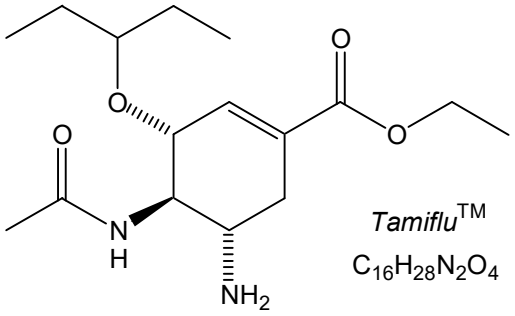
5. This question is about the synthesis of Tamiflu ™

Tamiflu is the anti-influenza drug currently being used to treat so-called 'Bird-flu'. Its structure is shown on the right. The bold wedged bond is coming out of the plane of the paper, the hashed bonds are going into the plane.



Tamiflu™

$C_{16}H_{28}N_2O_4$

In order to increase its solubility, Tamiflu is actually sold as the phosphate salt.

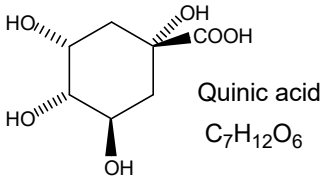
(a) On the structure in your answer booklet, circle the atom which will be protonated in the salt.

One of the problems in the synthesis of the drug is ensuring the correct stereochemistry at each of the stereogenic (chiral) centres in the structure.

(b) **i)** On the structure in your answer booklet, mark with an asterix each chiral centre.

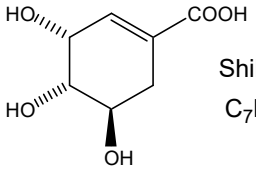
ii) What is the total number of stereoisomers possible for this structure?

Two syntheses of Tamiflu which have been tried start from the naturally occurring products *Quinic acid* and *Shikimic acid*.



Quinic acid

$C_7H_{12}O_6$

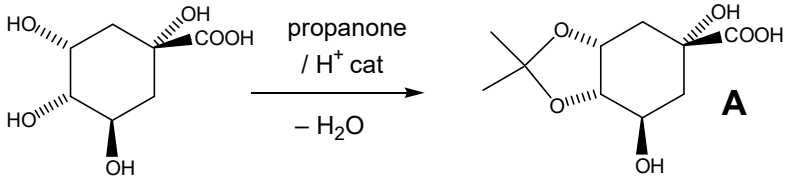


Shikimic acid

$C_7H_{10}O_5$

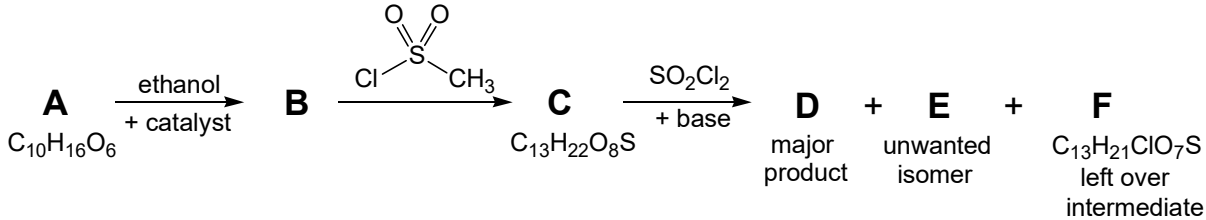
Shikimic acid has the advantage of already having the double bond in place but quinic acid has the advantage of being much cheaper.

One of the problems using either acid is trying to control which of the –OH groups reacts in a given step. The first step starting from quinic acid is therefore to protect the two –OH groups on the same side of the ring on adjacent carbon atoms by forming a so-called *acetal* group by the acid-catalysed reaction with propanone:

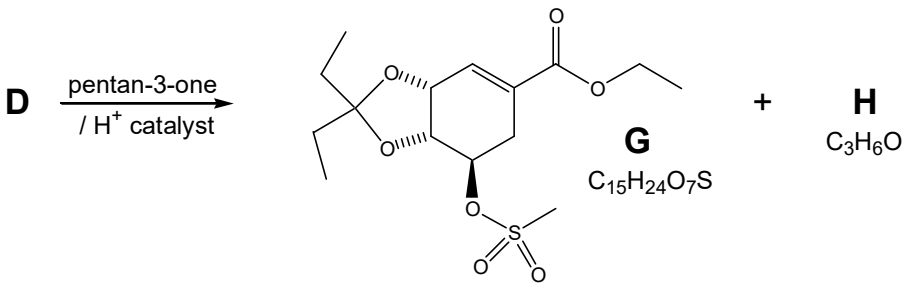


$C_7H_{12}O_6$ $C_{10}H_{16}O_6$

The next steps in the synthesis are outlined below. Inorganic by-products are not shown in the scheme.

