NAME:_____ Section:__A__ Student Number:_____

Spring 2015 **Chemistry 4000 Midterm** ____/ 42 marks

INSTRUCTIONS:

1) Please read over the test carefully before beginning. You should have 8 pages of questions and a periodic table.
2) Unless otherwise stated in the question, explain all of your answers fully. Use diagrams where appropriate. When invoking any argument based on resonance, you must draw all relevant resonance structures.
3) ALL structures must be drawn showing lone pairs, non-zero formal charges and reasonable bond angles – regardless of whether they are expanded, condensed or line-bond. Marks will be deducted for poorly drawn structures.
4) Marks will be deducted for incorrect information added to an otherwise correct answer.
5) If your work is not legible, it will be given a mark of zero.
6) Calculators are not allowed. You are not permitted to have any electronic devices with you during the exam unless authorized by the instructor.
7) You may use a molecular model kit.
8) You have 2 hours to complete this test.

Confidentiality Agreement:

I agree not to discuss (or in any other way divulge) the contents of this exam until after 8:00pm Mountain Time on Wednesday, March 11th, 2015. I understand that breaking this agreement would constitute academic misconduct, a serious offense with serious consequences. The minimum punishment would be a mark of 0/42 on this exam; the maximum punishment would include expulsion from this university.

Signature: _____ Date: _____

Course: CHEM 4000A (Medicinal Chemistry)
Semester: Spring 2015
The University of Lethbridge

Question Breakdown

Q1	/ 6
Q2	/ 12
Q3	/ 11
Q4	/ 3
Q5	/ 10
BONUS	/ 1

Total	/ 42

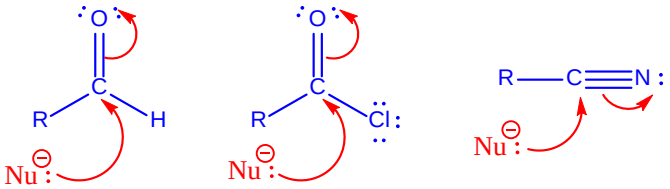
NAME:_____ Section:__A__ Student Number:_____

1. The main natural synthons are a^1, d^2 and a^3. Explain why each of these synthons has "natural" reactivity. Each explanation should include an example. **[6 marks]**

(a) a^1 synthon

In an a^1 synthon, the electrophilic carbon atom is directly attached to a more electronegative heteroatom (usually by a double or triple bond). This puts a partial positive charge on the electrophilic carbon atom (making it naturally electrophilic), and electron density can be shifted onto the electronegative heteroatom when a nucleophile attacks.

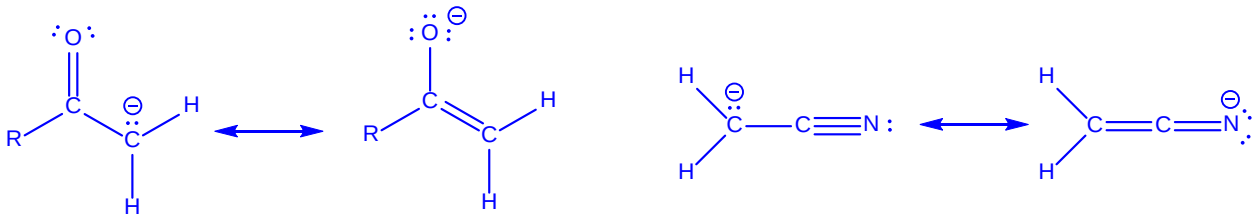
some a^1 synthons



(b) d^2 synthon

In a d^2 synthon, the nucleophilic carbon atom is typically α to a carbonyl, nitrile or similar group. Thus, deprotonation of the starting material gives a resonance stabilized anion. Thus, the nucleophile is readily formed.

