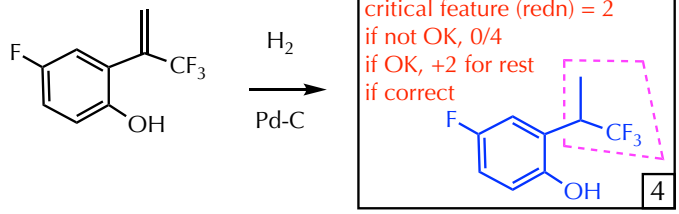
Question I (28 points) NAME _____

Complete the following transformations and answer the appended questions.

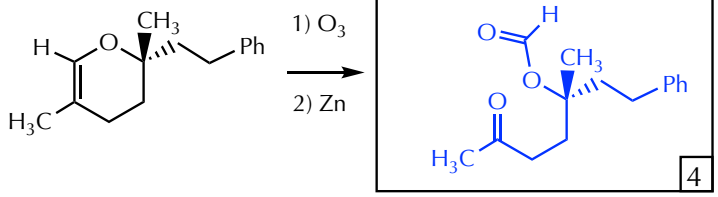
A. *ACS Med. Chem. Lett.* **2015**, *6*, 596.



The product (select one):
- [ ] is formed as a racemic mixture
- [X] is formed as a single enantiomer
- [ ] is formed as a diastereomeric mixture
- [ ] has no stereoisomers

2

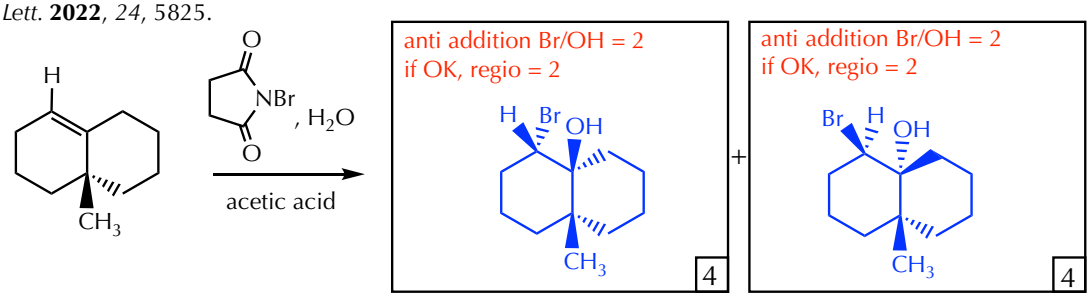
B. *ACS Med. Chem. Lett.* **2021**, *12*, 1464.



The product (select one):
- [ ] is formed as a racemic mixture
- [X] is formed as a single enantiomer
- [ ] is formed as a diastereomeric mixture
- [ ] has no stereoisomers

2

C. *Org. Lett.* **2022**, *24*, 5825.

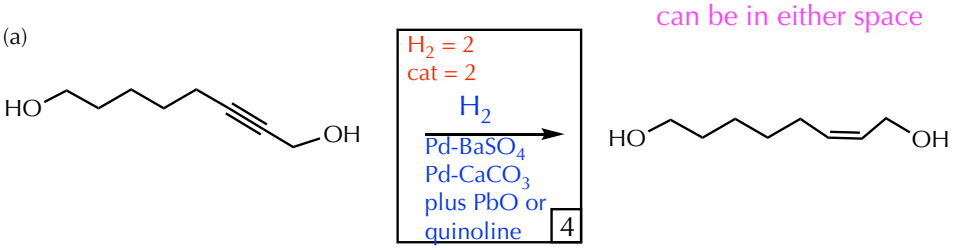


formed as a diastereomeric mixture, draw both of them

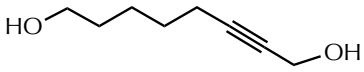
can be in either space

D. *J. Org. Chem.* **2022**, *87*, 9940.

(a)



(b) Select the fragments that, when assembled, would give the IUPAC name of the starting material. No partial credit.



