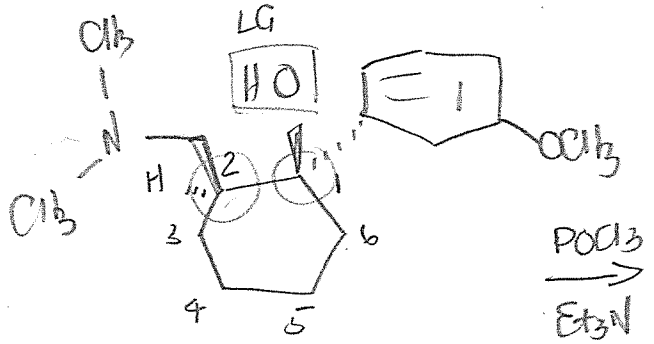
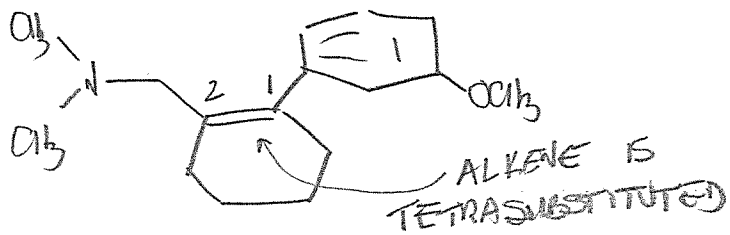
TRAMADOL (RACEMIC)

1. • TWO CHIRAL CENTERS
   • BOTH ENANTIOMERS REACT W/ $POCl_3$, Et_3N (E_2)

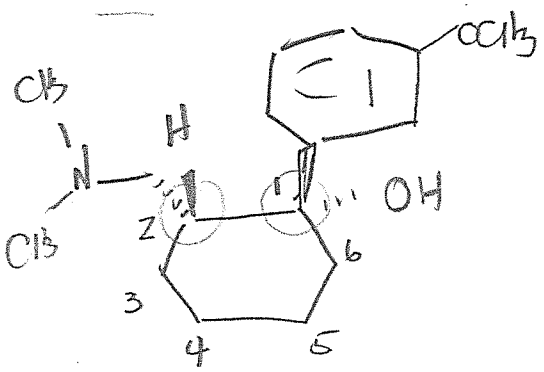
I.



C_1 and C_2 are CHIRAL
OH @ C_1 is ANTI TO H @ C_2

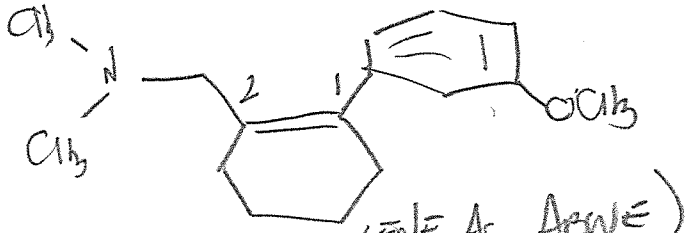


III.



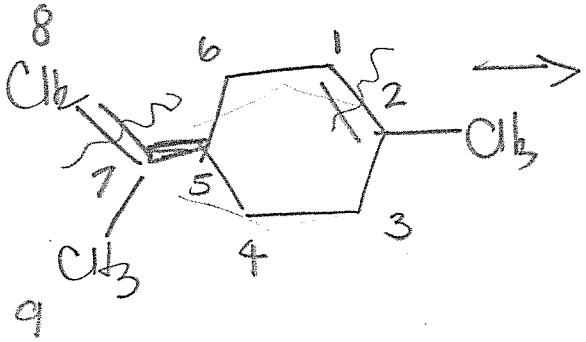
(B)

III IS AN ENANTIOMER OF I
I + III IS A RACEMIC MIXTURE
OH @ C_1 IS ANTI TO H @ C_2

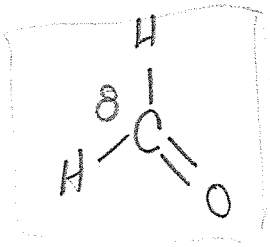


(SAME ALKENE AS ABOVE)

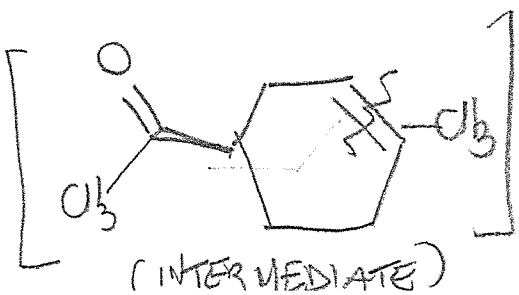
2. OZONOLYSIS: Reacts w/ alkenes to generate aldehyde/ketone products
   With excess reagent ($1.O_3$ $2.Zn, HCl$) all alkenes react.



+

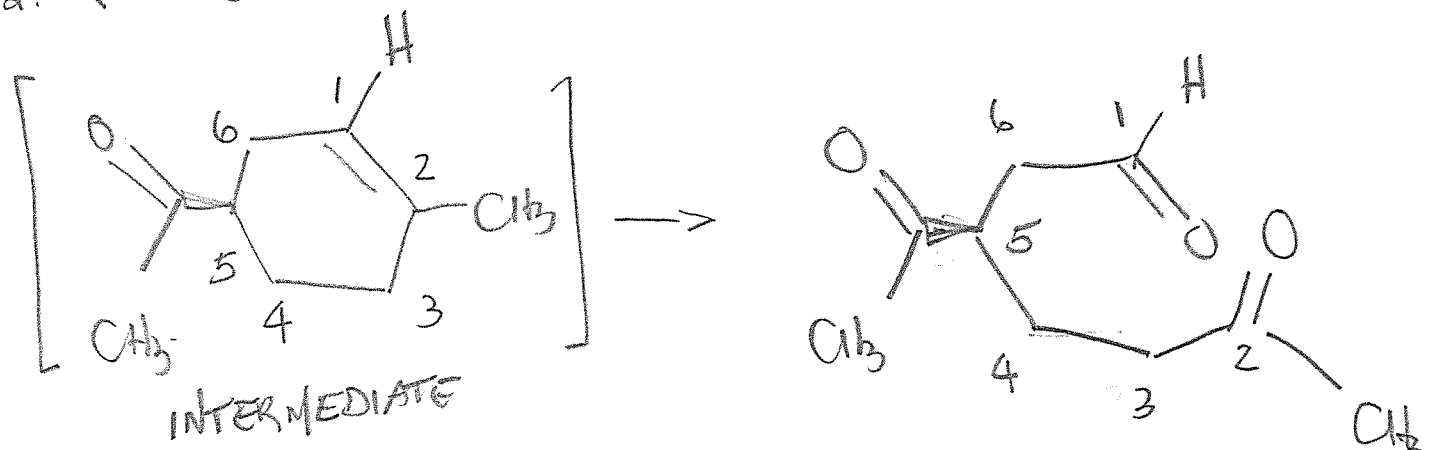


(IV)



(INTERMEDIATE)

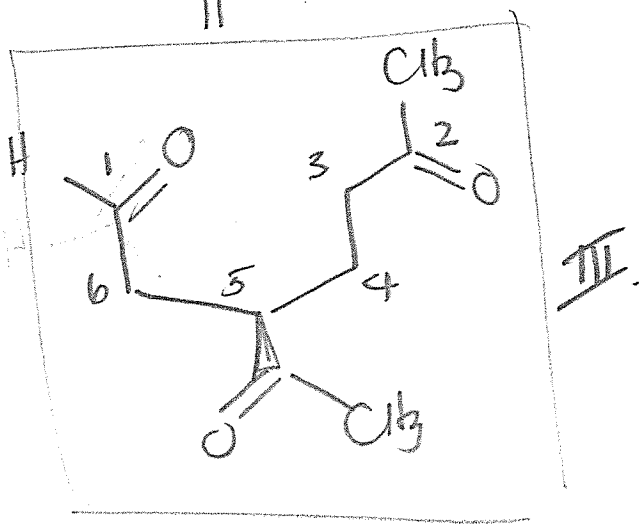
2. (cont'd)



(Different orientation)

Use numbering to match atoms in SM and product

II



III.

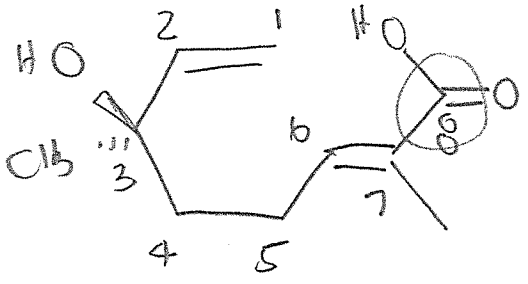
---

3. OXIDATION: ↑ # bonds to oxygen and/or ↓ # bonds to hydrogen

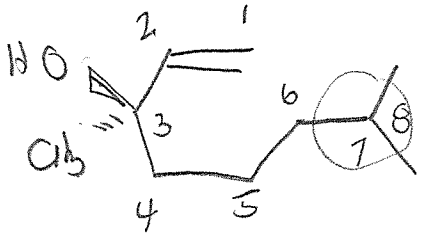
REDUCTION: ↑ # bonds to hydrogen and/or ↓ # bonds to oxygen

(# the atoms to match up structures. Monitor differences at some carbon(s) in each structure)

I.



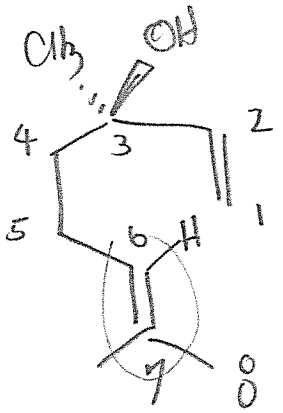
II.



I > II

3. (cont'd)

III.



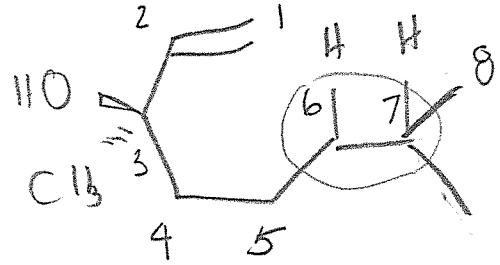
Compare II & III

In II, C_6 and C_7 bonded to more hydrogens than C_6 and C_7 in III.

