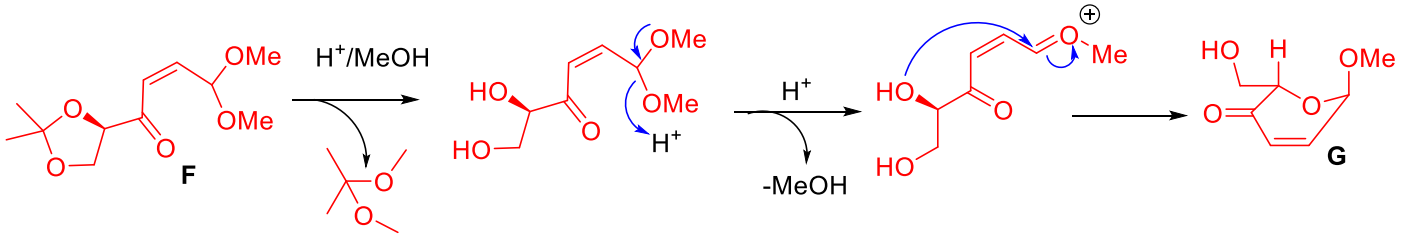


4. **Give Product F; What is the name of this reaction?**



It is an alcohol oxidation, called more precisely Swern oxidation.

5. **Compound F is treated by acid in methanol to give G. Try to explain with a scheme how G was formed.**



6. Give conditions **c)**, **d)**, **e)**, **f)**, and **g)** and Find structures **H**, **F** and **K**.