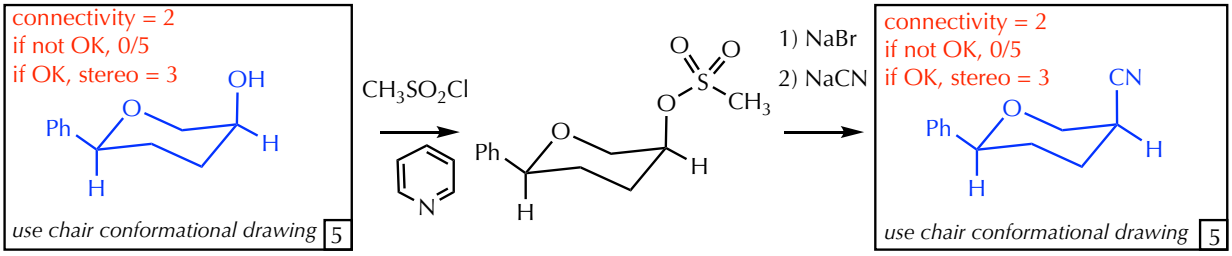
[ ] heptan-	[ ] hept-	no partial	
[X] 2-	[ ] 1,7-		
[X] diol	[X] oct-		
[ ] 3-	[X] yne-		
[ ] heptane-	[X] 1,8-		
[ ] 5-	[ ] ol		
[ ] octan-	[ ] octane-		
[ ] yn-	[ ] 6-	4	

A		/06
B		/06
C		/08
D		/08
		/28

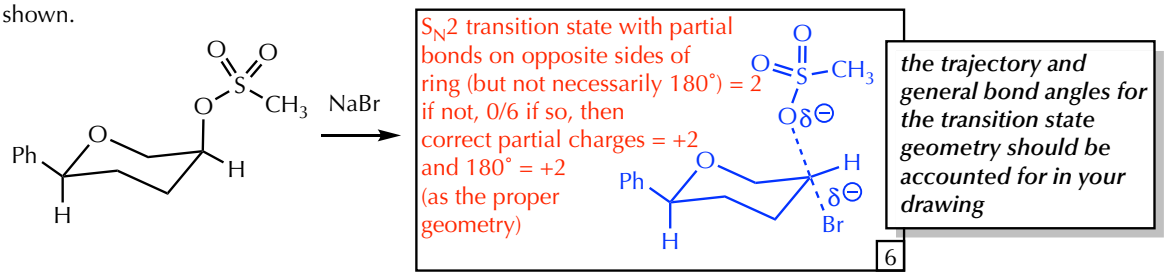
Question II (25 points) NAME _____

A. *Nat. Chem. Bio.* **2020**, *16*, 318.

(a) Complete the following two-step transformation. Include stereochemistry; use chair comformational drawings.

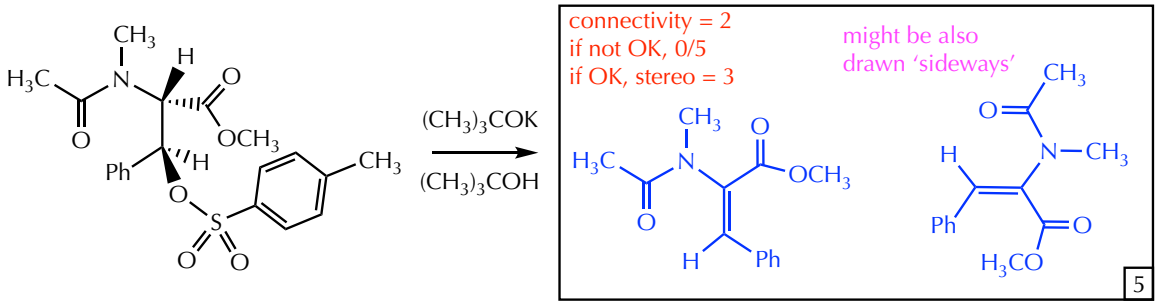


(b) Provide a drawing for the transition state of the reaction, above, in which NaBr is used. Include the stereochemistry, represent partial bonds and provide partial charges; non-bonding electrons do not need to be shown.