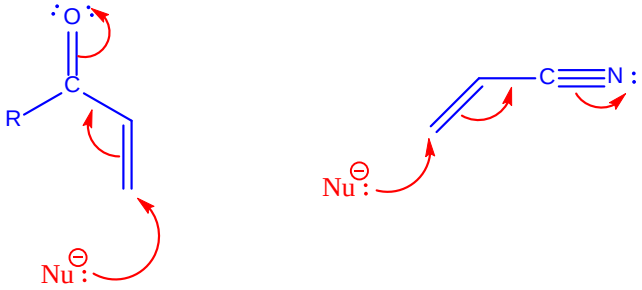
some d^2 synthons



(c) a^3 synthon

In an a^3 synthon, the electrophilic carbon is part of an extended pi system (usually an α,β-unsaturated carbonyl). Thus, when a nucleophile attacks, electron density can be shifted onto the electronegative heteroatom via the pi system:

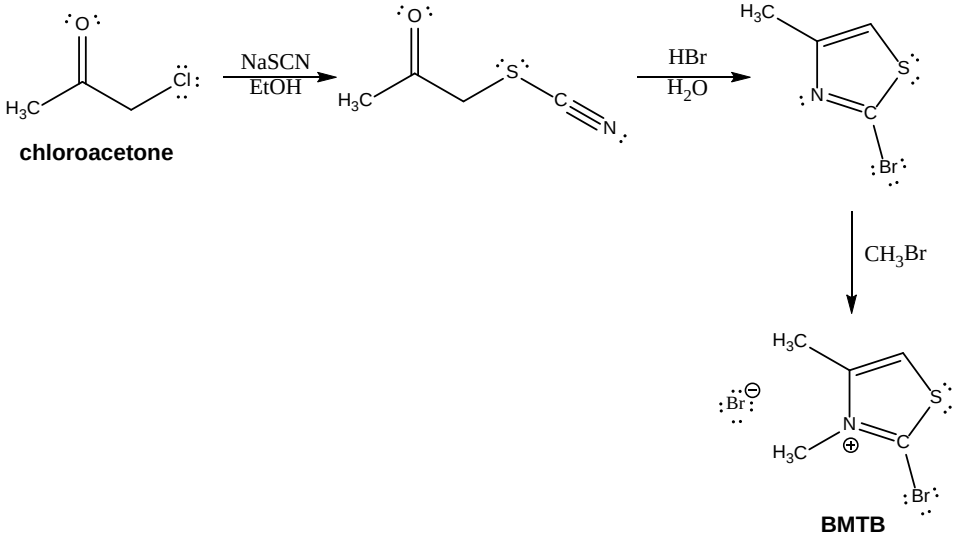
some a^3 synthons



NAME:_____ Section:__A__ Student Number:_____

2. 2-bromo-N-methylthiazolium bromide (BMTB) was developed as a peptide coupling agent that would be better at coupling sterically hindered amino acids better than the alternatives that existed at the time. It was made in three steps from chloropropanone (aka "chloroacetone"):

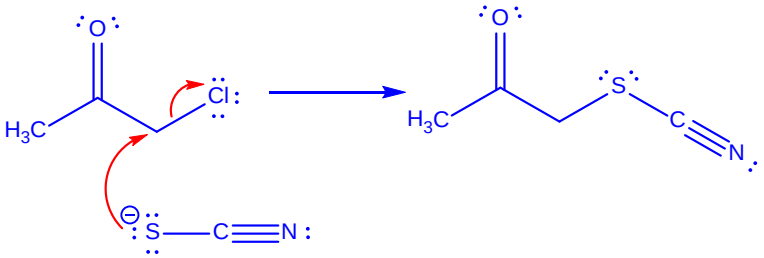
[12 marks]



(a) The thiocyanate ion (SCN^-) has two nucleophilic sites. Draw both resonance structures for SCN^- and identify the two nucleophilic sites. *[2 marks]*

The sulfur and nitrogen atoms are the two nucleophilic sites.

(b) Draw a mechanism for the reaction of SCN^- with chloroacetone and explain the regiochemistry of this reaction. In other words, why does SCN^- react using one nucleophilic site instead of the other one and why does chloroacetone react using one electrophilic site instead of the other one? *[5 marks]*



The two electrophilic sites in chloroacetone are the carbon attached to chlorine (shown as the electrophilic site in the mechanism above) and the carbonyl carbon. If the thiocyanate attacks the carbonyl carbon, giving the tetrahedral intermediate, the C=O bond will immediately re-form, kicking out the thiocyanate for no net reaction. If the thiocyanate attacks the carbon attached to chlorine, a chloride ion leaves. Since chloride is a much better leaving group than thiocyanate, this reaction is not reversible. Therefore, this is the active electrophilic site.

The active electrophilic site is soft. Therefore, we expect the thiocyanate ion to react at the softer nucleophilic site. Since the sulfur atom is significantly larger than the nitrogen atom, it will have a lower charge density and be softer than the nitrogen atom. For this reason, the sulfur atom attacks the electrophilic carbon of chloroacetone.

