Spivey Group Problem Session

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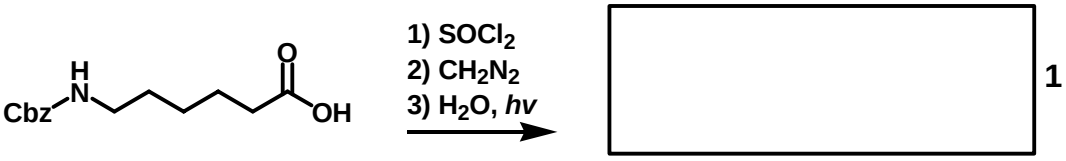
July 2008

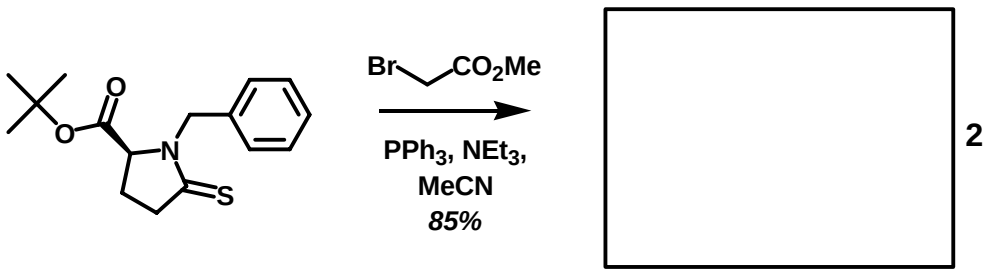
Part One – Named Reactions

Question 1)



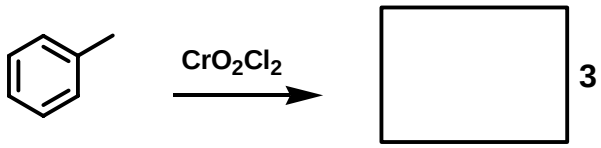
a) What is the structure of product **1**?
b) What is the mechanism?
c) What is the name of this reaction?

Question 2)



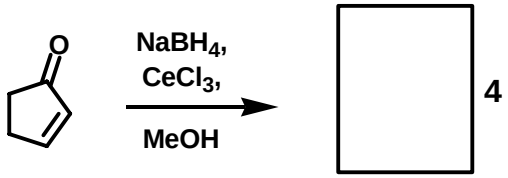
a) What is the structure of product **2**?
b) What is the mechanism?
c) What is the name of this reaction?

Question 3)



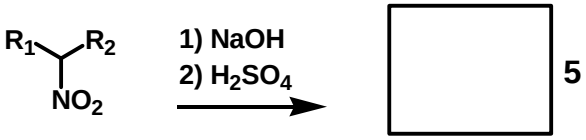
a) What is the structure of product **3**?
b) What is the mechanism?
c) What is the name of this reaction?

Question 4)



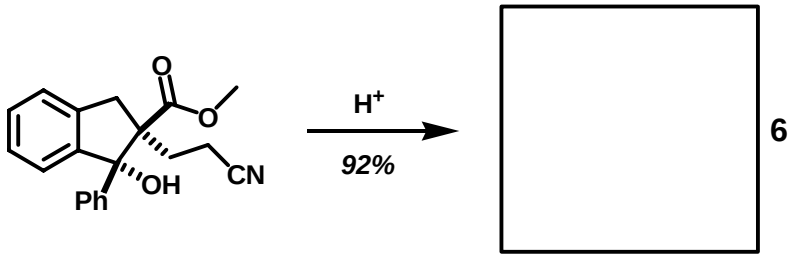
a) What is the structure of product **4**?
b) What would you expect the product to be if the $CeCl_3$ was absent from the reaction?
c) What is the mechanism?
d) What is the name of this reaction?