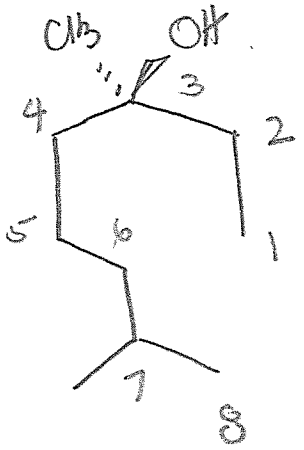
III > II

(MORE OXIDIZED)

II.



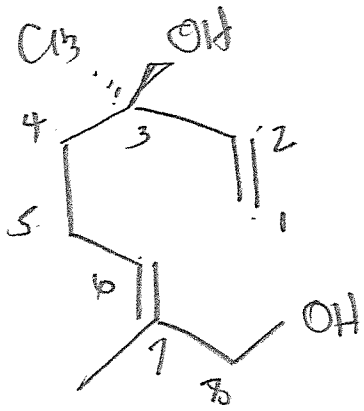
IV.



Compare II & IV

C_1 and C_2 in IV bonded to MORE H than in II. II more oxidized than IV

V.

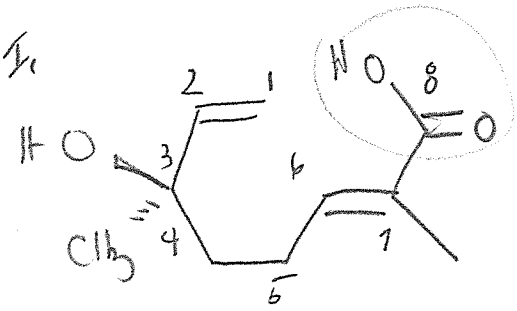


Compare III & V

C_8 oxidized in V compared to III.

3. (cont'd)

I.

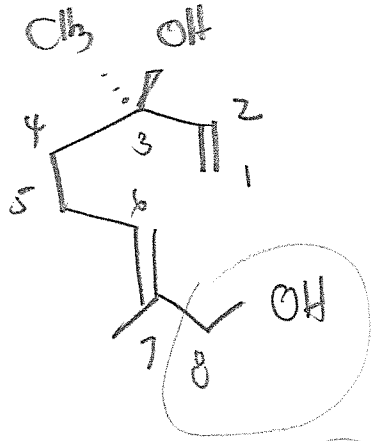


Compare I & V

C_8 more oxidized in I than V

I > V

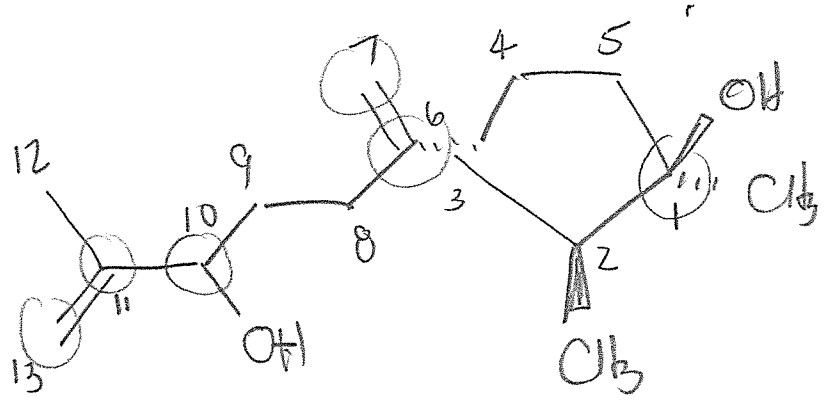
V.



I > V > III > II > IV

(E)

4. Reaction of CHOKOL B with strong acid can occur with the ALCOHOL (E_1) or with an ALKENE (Electrophilic addition)

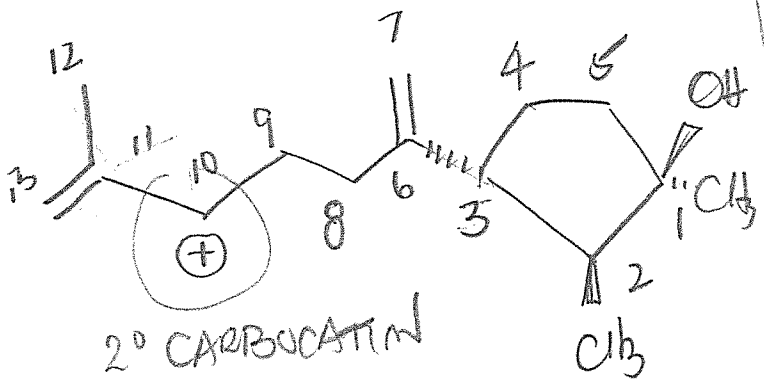


CHOKOL B

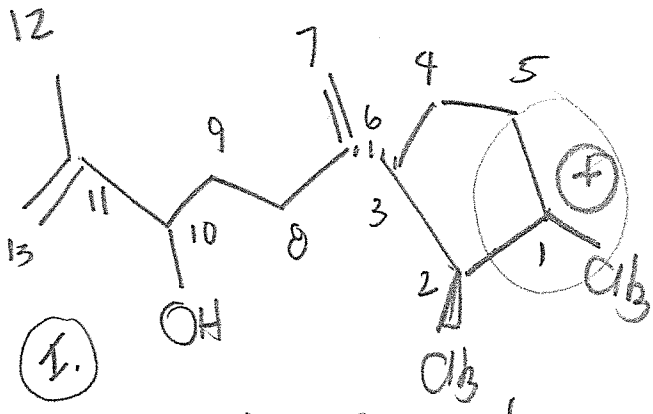
Both reactions involve formation of a CARBOCATION in the rate determing step. The carbocation that forms the fastest is the most stable carbocation. Carbocations may form at: C_1, C_3, C_7, C_{10}, C_{11} or C_{13}

4. (cont'd)

Carbocations form at C_1 or C_{10} by reaction of the alcohol with acid to form an oxonium ion, then carbocation (E_1)



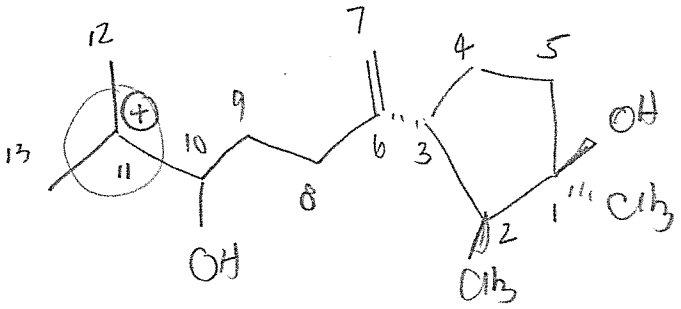
2° CARBOCATION



I.

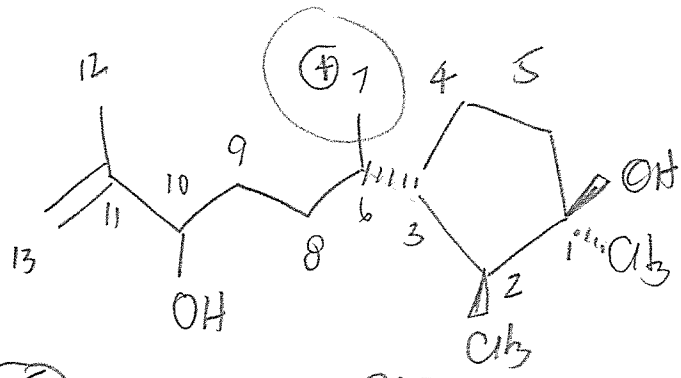
3° CARBOCATION

Carbocations form at C_6, C_7, C_{13}, C_{11} by reaction of the alkene w/ acid (Electrophilic addition)



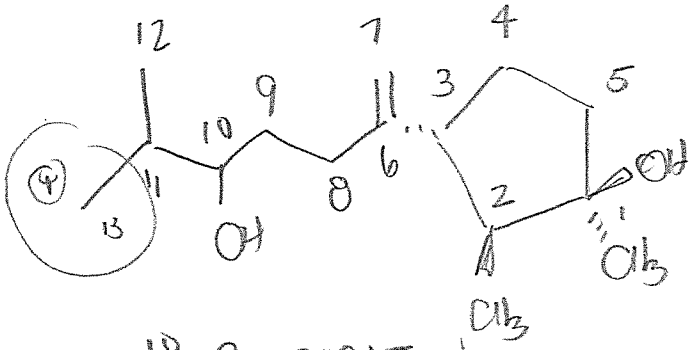
3° CARBOCATION

IV.

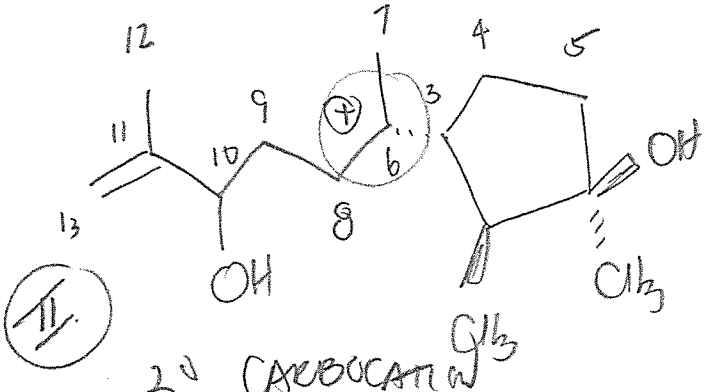


III

1° CARBOCATION



1° CARBOCATION
(NOT SHOWN)



II.