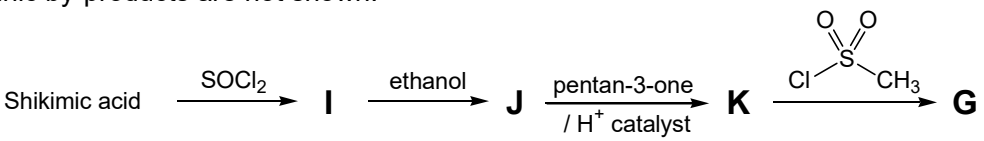


D reacts with an excess of pentan-3-one to give **G** as shown below.



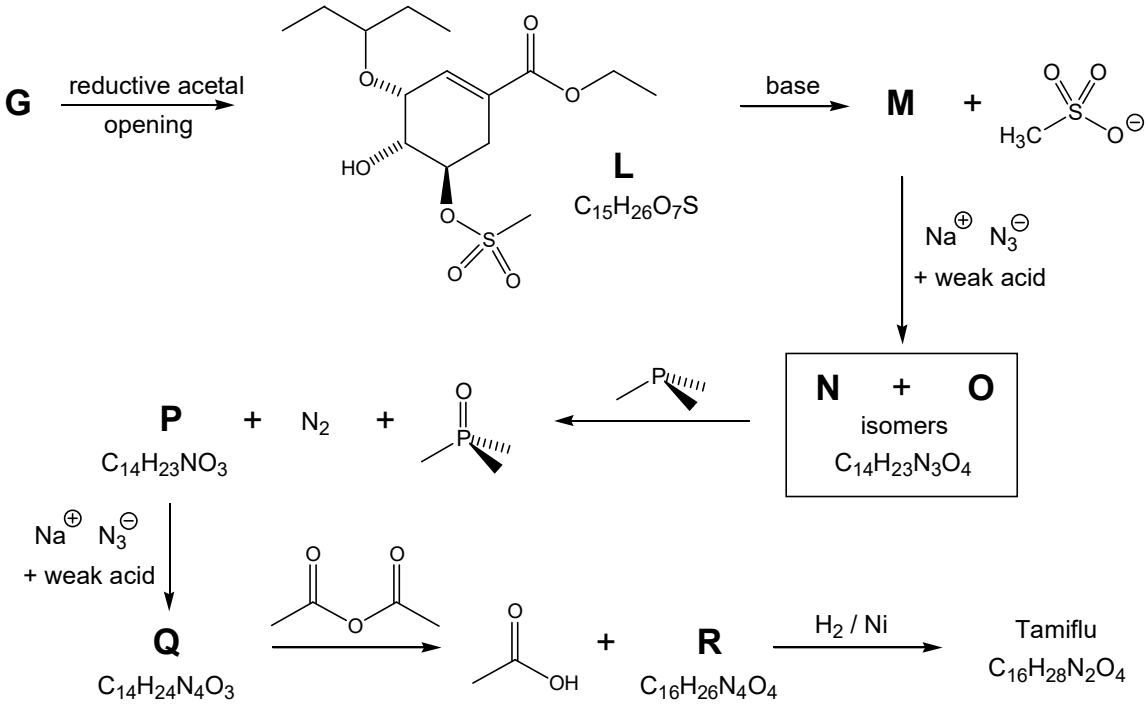
(c) Draw the structures of compounds **B**, **C**, **D**, **E** and **F** and for the by-product **H**, showing the correct stereochemistry by the use of bold and hashed bonds as appropriate.

G may easily be prepared from the more expensive Shikimic acid as outlined below. Inorganic by-products are not shown.



(d) Draw the structures of compounds **I**, **J**, and **K** showing the correct stereochemistry as appropriate.

The acetal in **G** may be opened up under reducing conditions to give mainly **L** (shown below). On treatment with base **L** cyclises to give **M** which contains a 3-membered ring. The new ring is opened up with sodium azide yielding a mix of isomers, **N** and **O** either of which yields the same cylic compound **P** on treatment with trimethylphosphine. Further treatment with sodium azide opens the new ring to give mainly **Q** which upon acylation and hydrogenation finally yields neutral Tamiflu as outlined below.



(e) On the structure in your answer booklet, circle the most acidic proton in **L** which is removed by the base.

(f) Draw the structures of compounds **M**, **N**, **O**, **P**, **Q** and **R** again showing the correct stereochemistry as appropriate.