Question 5)



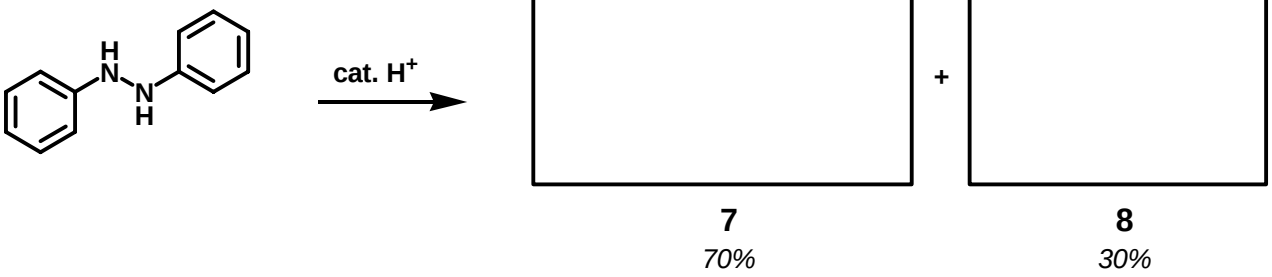
a) What is the structure of product **5**?
b) What is the mechanism?
c) What is the name of this reaction?

Question 6)



a) What is the structure of product **6**?
b) What is the mechanism?
c) Would you expect more than one diasteroismer? Why?
d) What is the name of this reaction?

Question 7)



a) What is the structure of products **7** and **8**?
b) What is the mechanism for each?
c) What is the name of this reaction?

Question 8)

Taking the first letter from each of the named reactions above, rearrange the letters to spell the common name of a drug first discovered in Australia.

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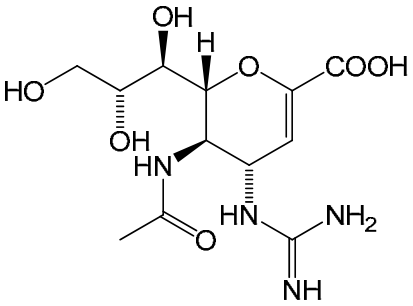
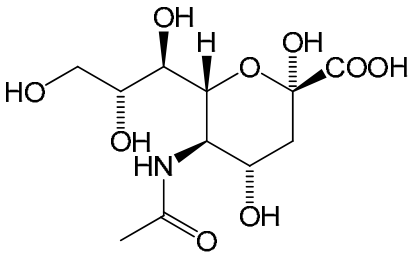
Some facts:

Relenza **1** (Zanamivir) was the first neuraminidase inhibitor ever developed for the treatment of influenza (effective against strains A and B). It was first developed by Mark von Itzstein and co-workers at the Victorian College of Pharmacy - Melbourne, Australia in 1989. Initial funding was provided from Biota a small Australian biotech company. In 1990 licensing of Relenza was sold to Glaxo (now GSK) to complete late stage development and bring the drug to market, with Biota to receive a 7% royalty on the sales. Arguably, it is described as an example of a rationally designed inhibitor, with it's origins derived from sialic acid **2** (the natural substrate of neuraminidase). Relenza's mojor competitor is Tamiflu **3** (Oseltamivir) which was marketed by Roche. Despite being first to market, Relenza is not as popular as Tamiflu – a fact that has been reflected in the rather poor sales of Relenza. One major reason is the differing routes of administered: Relenza is inhaled, while Tamiflu is taken orally. Both drugs work in a very similar way by inhibiting the neuraminidase enzyme found of the surface of the influenza virus. With this enzyme inhibited, the flu virus is unable to escape it's host cell, preventing further infection.

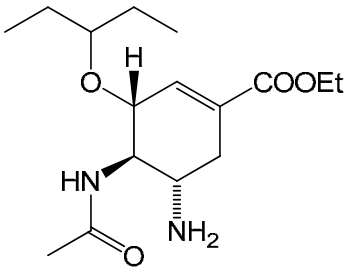
Compound	Flu A IC_{50} (nM)	Flu B IC_{50} (nM)
Relenza	5	4
Tamiflu	2	32



Relenza, **1**



Sialic Acid, **2**



Tamiflu, **3**

Questions:

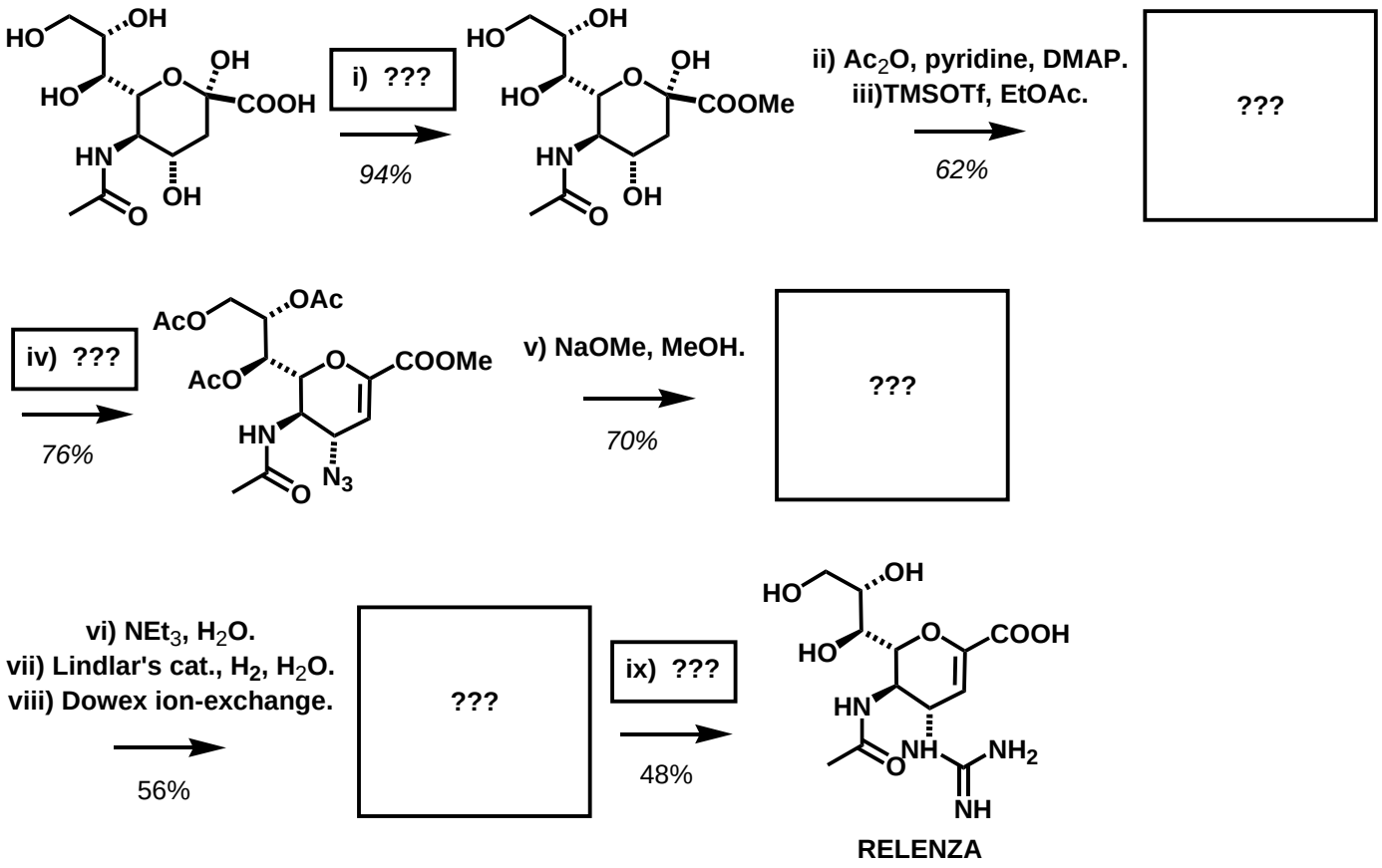
1) Can you define (*R* or *S*) the stereochemistry at each chiral centre for all three compounds shown above?
2) Relenza is not very bioavailable, can you suggest a reason why it cannot be administrated orally?
3) Tamiflu is a prodrug, can you draw the structure of the active species?

Synthesis to follow in Part 3!!!

Spivey Group Problem Session

Daniel Offermann - Aug 2008

Part Three - *Relenza Synthesis*



1) Please provide the missing reagents and structures in the above scheme.
2) Please provide a mechanism for each transformation as well.
3) What are some other methods for converting an azide to an amine?