NAME:_____ Section:__A__ Student Number:_____

Spring 2020 **Chemistry 4000 Midterm** ____/ 60 marks

INSTRUCTIONS:

1) Please read over the test carefully before beginning. You should have 7 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 Monday, March 9th, 2020. I understand that breaking this agreement would constitute academic misconduct, a serious offense with serious consequences. The minimum punishment would be a mark of 0/60 on this exam; the maximum punishment would include expulsion from this university.

Signature: _____ Date: _____

Course: CHEM 4000A (Medicinal Chemistry)
Semester: Spring 2020
The University of Lethbridge

Question Breakdown

Q1	/ 6
Q2	/ 7
Q3	/ 8
Q4	/ 16
Q5	/ 4
Q6	/ 9
Q7	/ 10

Total	/ 60

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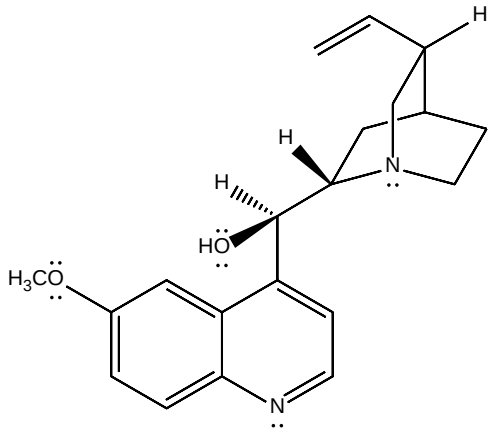
1. The molecule below is quinine, one of the oldest known treatments for malaria. The active ingredient in cinchona bark – which has been used to treat malaria since at least the 1600s – quinine has since been isolated and prescribed in pure form. While no longer recommended as a first line treatment due to side effects, it is still prescribed in cases where alternative medications don't work due to drug resistance. **[6 marks]**



(a) Identify one feature in the structure of quinine that would make it particularly challenging to synthesize. *[1 mark]*

(b) If you were going to propose a retrosynthetic analysis for quinine, what would be the first disconnection you would suggest? Draw it directly on the diagram above. In the space below, give two reasons for your choice. *[5 marks]*

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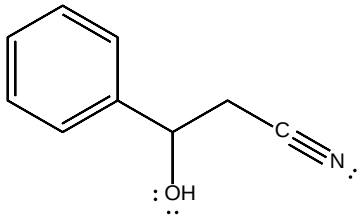
2. A chemist wants to make the molecule below: **[7 marks]**



There are four possible pairs of synthons corresponding to disconnections at carbon-carbon bonds between the two heteroatoms.

(a) Show the four possible pairs of synthons, labeling each synthon (as a^1, d^1, etc.) and identifying it as natural or umpoled. *[4 marks]*

(b) Choose **one** of your answers to part (a) and propose a reaction that would make the target molecule according to that approach. *You may use any reagents or reactants that you could reasonably expect to be commercially available.* *[3 marks]*

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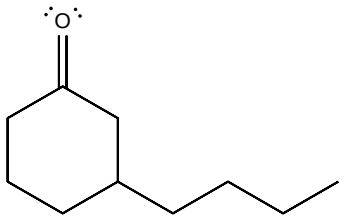
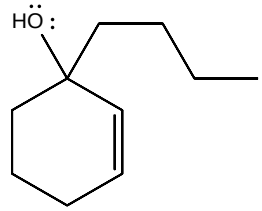
3. The products below can both be prepared by reaction of 2-cyclohexenone with butyllithium in THF followed by aqueous work-up. In one case, however, it is necessary to add a catalyst.

[8 marks]



Product A

vs



Product B

(a) Which of these two products is obtained by reacting only 2-cyclohexenone and butyllithium? *[1 mark]*

(b) Give an example of a catalyst you could add to the reaction flask that would favour production of the **other** product. *[1 mark]*

(c) Use hard-soft acid-base theory to explain why reaction of 2-cyclohexenone with butyllithium gives the product it does **and** why the other product is favoured if the catalyst is added.
Your answer must clearly identify the relevant nucleophilic/electrophilic sites and explain why each is hard or soft. *[6 marks]*

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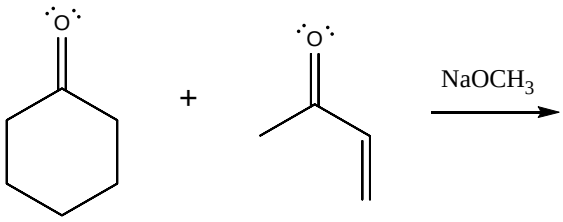
4. In a Robinson annelation, a conjugate addition is followed by an aldol reaction. This results in formation of a new ring. Draw a mechanism for the Robinson annelation reaction between cyclohexanone and butenone in the presence of sodium methoxide. **[16 marks]**