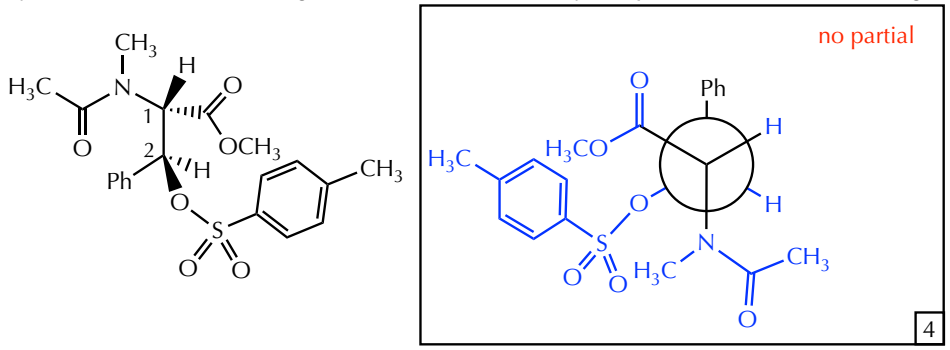


B. The following elimination reaction is observed to give one stereoisomeric product with both a high reaction rate and high selectivity (*Org. Lett.* **2014**, *16*, 4044).

(a) Draw the predicted outcome, clearly indicating the stereochemistry of any new sp^2 or sp^3 atoms you draw.



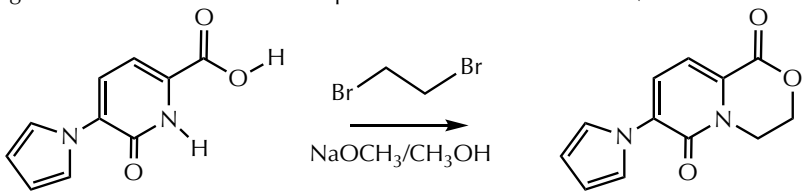
(b) Complete the following Newman Projection by showing the anticipated conformation for the C1-C2 bond that gives the fast elimination reaction described above (see numbers on the structure, below). The phenyl group has already been added to the drawing, which means there is only one placement for all the other groups that is correct.



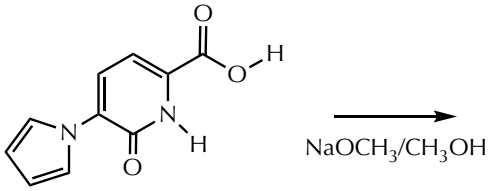
A		/16
B		/09
		/25

Question III (26 points) NAME _____

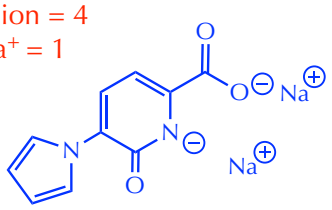
A. The following reaction was observed to take place under basic conditions (*ACS Med. Chem. Lett.* **2015**, *6*, 596).



(a) The NH starting material has a pK_a of about 11 and the OH has a pK_a of about 4. Consequently, when using excess of a Brønsted base (such as $NaOCH_3$), the starting material can be doubly deprotonated to give a dianion. Draw the complete ionic compound, including the appropriate cations.



dianion = 4
2 Na^+ = 1

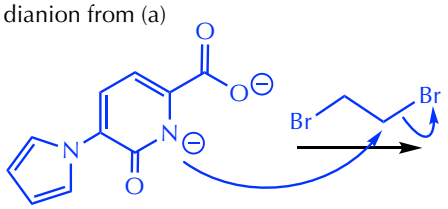


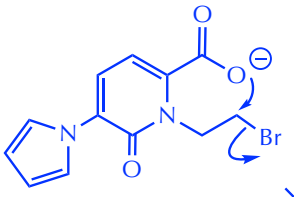
or the (-)O-C=N resonance form

5

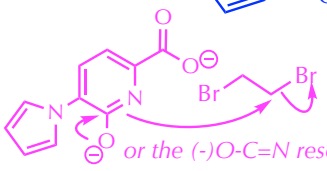
(b) Starting with this dianion, provide the curved arrow mechanism for the formation of the observed product. There is an obvious question to answer before you draw the mechanism: which of the anions is more reactive and will react first? This judgment derives from the pK_a values of NH and OH bonds in the starting material, so make your decision about the relative reactivity before drawing the mechanism.