3° CARBOCATION

4. (CONT'D)

$3^{\circ}C^{\oplus} > 2^{\circ}C^{\oplus} > 1^{\circ}C^{\oplus}$

MOST STABLE FORMS FASTEST

LEAST STABLE

I, II & IV are all $3^{\circ}C^{\oplus}$ and form EQUALLY Fast

I, II, IV

(E)

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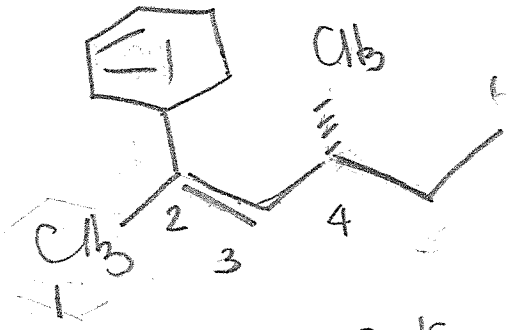
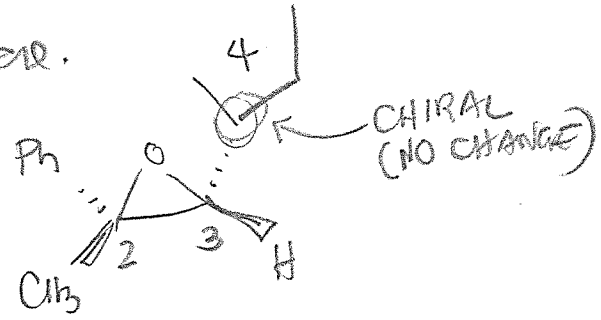
5. m-CPBA reacts with alkenes with syn stereochemistry and reacts from top & bottom of the alkene, RETAINING the original stereochemistry of the starting alkene.

I. Z-4R-methyl-2-phenyl-2-hexene.

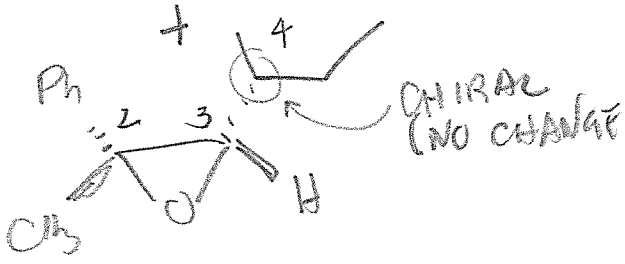


A



+

B

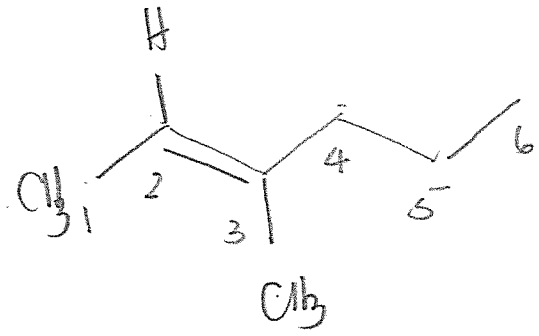


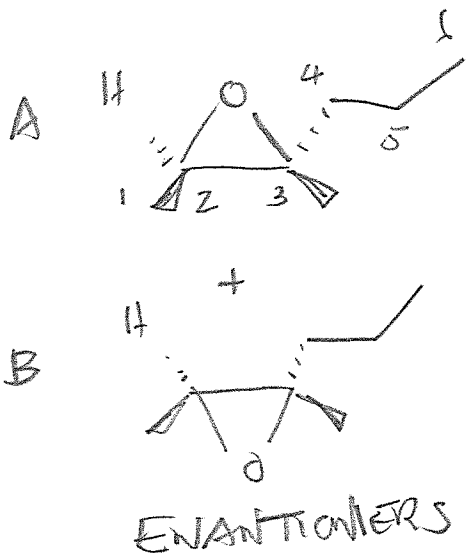
C_2, C_3 INVERTED CONFIG FROM A → B; C4 SAME

A + B DIASTEREOMERS

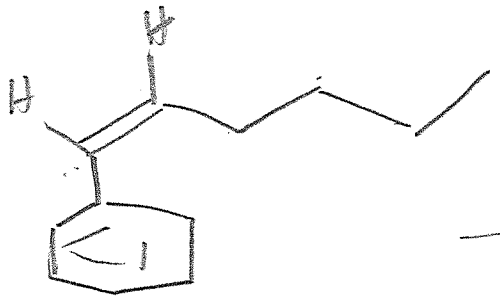
5. (CONT'D)

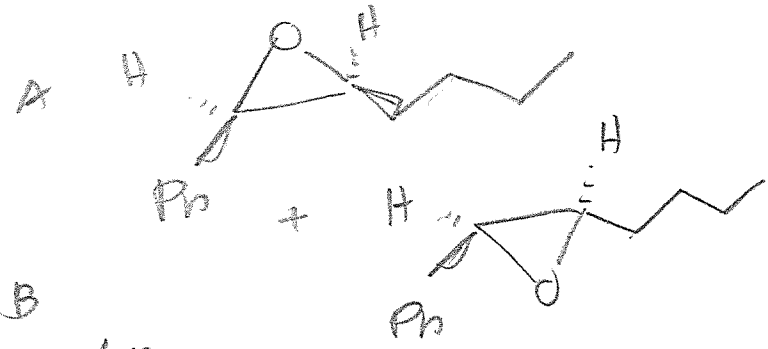
II.



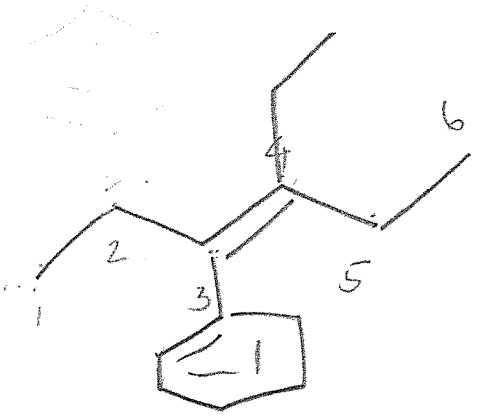


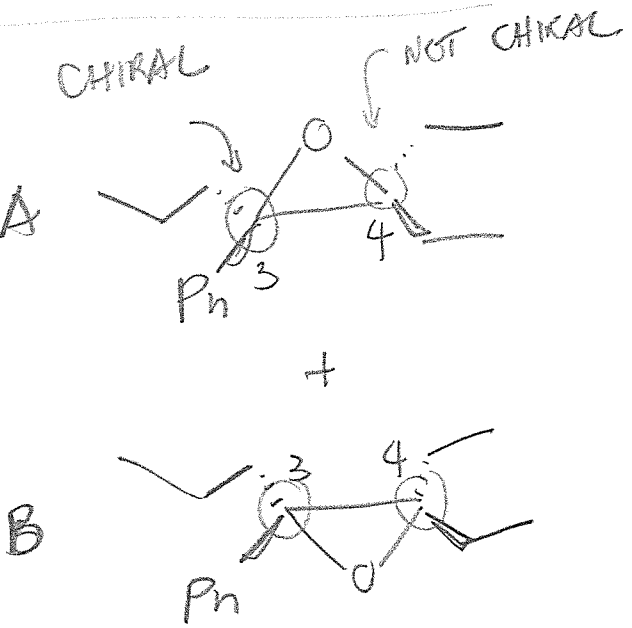
III.





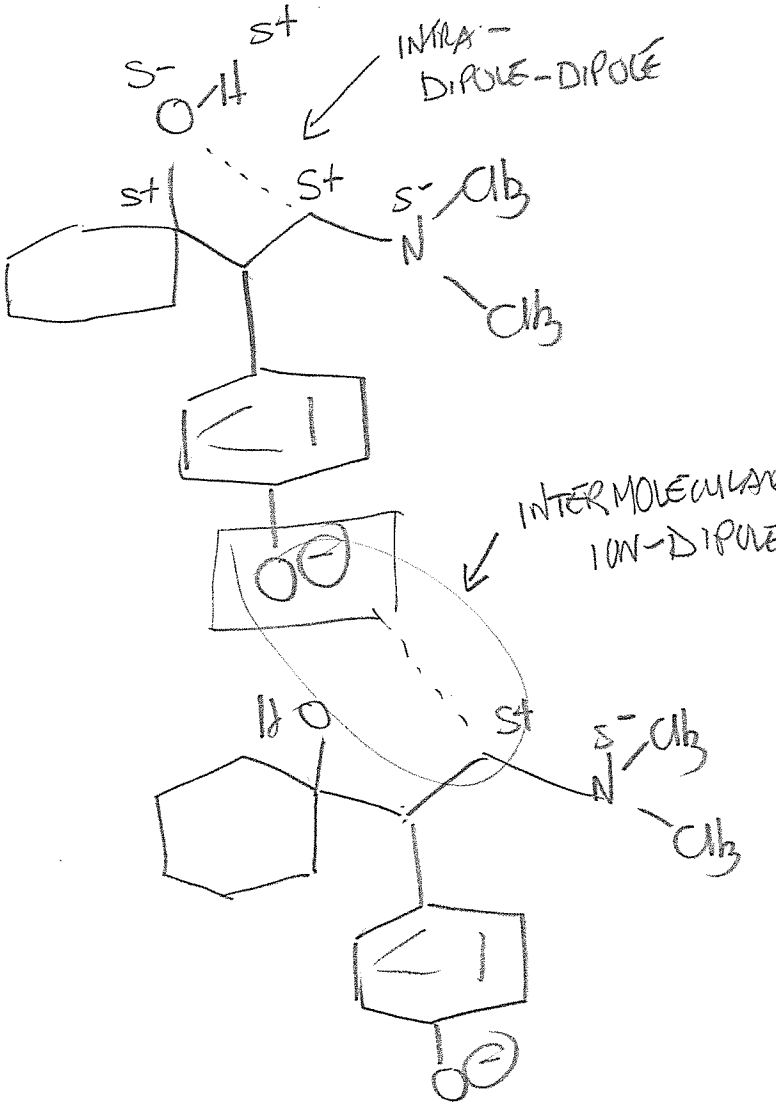
IV.





