

Chemistry 125
May 3, 2001

Second Semester Name _____
Final Examination

This exam is budgeted for 150 minutes, but you may have 180 minutes to finish it. Good Luck.

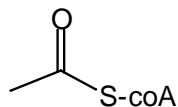
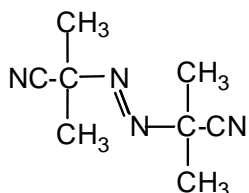
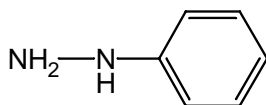
1. (12 min) Choose 6 (SIX ONLY) of the following eight reagents and give an example of its use. The more specific the better.

NBS / CCl₄

Cl-SO₂-Ar

LiAlH₄

CH₂I₂ / Zn(Cu)



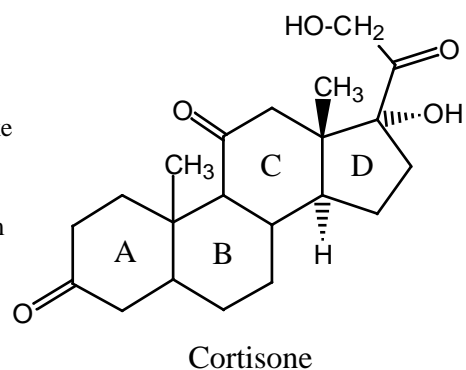
S-adenosylmethionine

Cortisone

The goal of Chemistry 125 has been to make you able to **understand** how organic molecules behave, In more specialized courses you can learn how to **design** clever syntheses for complex molecules, perhaps ones of medicinal importance like **Cortisone**.

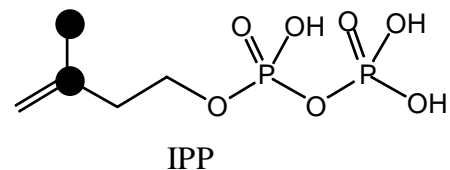
In 1951 R. B. Woodward, whom many regard as the best synthetic organic chemist ever, designed and supervised the multistep total synthesis of Cortisone from simple organic starting materials. By answering Questions 4-25 you will show that even if you are not yet able to design such a synthesis from scratch, you can understand important aspects of what went on in Woodward's thinking.

Note that the rings are labeled A-D. During the synthesis the rings will be identified with these letters as they are assembled.

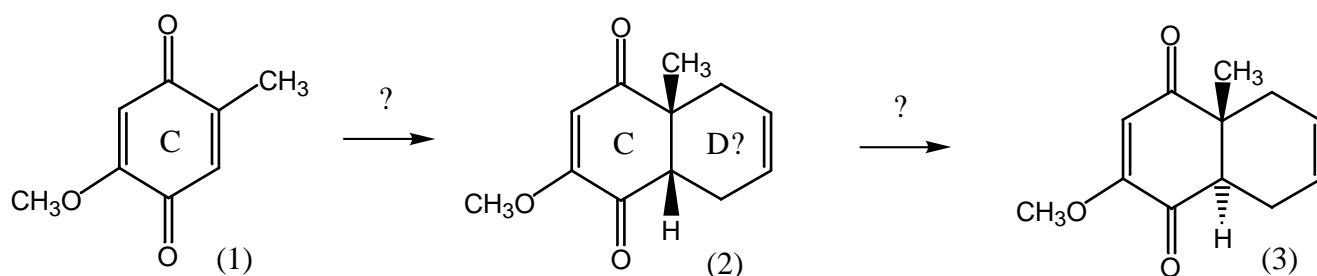


2. Cortisone is a “steroid” natural product, like lanosterol or cholesterol. Such compounds are known to be synthesized in nature from IPP.

a) (3 min) What is the role of the $\text{H}_3\text{P}_2\text{O}_7$ “pyrophosphate” and alkene groups in the assembly of the carbon skeleton of a steroid like Cortisone?



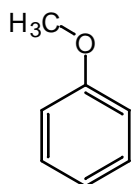
b) (4.5 min) Describe and explain expected differences in the ^{13}C -NMR methyl signals of a sample of Cortisone biosynthesized in the presence of added IPP that has been isotopically double-labeled in the positions indicated by filled circles.