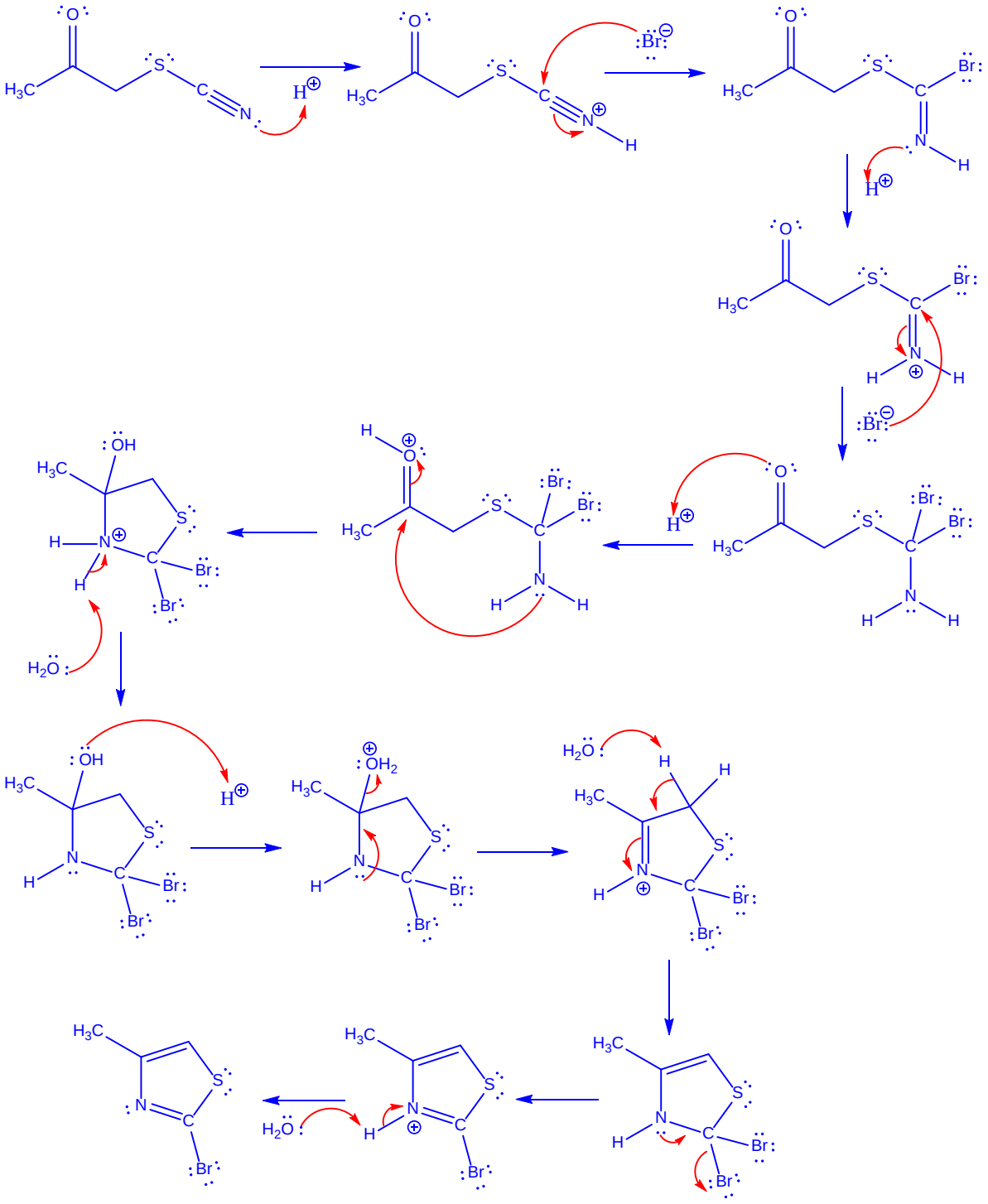
NAME:_____ Section:__A__ Student Number:_____

2. *continued…*

(c) Propose a reasonable mechanism for the second step in the synthesis of BMTB. *(shown below)*

[5 marks]