II, III, IV

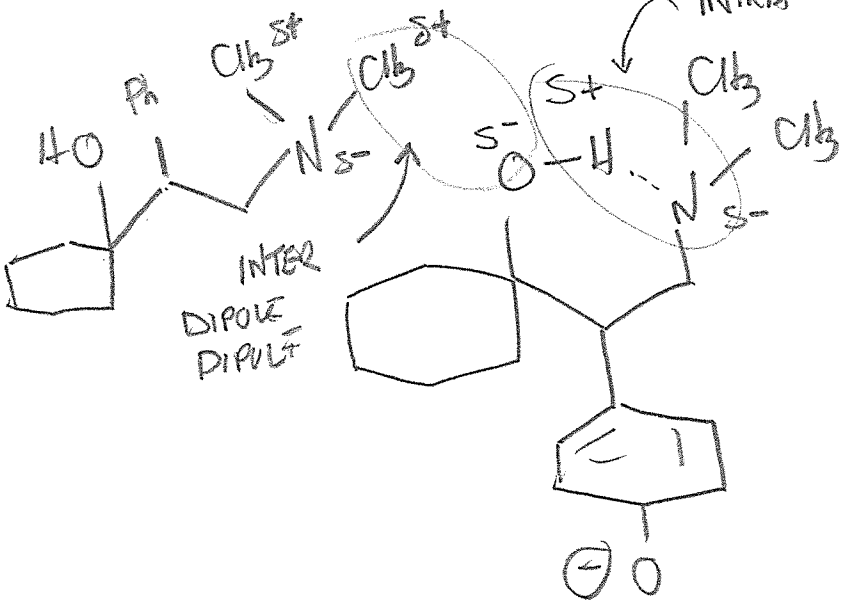
6. At pH = 12, the alcohol ($pK_a = 18.1$) and amine ($pK_a = 8.34$ of conjugate acid) are NOT IONIZED, but the phenol ($pK_a = 10.1$) IS IONIZED

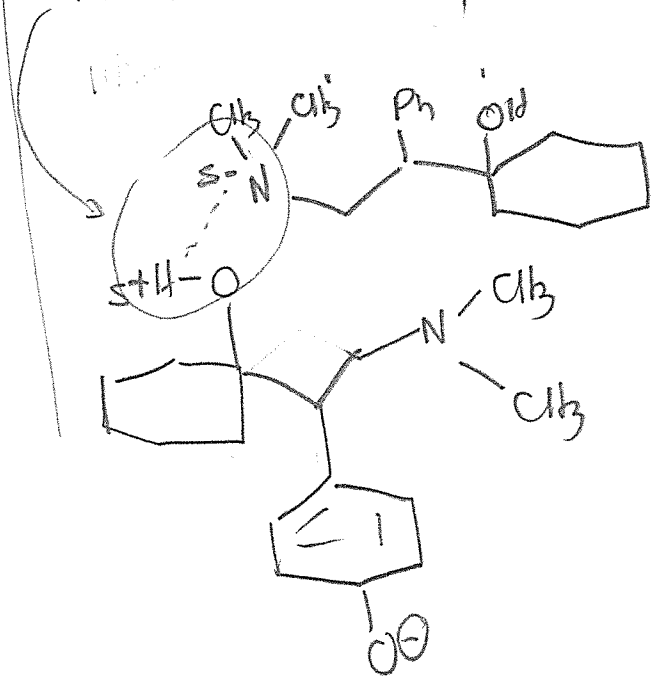


BUT CANNOT "REACH" δ+ WITHIN SAME MOLECULE SO NO INTRA ION-DIPOLE

6. (cont'd)

Can also have intra-H bonding

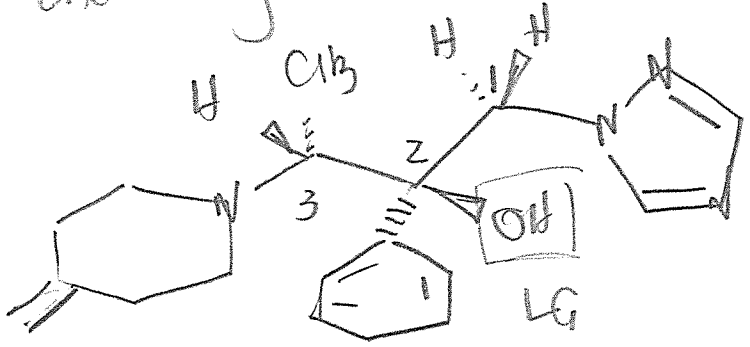




I, II, ~~III~~, V, ~~VI~~

(E)

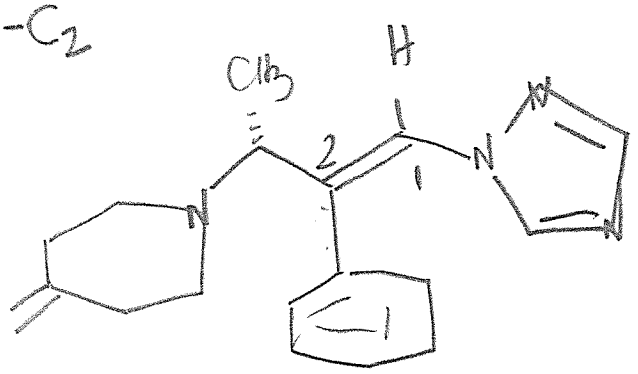
7. E_2 Elimination MAJOR THERMODYNAMIC PRODUCT is the most stable alkene possible where LG and adjacent H is anti peri planar.



- OH LG bonded to C_2
- E_2 can occur across C_1-C_2 or C_2-C_3

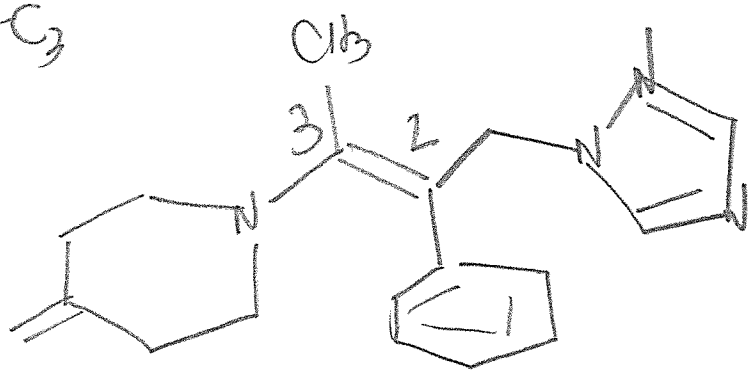
7. (cont'd)

If C_1-C_2



TRISUBSTITUTED

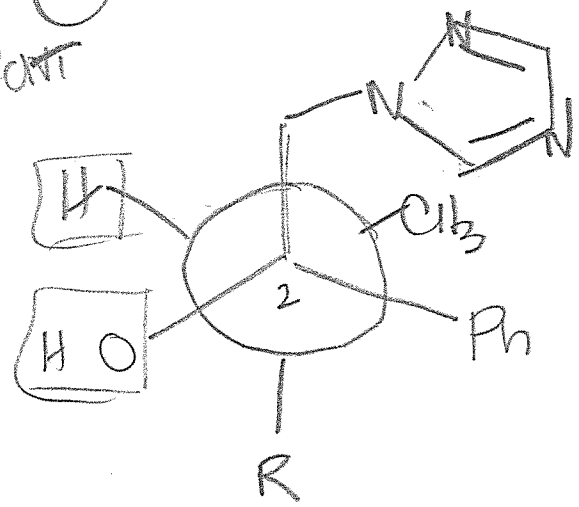
If C_2-C_3



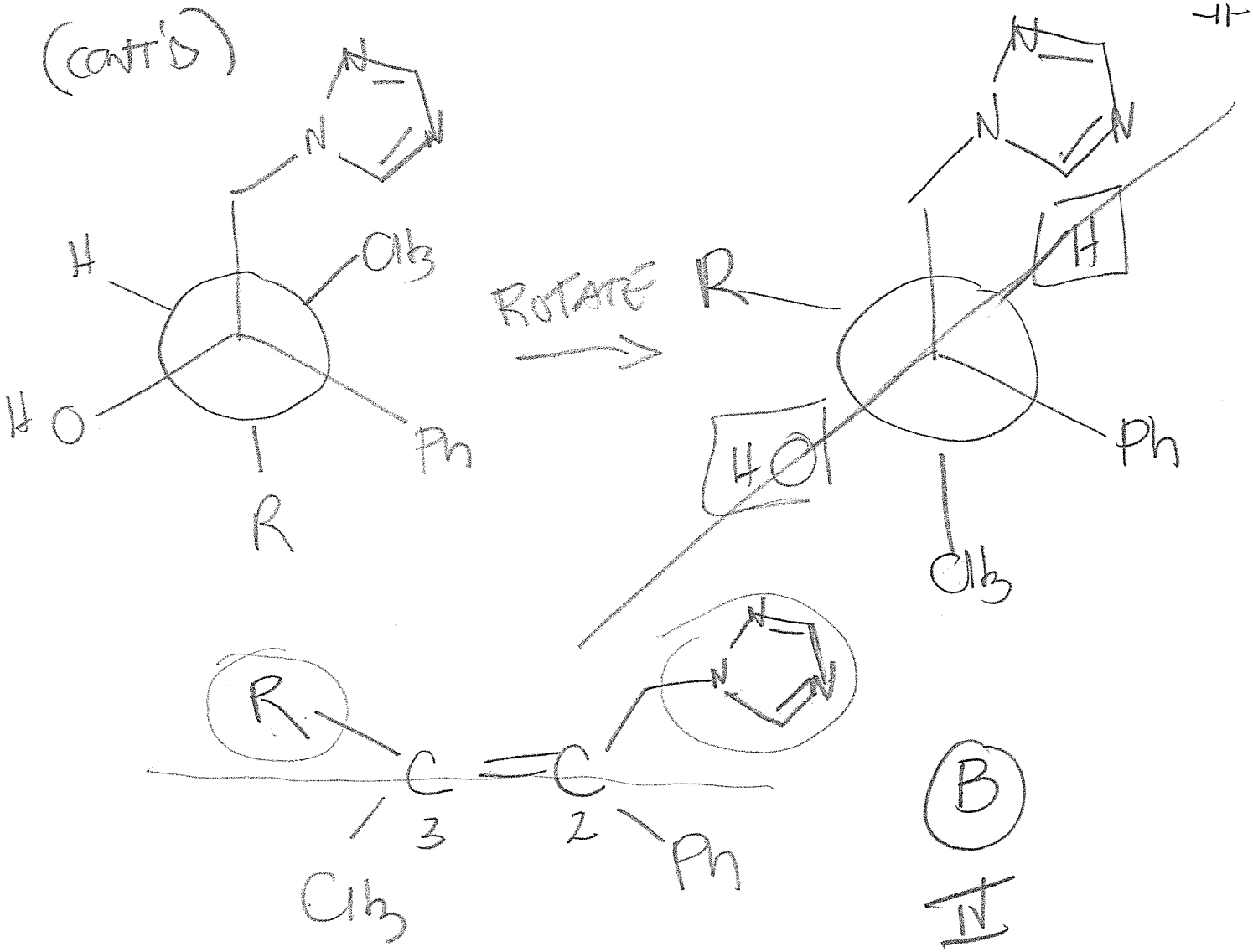
TETRASUBSTITUTED

Tetrasubstituted is more STABLE than Tri, so E2 occurs across C_2-C_3 but must determine if Z- or E- alkene is possible. based on stereochemistry / orientation of OH @ C_2 and H @ C_3. Draw Newman projection w/ C_2 in Front