dianion from (a)

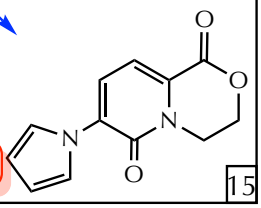




S_N2 with N^- = 5
intermediate O^- = 5
intramolecular S_N2 = 5



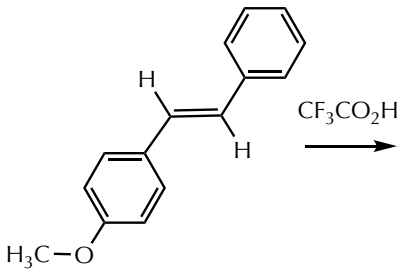
or the (-)O-C=N resonance form



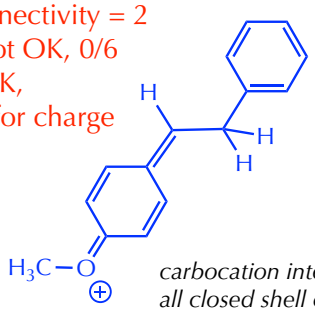
if O^- selected for first reaction, -5 for first step, rest can be consistent

15

B. The following reaction raises an issue encountered in *Org. Lett.* **2009**, *11*, 4216. The electrophilic addition reaction of trifluoroacetic acid (CF_3CO_2H, pK_a 0.23) to the following alkene is highly regioselective. A single, closed shell resonance contributor for the carbocation intermediate is used to explain the high regioselectivity. Draw the all closed shell atom resonance contributor of the carbocation intermediate.



connectivity = 2
if not OK, 0/6
if OK,
+2 for charge



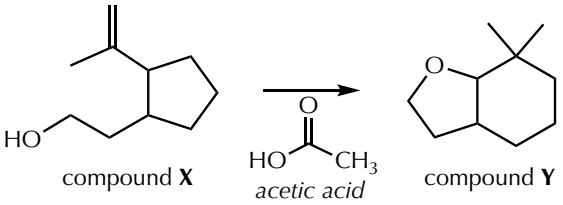
carbocation intermediate: all closed shell contributor

6

A		/20
B		/06
		/26

Question IV (31 points) NAME _____

Adapted from a 1922 report that was studied in depth in 2011 (*Molecules* **2011**, *16*, 2443): the following transformation was observed to occur in acetic acid.

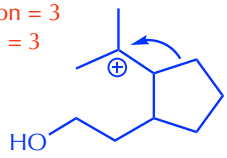


compound **X** *acetic acid* compound **Y**

The first step in the mechanism is a protonation reaction that gives the most favored carbocation intermediate.

(a) The initially formed carbocation is proposed to undergo a 1,2-alkyl shift that expands the size of the ring. Draw the anticipated carbocation that results from the protonation step (no mechanism required, start with the carbocation derived from compound **X**), and then show the mechanism for the 1,2-alkyl shift that moves the structure towards the observed product. The new carbocation that results goes into space (b)

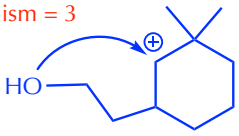
(a)
proper cation = 3
mechanism = 3



6

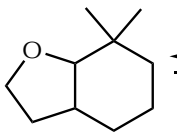
(b) Draw the new carbocation that results from the 1,2-alkyl shift in part (a). This carbocation is captured to give a new cationic intermediate with all closed shell atoms. Provide the mechanism. The new cationic intermediate goes into box (c).