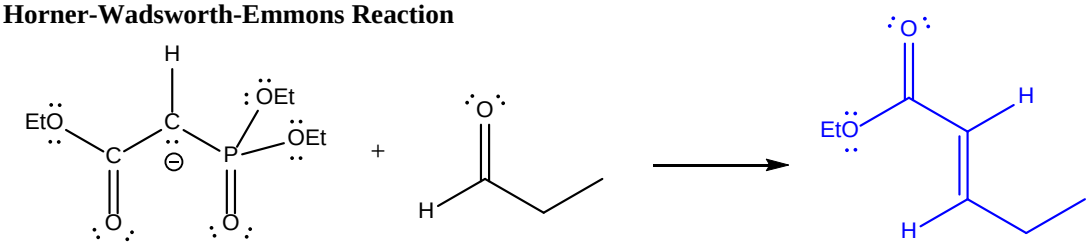
I accepted at least three different mechanisms as being reasonable. One of those approaches, however, involved intermediates containing a linear atom in a five-atom ring – which is not actually all that reasonable (ring strain!). For this reason, I suspect that a mechanism similar to the one shown below is the most likely to be correct.



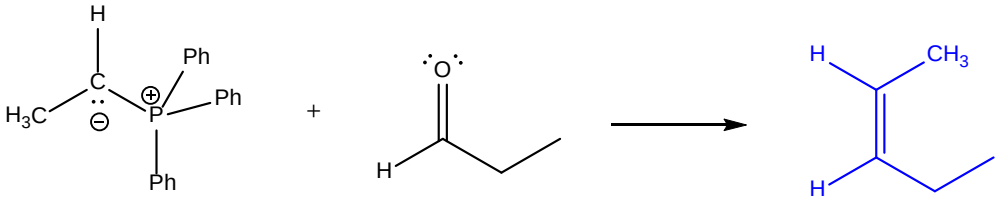
NAME:_____ Section:__A__ Student Number:_____

3. The Horner-Wadsworth-Emmons reaction is very similar to the Wittig reaction: **[11 marks]**

Horner-Wadsworth-Emmons Reaction



Wittig Reaction



(a) In the space provided above, draw the major organic product of each reaction. *[4 marks]*

Wittig reactions in which there is no extra resonance stabilization of the ylide give the *Z*-alkene as the major product.

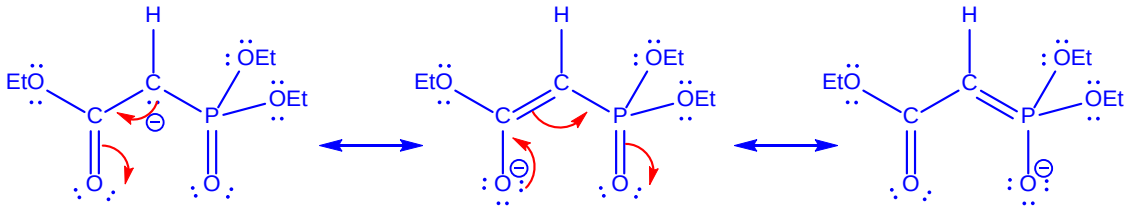
Horner-Wadsworth-Emmons reactions give the *E*-alkene as the major product.

(b) The Wittig reagent is made by reacting the $CH_3CH_2PPh_3^+$ cation with a very strong base such as BuLi; however, the Horner-Wadsworth-Emmons reagent can be made by reacting $CH_2(CO_2Et)(PO(OEt)_2)$ with a less strong base such as NaH.

i. Why does preparation of the Horner-Wadsworth-Emmons reagent not require such a strong base? *(compared to preparation of the Wittig reagent)* *[4 marks]*

If the Horner-Wadsworth-Emmons reagent does not require such a strong base to make, that means that the acidic hydrogen in $CH_2(CO_2Et)(PO(OEt)_2)$ must be more acidic (than the acidic hydrogen in the $CH_3CH_2PPh_3^+$ cation). Therefore, the Horner-Wadsworth-Emmons reagent must be more stable than the Wittig reagent.

The reason that the Horner-Wadsworth-Emmons reagent is more stable is that the negative charge is delocalized over more atoms (and more electronegative atoms):



You did not get full marks if you told me that the Wittig reagent has no resonance stabilization. There are two resonance structures for the Wittig reagent; however, there are three resonance structures for the Horner-Wadsworth-Emmons reagent – and they delocalize a large amount of negative charge onto electronegative oxygen atoms.