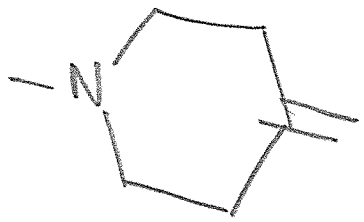
H and OH are NOT ANTI so must ROTATE before doing E2



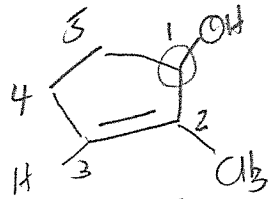
7. (CONT'D)



R =



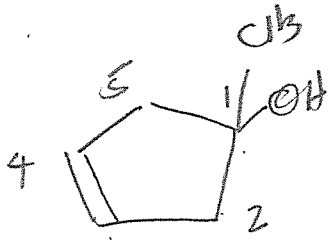
8. I. 2-methylcyclopent-2-en-1-ol



TRISUB

2° ALCOHOL

II. 1-methylcyclopent-3-en-1-ol

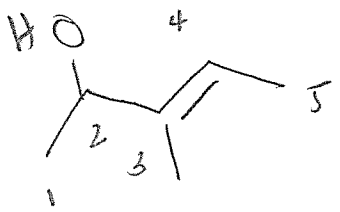


DISUBSTITUTED

3° ALCOHOL

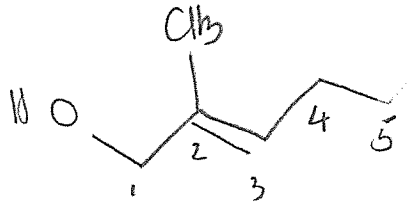
8. (CONT'D)

III. 3-methylpent-3-en-2-ol



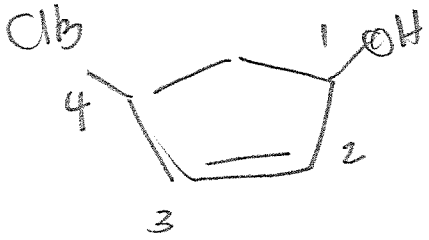
2° ALCOHOL
TRI SUBSTITUTED

IV. 2-methylpent-2-en-1-ol



1° ALCOHOL
TRI SUBSTITUTED

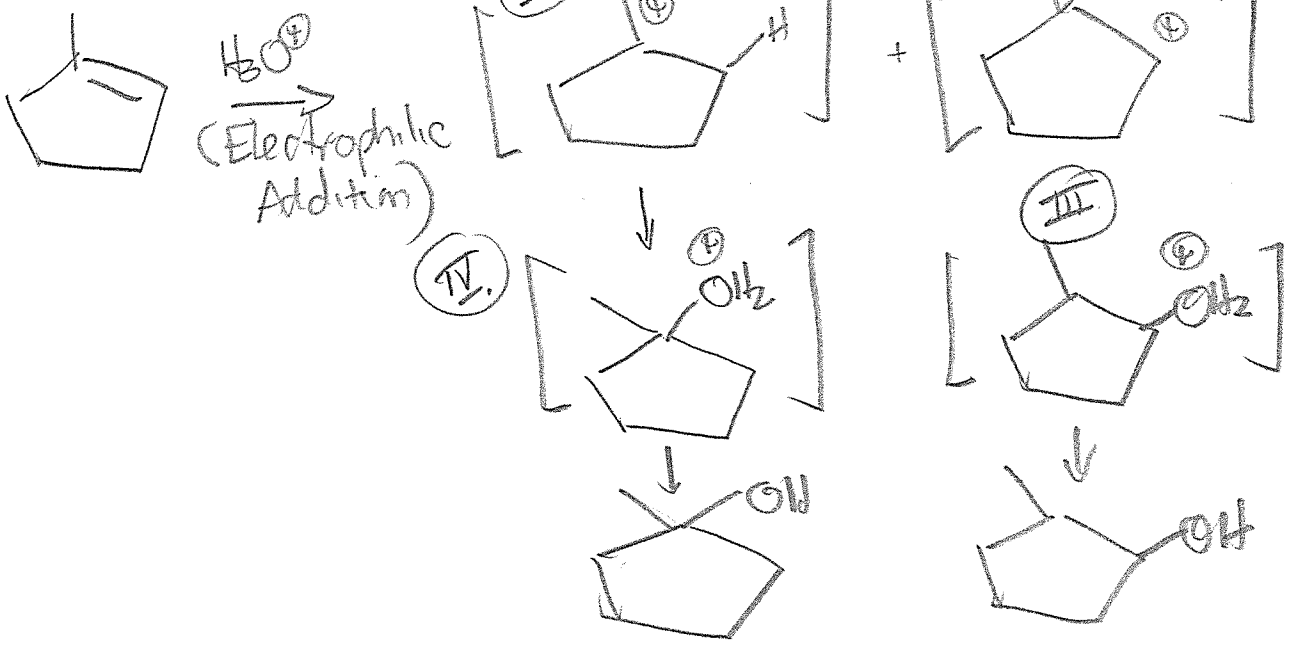
V. 4-methylcyclopent-2-en-1-ol



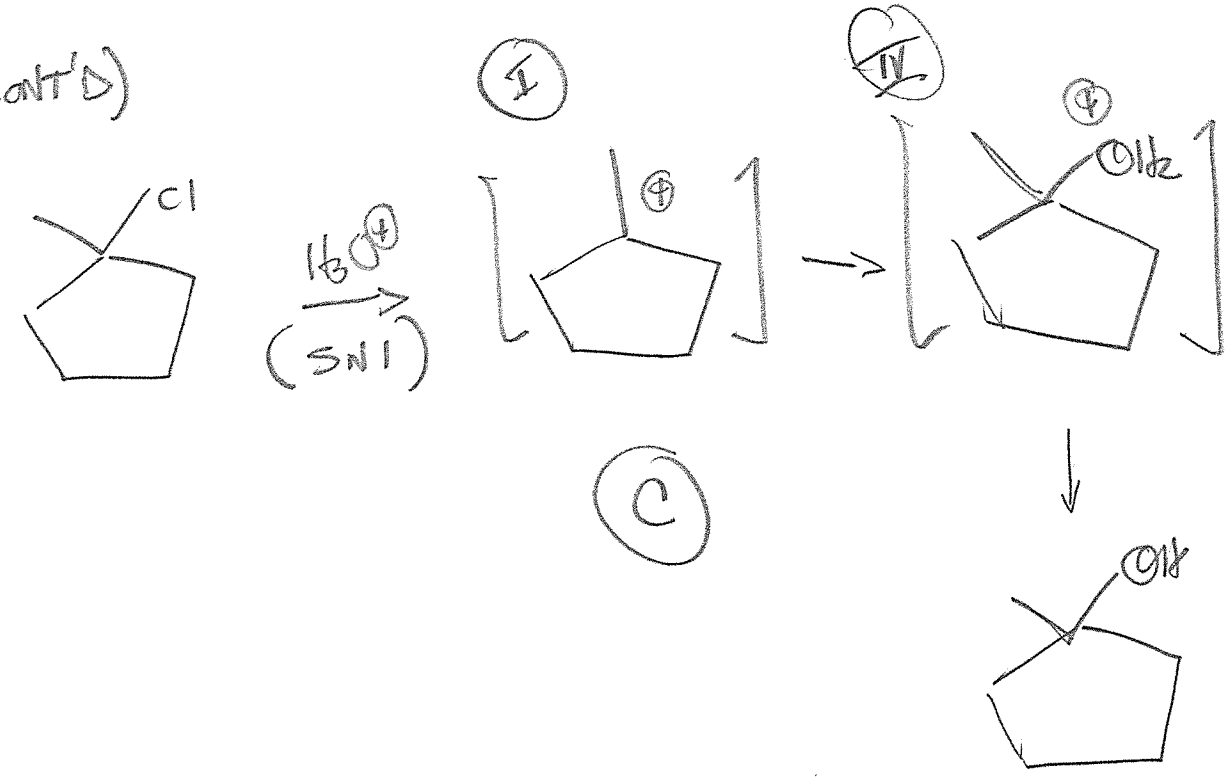
DISUBSTITUTED
2° ALCOHOL

(D)

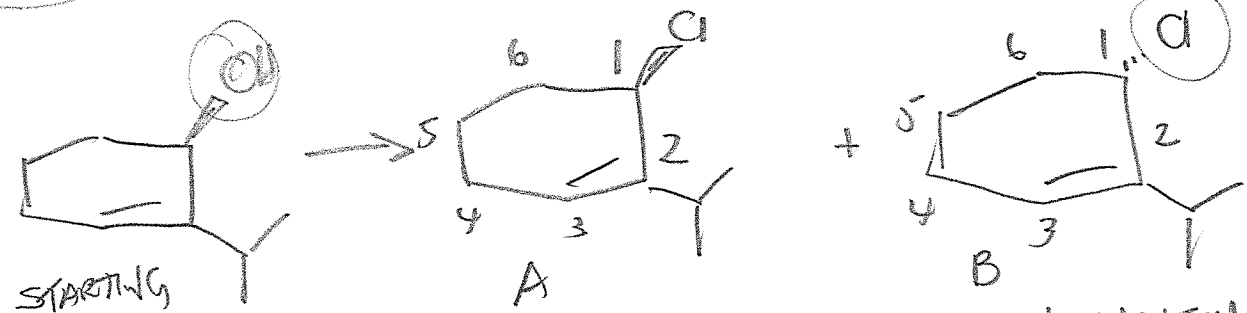
9.