3. (6 min) Compound **1** was the starting material in Woodward's synthesis. One might have begun with still simpler compounds using Friedel-Crafts **methylation** of methoxybenzene ("anisole") to prepare p-methylanisole, a possible precursor of **1**.

WHAT **REAGENT**(s) might one use to supply the methyl group?

EXPLAIN whether one would expect the methoxy group to be **activating or deactivating**, and whether **o,p-directing** or **m-directing**, for such an electrophilic aromatic substitution.



Anisole

4. (6 min) Woodward's first reaction was **1** -> **2**, adding ring D to Ring C (D is the wrong size, it should have 5 carbons. He fixes this up later - compound 22, p. 9).

What **REAGENT** could be used for this reaction?

What is the **NAME** of this reaction?

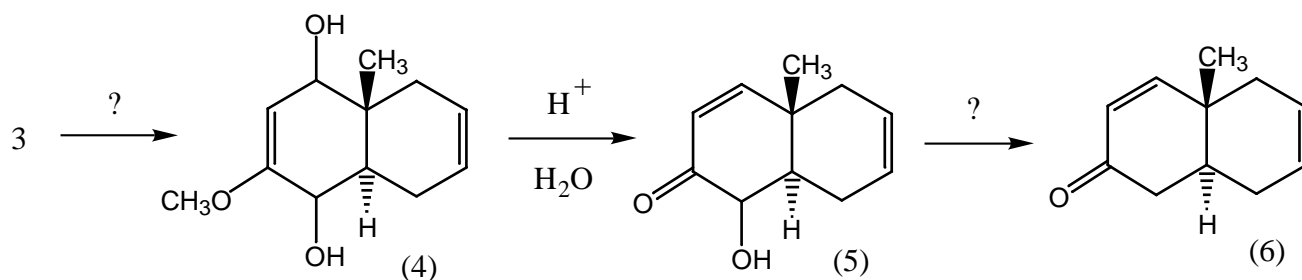
Draw **another product** that might have formed if Woodward had been unlucky?

What **HOMOs and LUMOs** are involved in this reaction?

5. (4.5 min) Woodward then corrected the stereochemistry of the proton between Rings C and D by the reaction **2** -> **3**. Tell **what reagent** he could use to remove and readd the proton.

Explain why it was important to make the correction **before** the next reaction, **3** -> **4**.

Cite some **relevant pKa** values (give numbers).



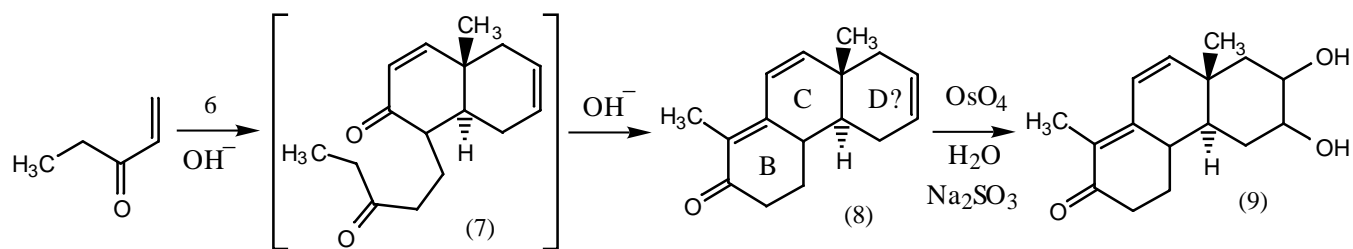
6. (2.5 min) **What reagent** might be appropriate for converting 3 \rightarrow 4?

7. (10 min) As a model for the acid-catalyzed reaction 4 \rightarrow 5, **draw a mechanism** with several steps for the conversion below. Use **curved arrows** and show intermediates. [There are two good mechanisms, either is fine. **Hint:** Think about how to replace the CH_3O group.]



8. (3 min) The reaction 5 \rightarrow 6 is presumably unfamiliar to you, and you don't need to know its mechanism to answer **which reagent** Woodward used, **Zn metal or ZnCl_2** ?