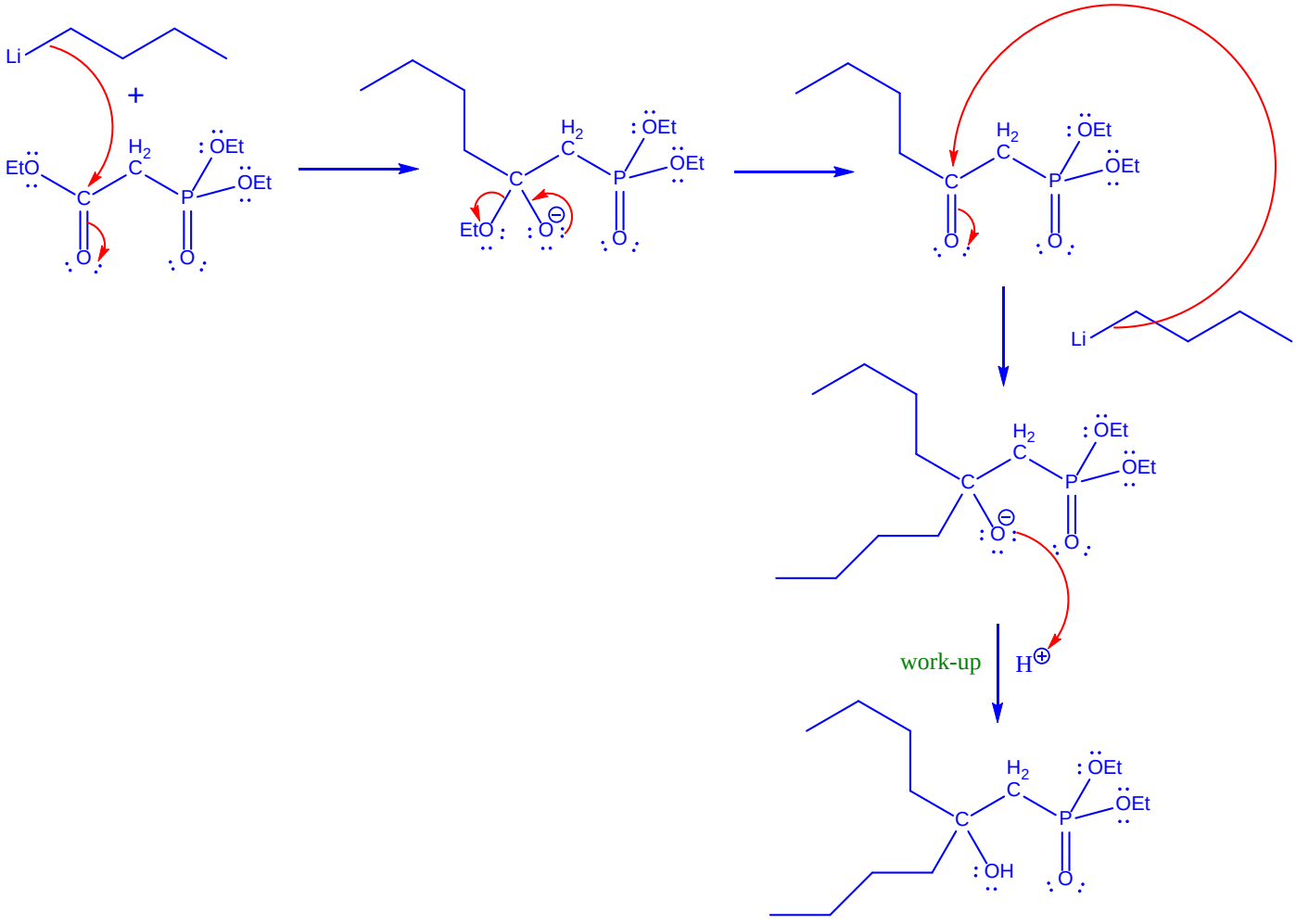
NAME:_____ Section:__A__ Student Number:_____

3.