9. (CONT'D)



10.



STARTING MATERIAL

A

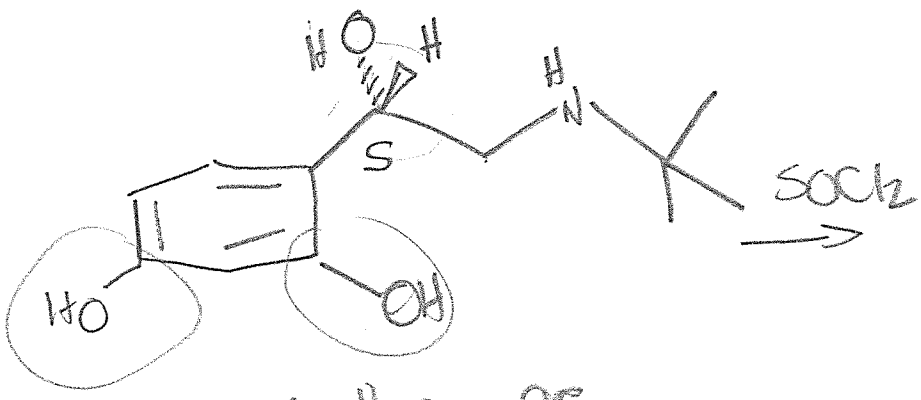
B

NOT AN ENANTIOMER OF SM, SM HAS OH, B HAS Cl

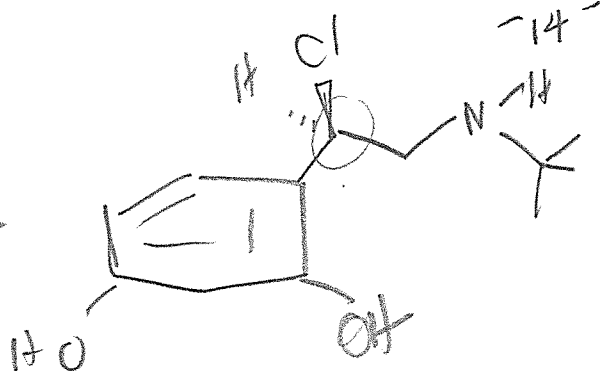
A & B ARE ENANTIOMERS
There is one chiral center at C1 and it is INVERTED going from A to B.
So they are NOT diastereomers

Since both A and B form, must be SN1. SN2 would give ONLY B.

11.



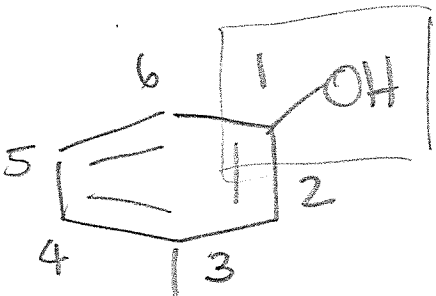
Both of these are PHENOLS and do not react in S_N2 with $SOCl_2$



CHIRAL

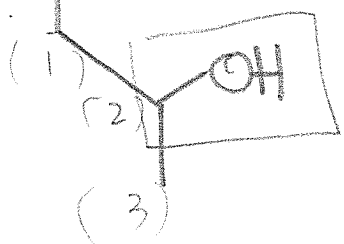
Reaction of 2° alcohol w/ $SOCl_2$ occurs with INVERSION of configuration.

12.



PHENOL
$pK_a = 8$

IONIZES @ $pH \geq 9$
DOES NOT IONIZE IN ACID

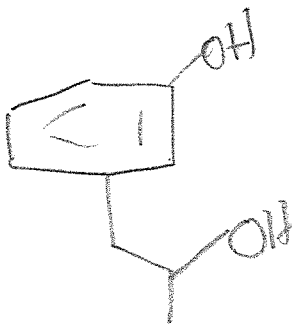


ALCOHOL
$pK_a = 17$

IONIZES @ $pH \geq 10$
(to conjugate base)

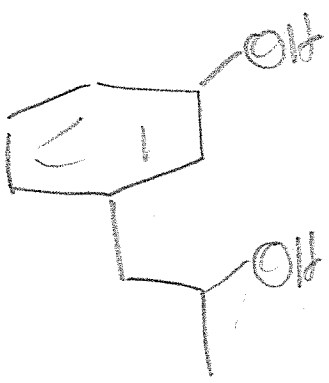
IONIZES @ $pH \leq -3.6$

$pH = 1.6$
A



IV

$pH = 6.8$
B

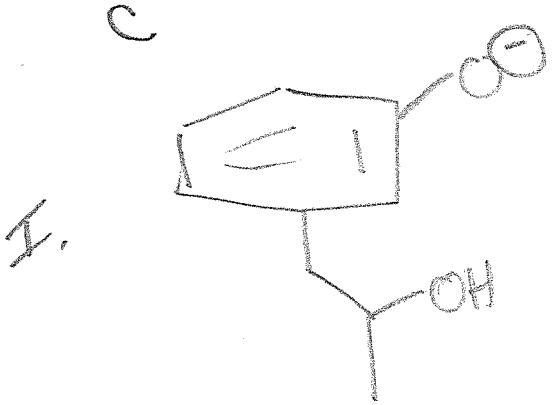


IV

12. (cont'd)

pH = 13.1

C



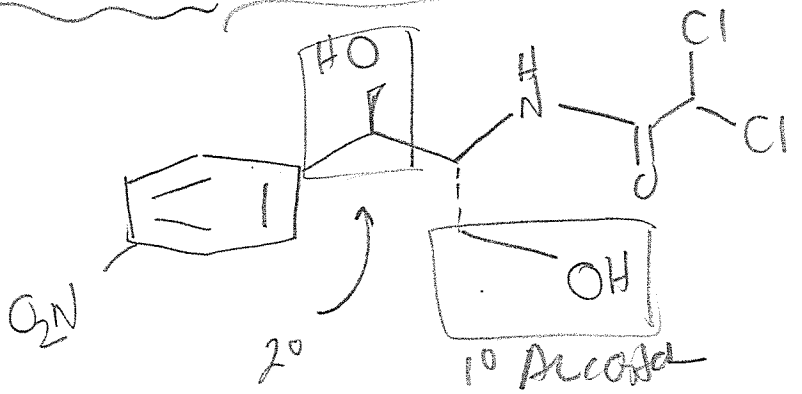
I.

A = IV

B = II (D)

C = I

13.



2° Alcohol → Ketone

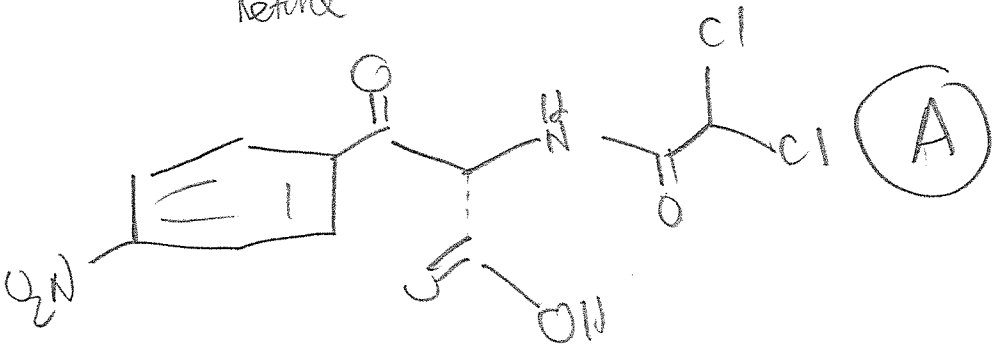
1° Alcohol → C.A

Jones Reagent (Oxidizing Agent)

1° ROH → Carboxylic Acid

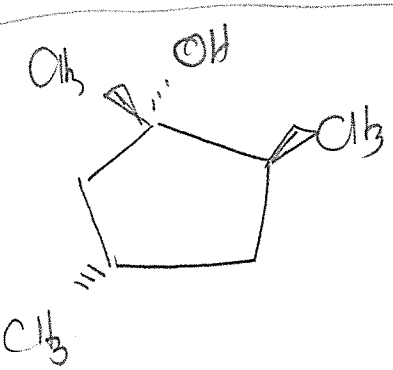
2° ROH → Ketone

Aldehyde → Carboxylic Acid



(A)

14.