Explain your choice:



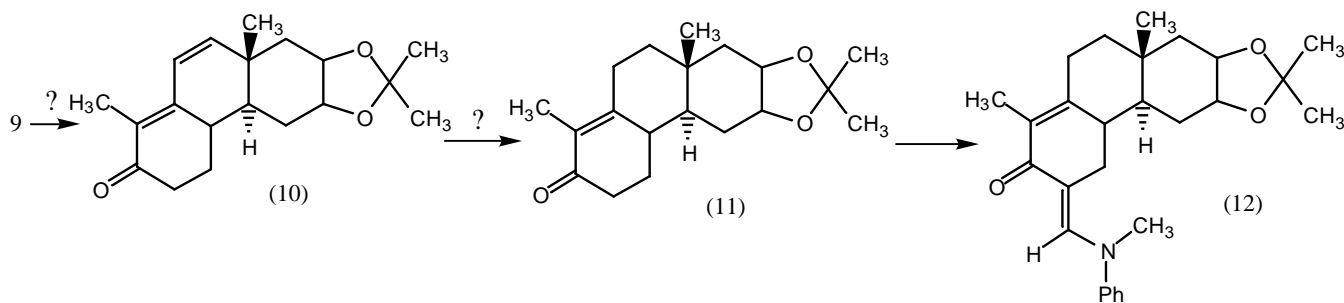
9. (7 min) The reaction 6 \rightarrow 7 involves a Michael addition. Show that you understand such a reaction by drawing the **curved-arrow mechanism** of the analogous reaction **with acetone** replacing compound 6. [This question is appropriate, because this method for forming Ring B was originally devised by Robert Robinson, who introduced curved arrows.]



10. (5 min) The conversion 7 \rightarrow 8 involves a familiar named reaction with an isolable intermediate that converts slowly to product. Give the **name** of the reaction **and draw** the isolable intermediate.
11. (6 min) The conversion 8 \rightarrow 9 involves initial reaction with OsO_4 , an osmium atom with four double bonds to oxygen, to form an "osmate ester" intermediate with a new 5-membered ring.

Draw **curved arrows** showing the 5-membered ring formation, and **explain the analogy** with reaction 1 \rightarrow 2 (page 3)

Which atoms change formal oxidation states during formation of the 5-membered ring, and by **how much**?



12. (6 min) Name the new functional group with two oxygens formed in the conversion **9** → **10**.

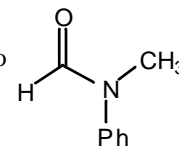
What other reagent, besides **9** was used to form this new functional group?

Should one choose **acid** or **base catalysis** for **9** → **10**? Explain.

13. (4 min) What **reagent(s)** might be used for **10** → **11**?

Why should this conversion **not** be performed **before 8** → **9**?
[This is a good example of the importance of order in a complex synthesis.]

14. (16 min) The new group introduced at the bottom of the molecule by **11** → **12** comes from **N-methyl-N-phenylformamide**. It is introduced using basic catalysis, in analogy to an aldol reaction (you do not need to write this mechanism here).



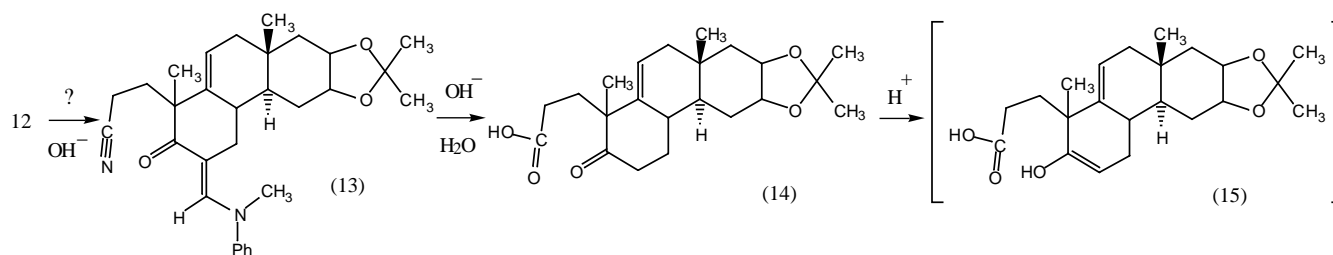
a) Why is this group put onto the molecule? (It comes off just two steps later, **13** → **14**, p. 7)
[Hint: Wait until you look at **12** → **13** before answering]