(b) *continued…*

ii. Why would it be a bad idea to use BuLi as the base in preparing a Horner-Wadsworth-Emmons reagent from $CH_2(CO_2Et)(PO(OEt)_2)$? Show what would happen. *[3 marks]*

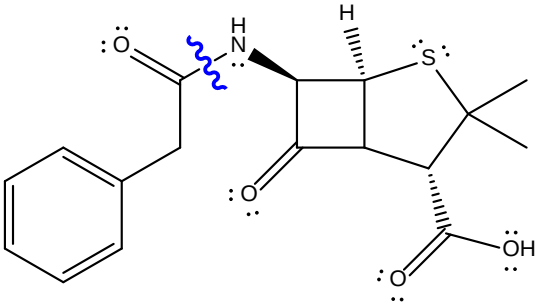
In addition to being a strong base, BuLi is also a strong nucleophile. The BuLi would attack the carbonyl carbon of the ester, giving a ketone (an even better electrophile) which would also be attacked by BuLi, giving a tertiary alcohol (after mild acidic work-up):



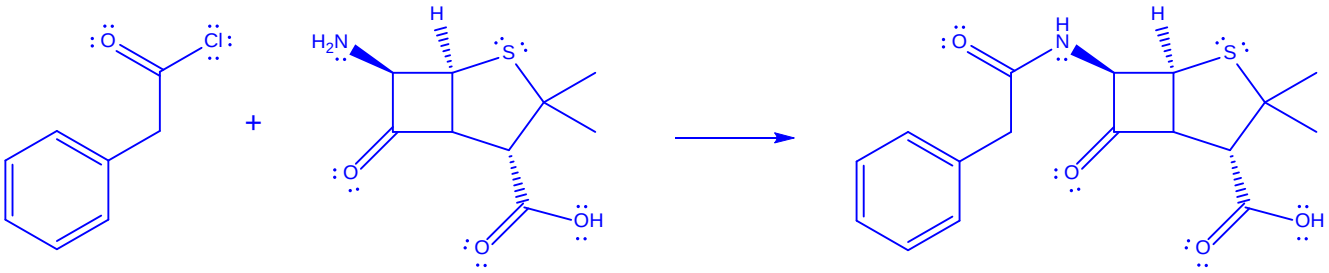
NAME:_____ Section:__A__ Student Number:_____

4. The structure of penicillin is shown below. Identify **one** disconnection that you would make if you were tasked with synthesizing penicillin. Explain your choice. Show the corresponding forward reaction for that step. **[3 marks]**

DO NOT TRY TO PROPOSE A WHOLE SYNTHESIS OF PENICILLIN!!!



When I look at this molecule, the disconnection that "jumps out at me" is the bond between the C and the N of the amide. On the right side of that disconnection is a nitrogen atom, and nitrogen atoms are typically good nucleophiles. On the left side of that disconnection is an a[1] synthon. I imagine an acid chloride as a good electrophile. So, the forward reaction would look something like:



NAME:_____ Section:__A__ Student Number:_____

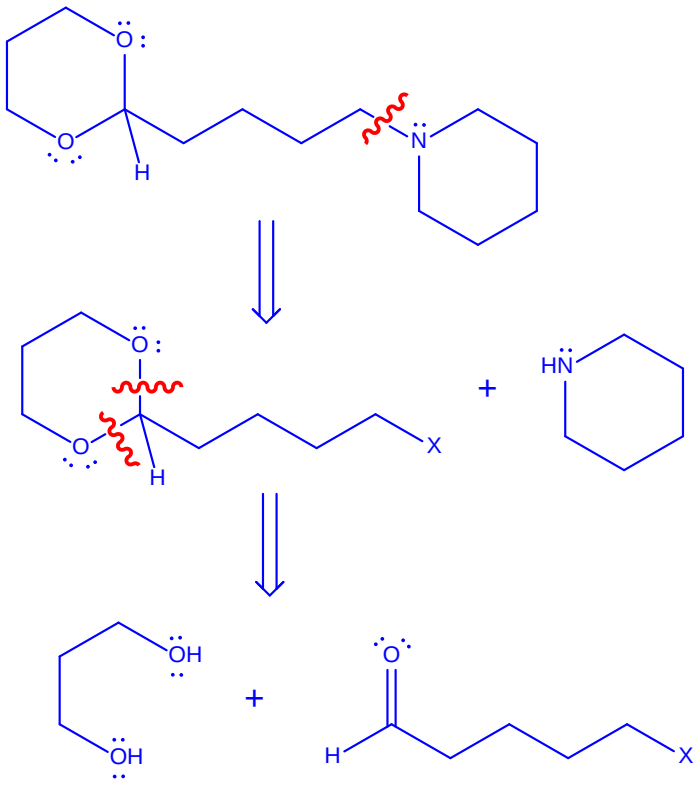
5. How would you make the molecule below? **[10 marks]**

Your answer should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Write an equation for each reaction. Show all required reagents, and number steps within a reaction if order of addition is important.