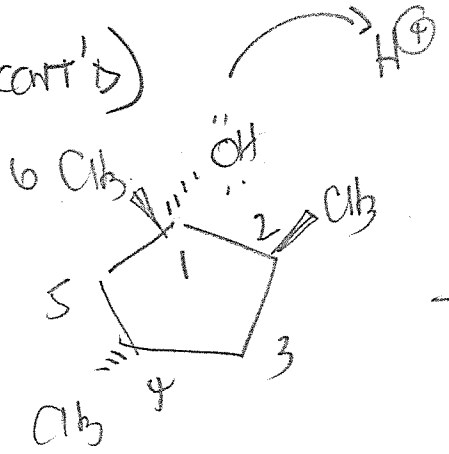


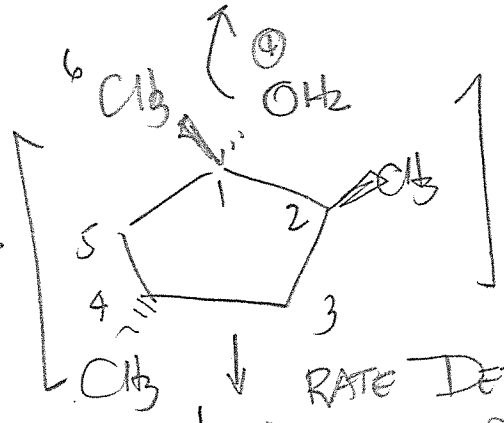
H_3PO_4 →

E1 Elimination

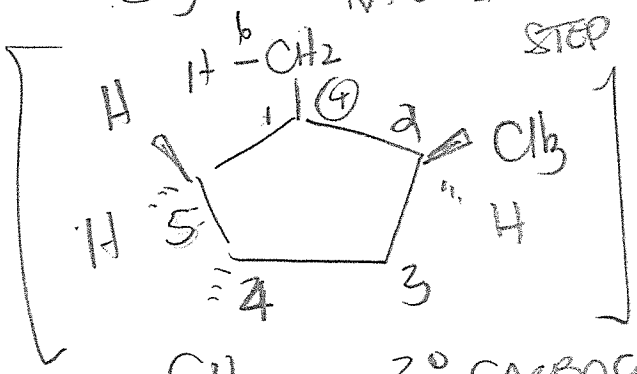
Major kinetic products are derived from the most stable $C^{\oplus}$ formed in the rds

14. (CONT'D)





RATE DETERMING STEP

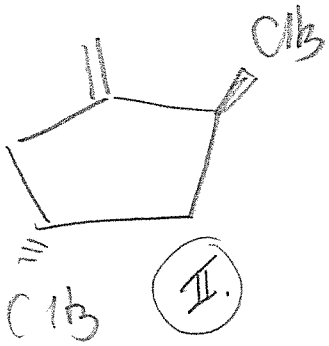


3° CARBOCATION

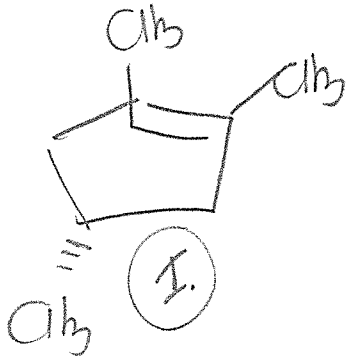
- 3 possible adjacent H

C_2, C_5, C_6

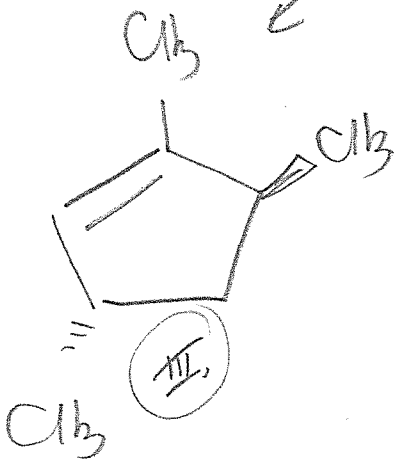
ALL DERIVED FROM SAME $C^{\oplus}$



II.



I.

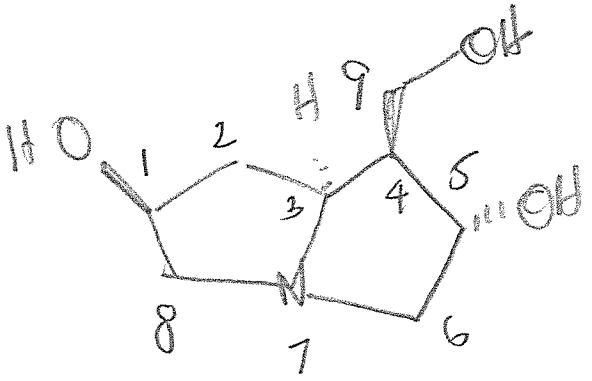


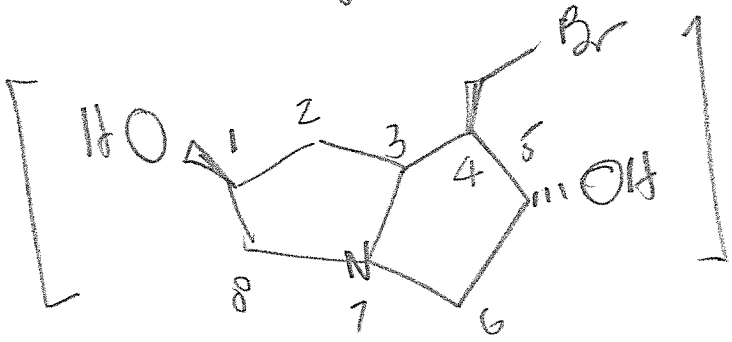
III.

E

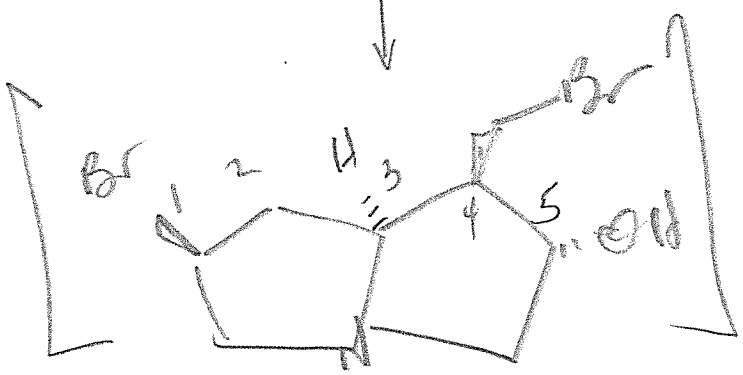
15. HBr with with 1°, 2°, 3° alcohols occurs via SN1 mechanism. When the starting alcohol is chiral, both configurations are generated as products - All react b/c Excess # Br

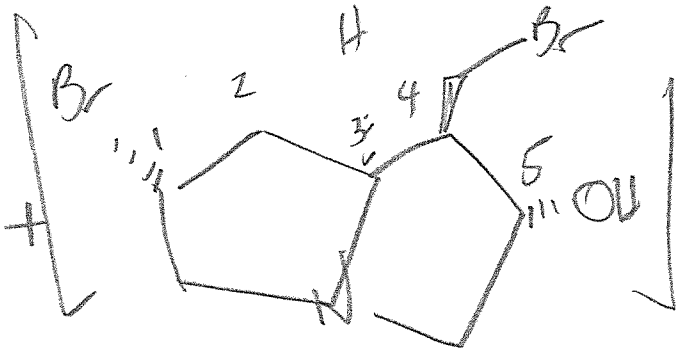
C_9 is 1°; NOT CHIRAL
C_4 is a NON-REACTING CARBON





C_1 IS CHIRAL, BOTH CONFIGURATIONS GENERATED @ C_1

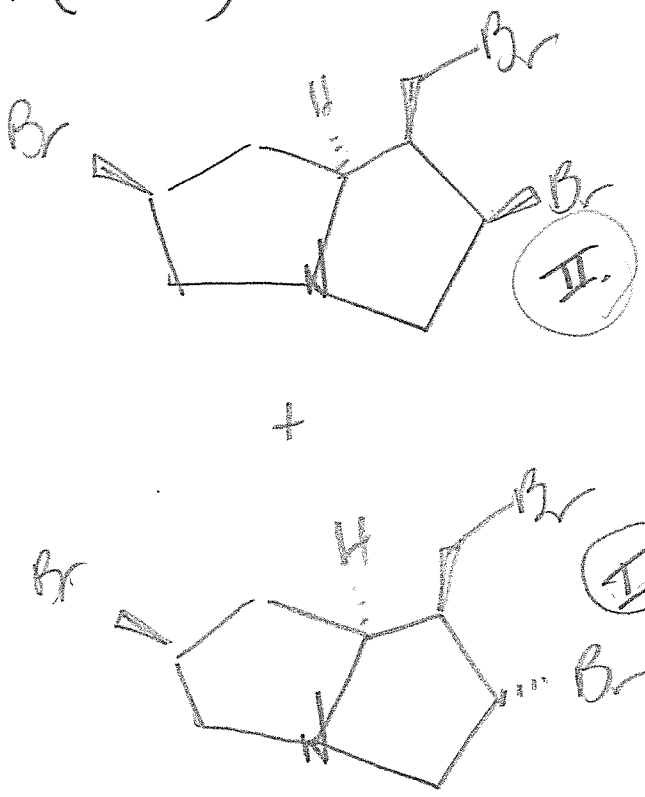




(see next)

(see next)

15. (cont'd)



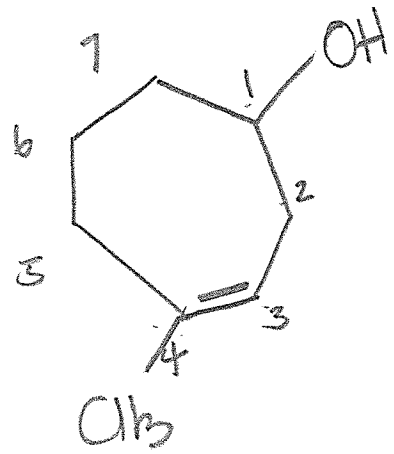
I, II, ~~III~~, ~~IV~~.

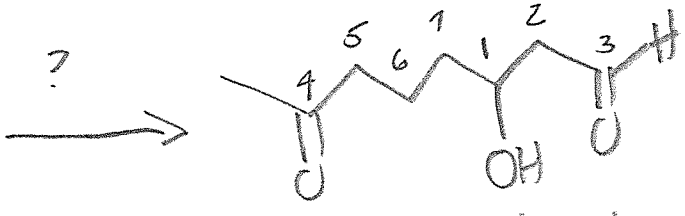
(C)

C_5 is also chiral so both configurations form.