[Use the **back of this sheet** to answer the following **two spectroscopic questions**.]

b) Describe or sketch the **proton NMR spectrum** for N-methyl-N-phenylformamide, and **explain** briefly why it might look different at **high and low temperature**.

c) Draw lines to connect each of the following compounds with its **C=O stretching frequency** in the IR (cm^{-1}).
Explain on the back of this sheet.

Acetone	Compound 11 (above)	acetyl chloride	N-methyl-N-phenylformamide
1800	1715	1690	1675

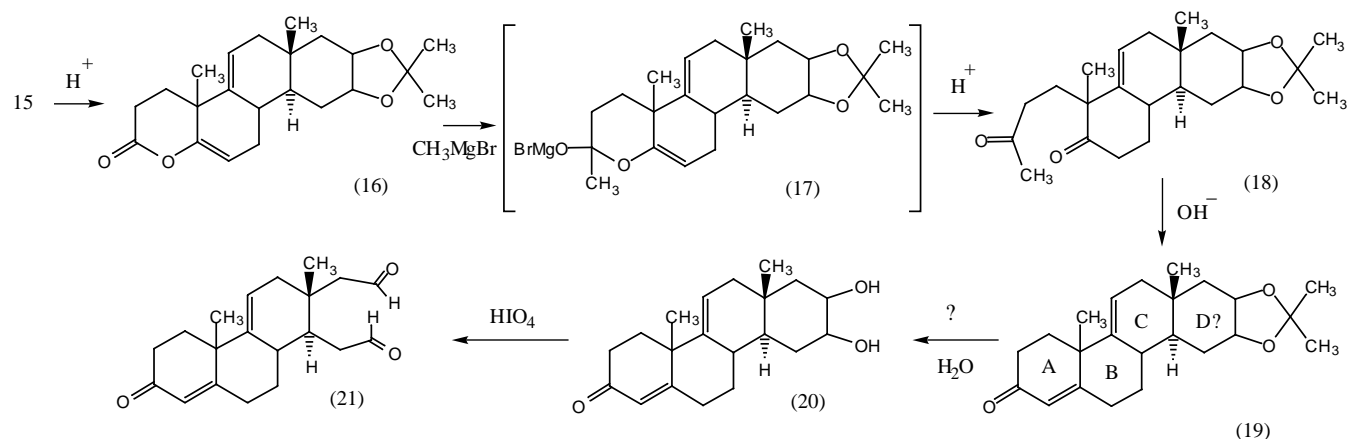


15. (5 min) For the conversion 12 \rightarrow 13, the base abstracts a proton to make an enolate which performs Michael addition to a compound with 3 carbons (and other atoms). **What is the other compound and what is its LUMO?**

16. (5 min) Two functional groups are transformed in the conversion 13 \rightarrow 14. Write the **curved-arrow mechanism for one of them** (your choice which).

17. (5 min) **Predict the equilibrium constant for 14 \rightarrow 15** from the following values of average bond energies (kcal/mole)

C-C 83 ; C=C 146 ; C-O 86 ; C=O 179 ; C-H 99 ; O-H 111



18. (2.5 min) **EITHER** give the chemist's **name** associated with the reaction 15 \rightarrow 16, **OR** draw the reaction **mechanism**.



19. (7 min) Notice that compound 16 is a sort of ester, a cyclic one, and that in 16 \rightarrow 17 it reacts with one mole of the Grignard reagent. An acyclic ester would usually react with two moles of a Grignard reagent and give a different product.

What would the **product of double reaction** of **methyl acetate** with CH_3MgBr be?

Explain how entropy might explain the reluctance of cyclic 17 to react twice with Grignard reagent.