You may use any reagents that you could reasonably expect to be commercially available <u>and</u> that contain no more than 6 carbon atoms. (Exception: Reagents may contain one or more benzene rings in addition to the 6 carbon limit.)

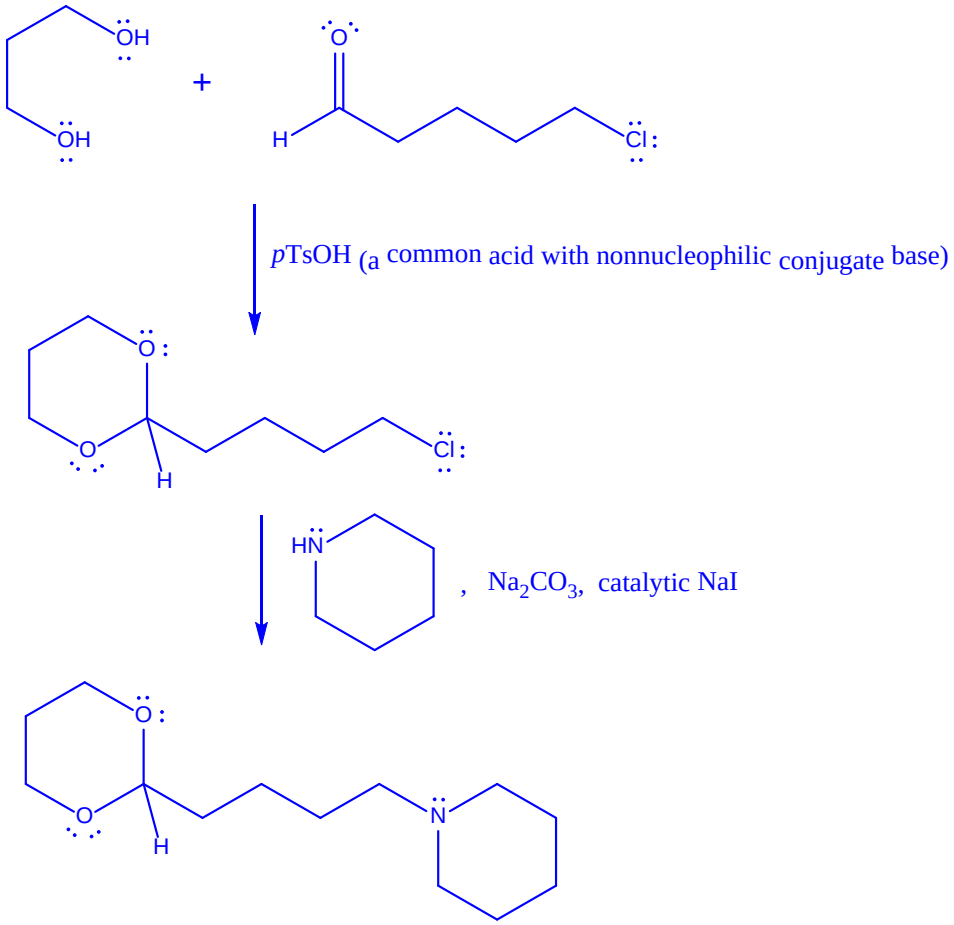
I think that the disconnections shown below give the shortest/simplest synthetic approach to this molecule. The acetal group can be formed from an aldehyde plus a diol. The C-N bond can be formed by having an amine attack an electrophilic carbon atom. Because the product is a tertiary amine, we don't have to worry about two of them attacking electrophilic carbon atoms, simplifying the approach somewhat (see the Fall 2012 midterm for when this would be a problem). The main potential side reaction would be attack of the amine at the aldehyde rather than at the desired site if both electrophilic sites are available when the amine is added. For this reason, I would form the acetal first <u>then</u> react the other end of the chain with the amine.

Retrosynthetic analysis:



NAME:_____ Section:__A__ Student Number:_____

Proposed synthetic route:



The sodium carbonate is to deprotonate the nitrogen <u>after</u> it has attacked the electrophilic carbon atom. Carbonate is <u>not</u> a strong enough base to deprotonate an amine – and we do not need to deprotonate the amine. Neutral nitrogen atoms are reasonably good nucleophiles.