(b)
proper cation = 3
mechanism = 3



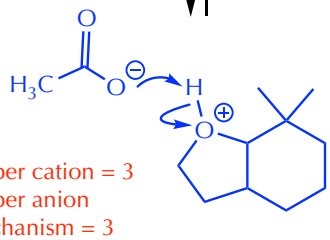
6

(c) Draw the new cationic intermediate generated in part (b) and the mechanism of its reaction with the conjugate base of acetic acid to result in the formation of the observed product, compound **Y**.



compound **Y**

(c)



proper cation = 3
proper anion
mechanism = 3

9

(d) If the reaction was carried out on 100% of the (*R*, *R*)-stereoisomer of compound **X**, how many stereoiomers of compound **Y** would be anticipated to form from the pathway that involved the rearrangement?

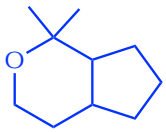
(d) 2
no
partial

4

(e) If the initially formed carbocation derived from compound **X** did NOT undergo a rearrangement, but the rest of the reaction proceeded as the one described above, what would have been the structure of the outcome?

Note that this product is a structural isomer of the one that was observed.

(e)
no
partial



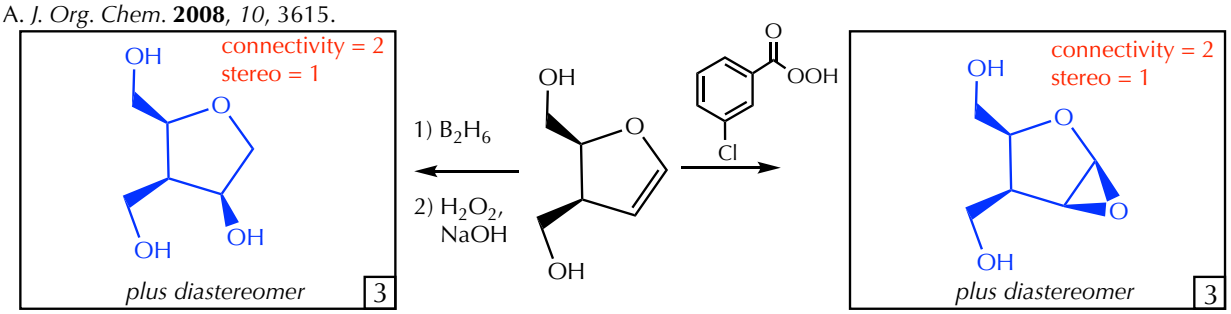
6

a		/06
b		/06
c		/09
d		/04
e		/06
		/31

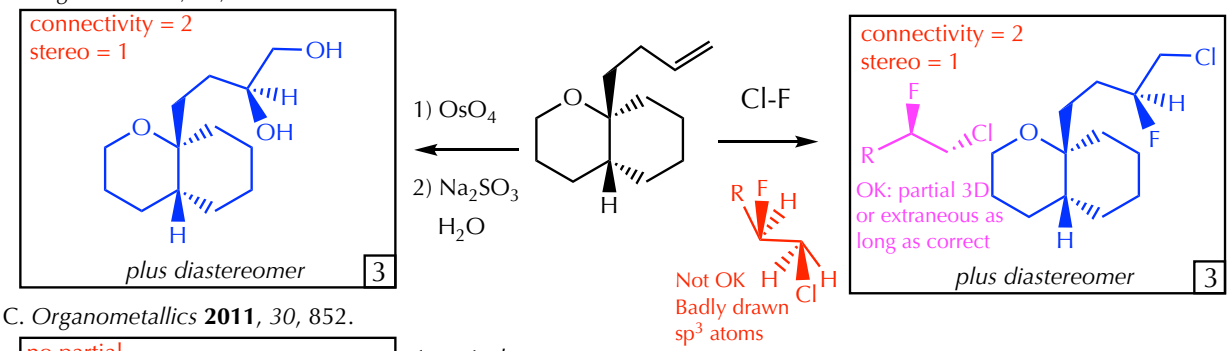
Question V (30 points) NAME _____

Complete the following transformations and answer the appended questions. If more than one stereoisomer product is predicted, draw one of them.