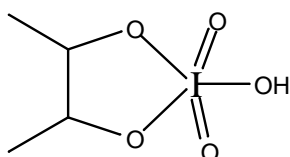
20. (1.5 min) **Which previous transformation** in this series of reactions is like 18 \rightarrow 19?

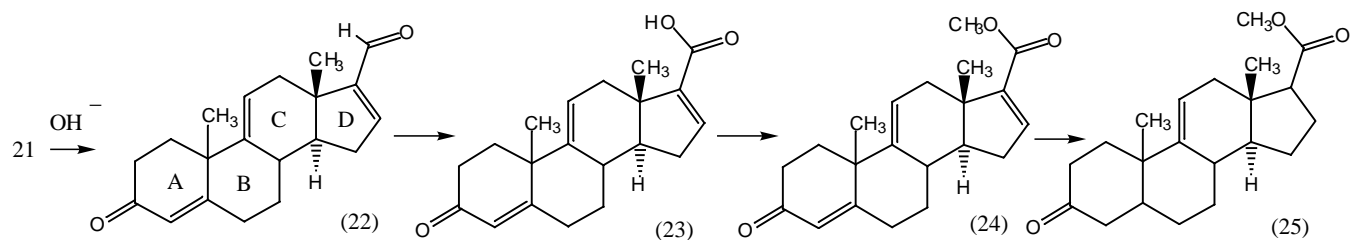
21. (4 min) Does the question mark for 19 \rightarrow 20 represent **acid or base**?

Note that this reaction restores the diol that was already present in compound 9.

Which of the intervening steps required that the diol be protected?

22. (3.5 min) The reaction with HIO_4 involves an intermediate 5-membered ring. Use curved arrows to show how this intermediate can "unzip" to give a dialdehyde, as in 21.



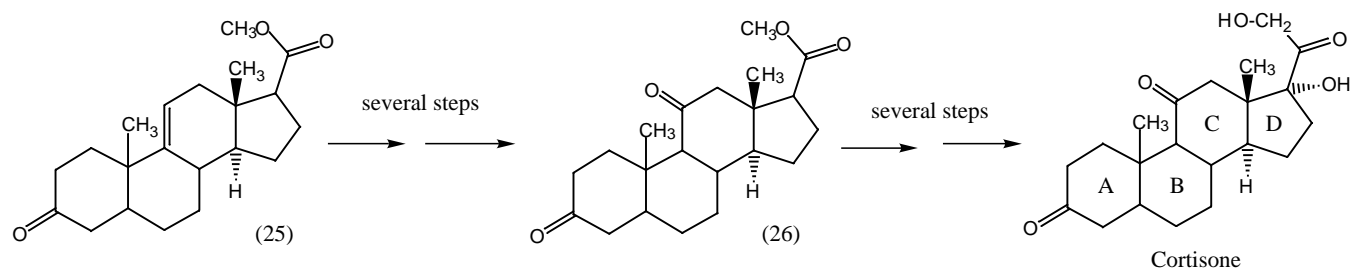


23. (4 min) Finally in **21** \rightarrow **22** the six carbons that were introduced as a 6-membered D-ring in the very first reaction (page 3) are formed into the 5-membered D-ring needed for Cortisone. This shows how far ahead Woodward was planning. There was a risk that an isomeric compound would have formed instead. **What would the isomer of 22 be?**

24. (10 min) One might try oxidizing the aldehyde group of **22** to the acid group of **23** with peroxyacetic acid ($\text{CH}_3\text{-CO-OOH}$). Write the **mechanism** for this reaction and **show how an important step is analogous** to an important step in the conversion of a trialkylborane, BR_3 , to a borate ester, B(OR)_3 .

Draw **another product** that might have formed by treating **22** with peroxyacetic acid.

When Woodward got to compound **25** he declared victory, because other chemists had already been able to convert this compound to Cortisone. One conversion they had had to accomplish involved converting the “vertical” C=C group of compound **25** to the new carbonyl group of compound **26**.



25. (7 min) Suggest a way to convert **25** to **26** in several steps. Obviously you must somehow get an oxygen on the correct carbon atom and convert it into a ketone.