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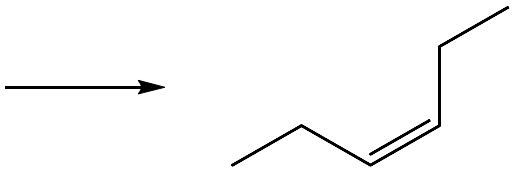
5. It is often important to control the stereochemistry of double bonds when they are produced. **[4 marks]**

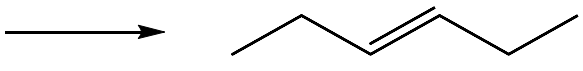
(a) Write a reaction equation showing the preparation of the *cis* double bond in *cis*-3-hexene.

The reaction should be forming a <u>new</u> bond between the two central carbon atoms – not just converting a single or triple bond into a double bond. If your approach requires a sequence of reactions, the order in which the reagents are added must be clear. You do not, however, need to show a mechanism or intermediate structures.



(b) Write a reaction equation showing the preparation of the *trans* double bond in *trans*-3-hexene.

The reaction should be forming a <u>new</u> bond between the two central carbon atoms – not just converting a single or triple bond into a double bond. If your approach requires a sequence of reactions, the order in which the reagents are added must be clear. You do not, however, need to show a mechanism or intermediate structures.



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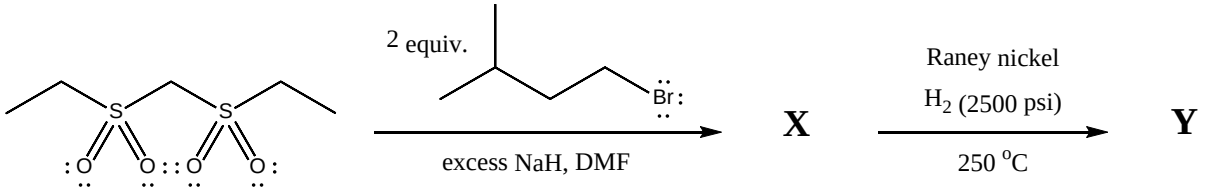
6. We saw that sulfone groups can be useful tools in organic synthesis, helping to direct the course of reactions even if they are not required in the final product.

Bis(sulfones) are compounds containing two sulfone groups, and they can also be very useful for this purpose. The first published example of this chemistry is shown in the figure below.

[9 marks]



(a) What is the term we used to describe a functional group that helps direct the course of a reaction but is not a part of the final product? *[1 mark]*

(b) Draw the structure of **X** (the product of the first step in the reaction sequence above). *[2 marks]*

(c) Draw the structure of **Y** (the product of the second step in the reaction sequence above). *[2 marks]*

The Raney nickel and hydrogen gas do the same thing as Na in NH_3.

(d) What would be the advantage of having two sulfone groups instead of one? Give two reasons why the reaction above works better with the bis(sulfone) shown than it would have with $CH_3SO_2CH_3$. *[4 marks]*

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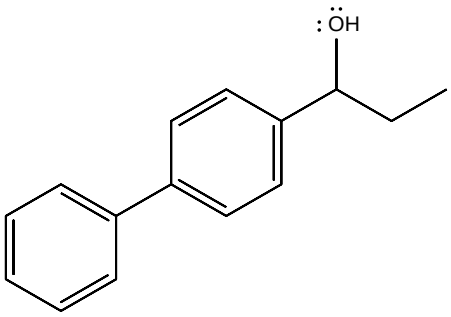
7. How would you make the molecule below? **[10 marks]**

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 reactants that you could reasonably expect to be commercially available <u>and</u> that **<u>contribute no more than 6 carbon atoms to the final product</u>**. (This means that you are allowed to use reagents like PPh_3 or mcpba – even though they contain more than 6 carbon atoms – because they do not add more than 6 carbon atoms to the final product. These examples should not be construed as a hint; just a clarification.)*



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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**	(265) **Rf** 104	(268) **Db** 105	(271) **Sg** 106	(270) **Bh** 107	(277) **Hs** 108	(276) **Mt** 109	(281) **Ds** 110	(280) **Rg** 111	(285) **Cn** 112	(284) **Nh** 113	(289) **Fl** 114	(288) **Mc** 115	(293) **Lv** 116	(294) **Ts** 117	(294) **Og** 118

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	(262) **Lr** 103

Developed by Prof. R. T. Boeré (updated 2016)