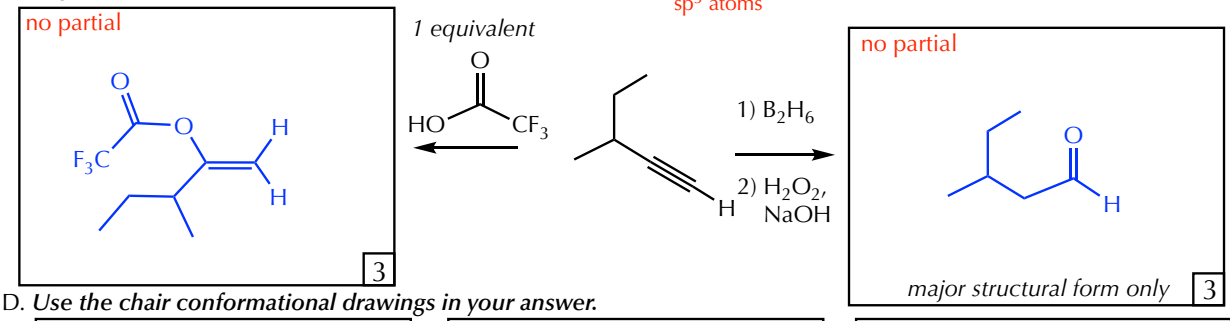
A. *J. Org. Chem.* **2008**, *10*, 3615.



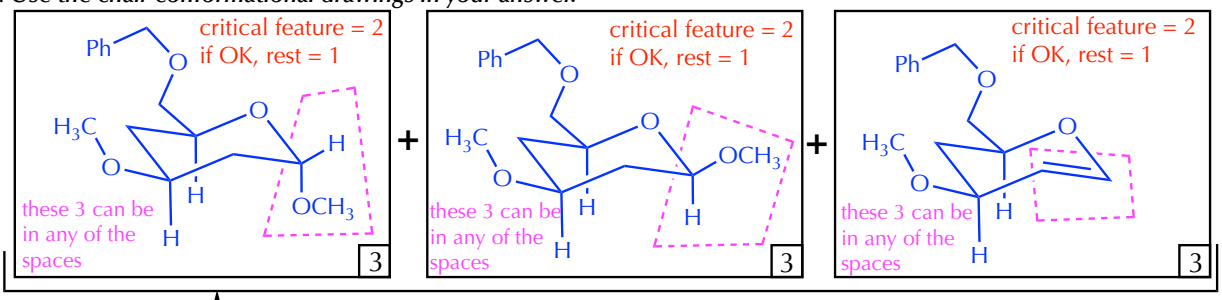
B. *Org. Lett.* **2022**, *24*, 5356.

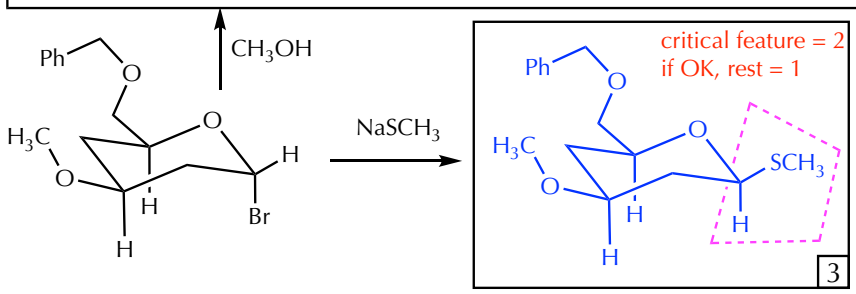


C. *Organometallics* **2011**, *30*, 852.



D. ***Use the chair conformational drawings in your answer.***





A		/06
B		/06
C		/06
D		/12
		/30