The sodium iodide is to displace the chloride, making a better leaving group (may not actually be necessary – but it won't hurt).

NAME:_____ Section:__A__ Student Number:_____

BONUS I recently came across a website in which a chemistry instructor told his students this following: "…begin mechanisms by drawing the most important resonance structure (lowest energy)…" Part of this statement is very VERY VERY wrong. Which part? Why? *[1 mark]*

Resonance structures are different ways of drawing the same molecule.

Resonance structures are not "real things" and cannot have energies of their own.

A molecule exists as a weighted average of its resonance structures.

A molecule can only have one energy.

It is entirely valid to talk about "better"/"worse" or "major"/"minor" resonance structures. But there's no such thing as a "lower energy" resonance structure!

Rant over… ☺

NAME:_____ Section:__A__ Student Number:_____

CHEM 1000 Standard Periodic Table

1												13	14	15	16	17	18
1.0079 **H** 1	2																4.0026 **He** 2
6.941 **Li** 3	9.0122 **Be** 4											10.811 **B** 5	12.011 **C** 6	14.0067 **N** 7	15.9994 **O** 8	18.9984 **F** 9	20.1797 **Ne** 10
22.9898 **Na** 11	24.3050 **Mg** 12	3	4	5	6	7	8	9	10	11	12	26.9815 **Al** 13	28.0855 **Si** 14	30.9738 **P** 15	32.066 **S** 16	35.4527 **Cl** 17	39.948 **Ar** 18
39.0983 **K** 19	40.078 **Ca** 20	44.9559 **Sc** 21	47.88 **Ti** 22	50.9415 **V** 23	51.9961 **Cr** 24	54.9380 **Mn** 25	55.847 **Fe** 26	58.9332 **Co** 27	58.693 **Ni** 28	63.546 **Cu** 29	65.39 **Zn** 30	69.723 **Ga** 31	72.61 **Ge** 32	74.9216 **As** 33	78.96 **Se** 34	79.904 **Br** 35	83.80 **Kr** 36
85.4678 **Rb** 37	87.62 **Sr** 38	88.9059 **Y** 39	91.224 **Zr** 40	92.9064 **Nb** 41	95.94 **Mo** 42	(98) **Tc** 43	101.07 **Ru** 44	102.906 **Rh** 45	106.42 **Pd** 46	107.868 **Ag** 47	112.411 **Cd** 48	114.82 **In** 49	118.710 **Sn** 50	121.757 **Sb** 51	127.60 **Te** 52	126.905 **I** 53	131.29 **Xe** 54
132.905 **Cs** 55	137.327 **Ba** 56	**La-Lu**	178.49 **Hf** 72	180.948 **Ta** 73	183.85 **W** 74	186.207 **Re** 75	190.2 **Os** 76	192.22 **Ir** 77	195.08 **Pt** 78	196.967 **Au** 79	200.59 **Hg** 80	204.383 **Tl** 81	207.19 **Pb** 82	208.980 **Bi** 83	(210) **Po** 84	(210) **At** 85	(222) **Rn** 86
(223) **Fr** 87	226.025 **Ra** 88	**Ac-Lr**	(261) **Rf** 104	(262) **Db** 105	(263) **Sg** 106	(262) **Bh** 107	(265) **Hs** 108	(266) **Mt** 109	(281) **Dt** 110	(283) **Rg** 111							

138.906 **La** 57	140.115 **Ce** 58	140.908 **Pr** 59	144.24 **Nd** 60	(145) **Pm** 61	150.36 **Sm** 62	151.965 **Eu** 63	157.25 **Gd** 64	158.925 **Tb** 65	162.50 **Dy** 66	164.930 **Ho** 67	167.26 **Er** 68	168.934 **Tm** 69	173.04 **Yb** 70	174.967 **Lu** 71
227.028 **Ac** 89	232.038 **Th** 90	231.036 **Pa** 91	238.029 **U** 92	237.048 **Np** 93	(240) **Pu** 94	(243) **Am** 95	(247) **Cm** 96	(247) **Bk** 97	(251) **Cf** 98	(252) **Es** 99	(257) **Fm** 100	(258) **Md** 101	(259) **No** 102	(260) **Lr** 103

Developed by Prof. R. T. Boeré