---

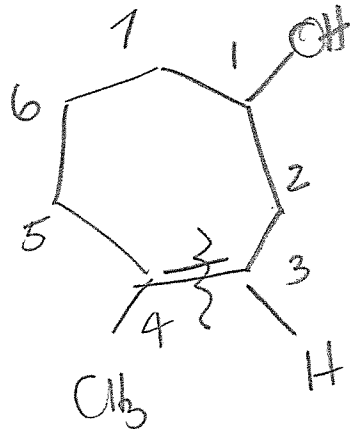
16. 4-methylcyclohept-3-en-1-ol

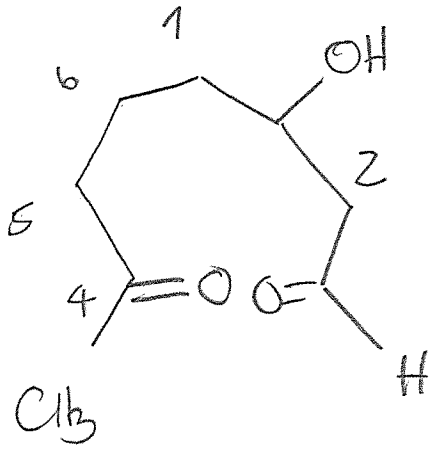




The product is oxidized
Ring is opened ⇒ ALKENE undergoes OXIDATIVE CLEAVAGE

16. (CONT'D)





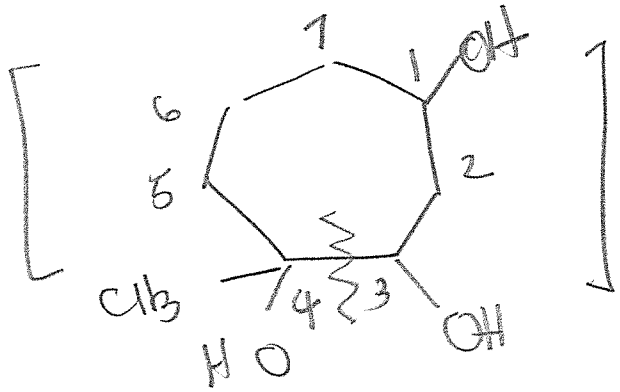
I. 1. O_3 2. Zn, HCl

Alkene → Aldehyde / Ketone

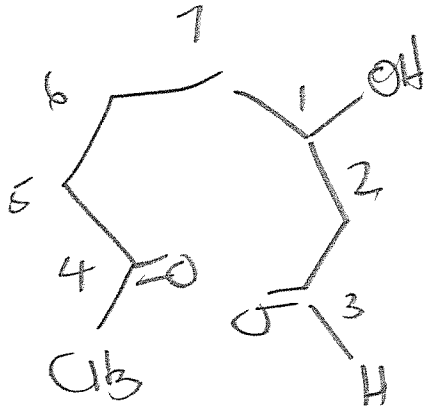
cold, dilute KMnO4

Alkene → 1,2-diol → Aldehyde / Ketone

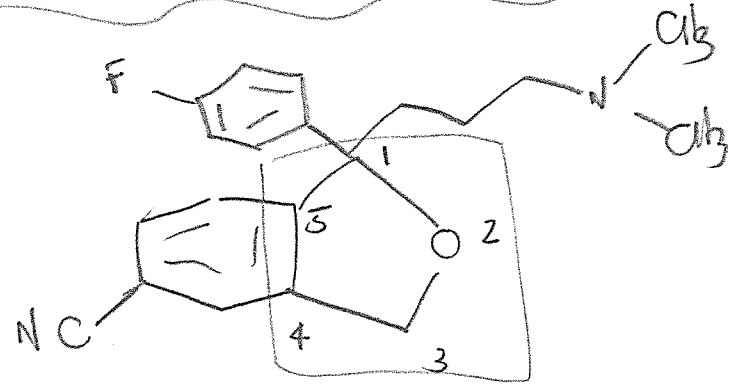
II 1. cold $KMnO_4$
2. HIO_4



HIO_4 →



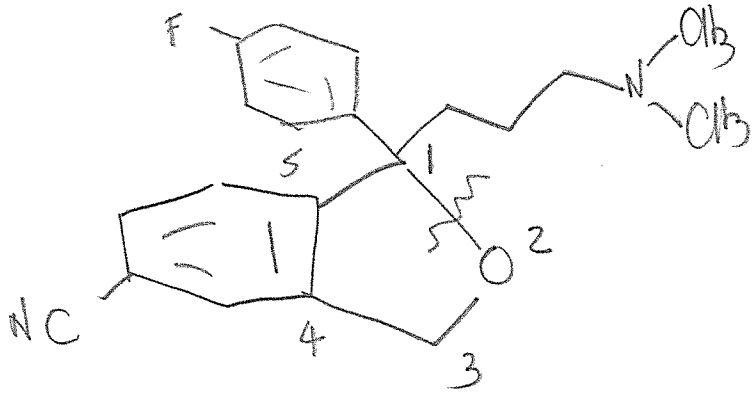
17.



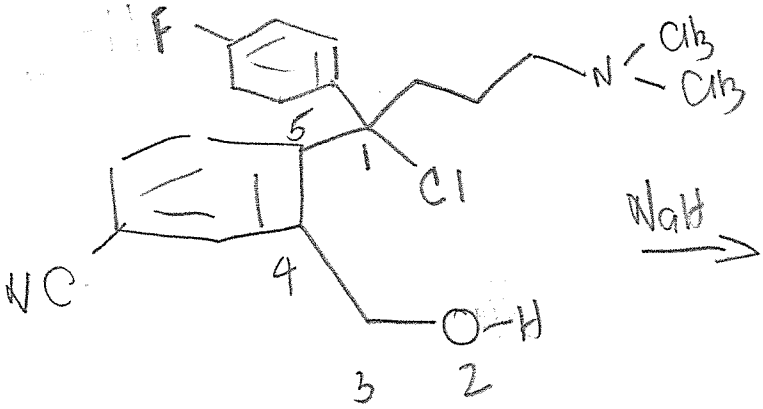
ETHER

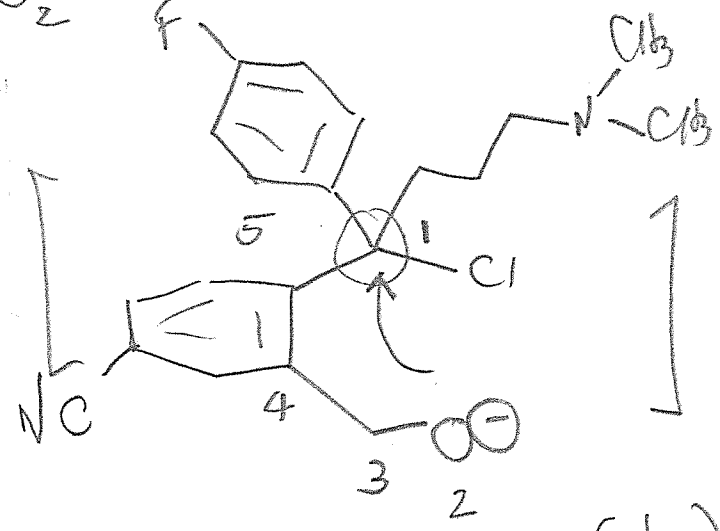
C_1 and C_3 bonded to oxygen of ether

17. (cont'd)



If ether is formed via C_1-O_2 bond, C_1 could be alkyl halide and O_2 the Nu!

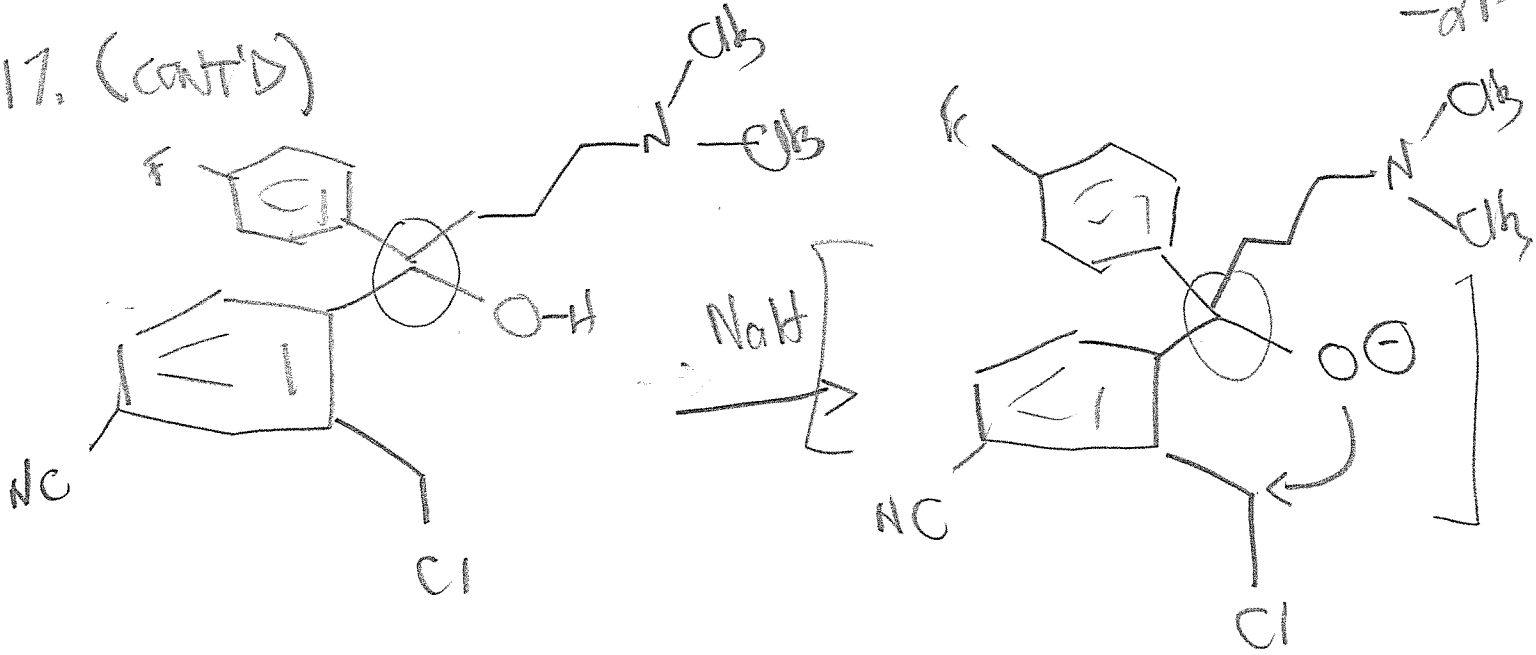




This requires $O^{\ominus}$ (Nu!) to react w/ 3° alkyl chloride. UNFAVORABLE in S_N2 rxn.

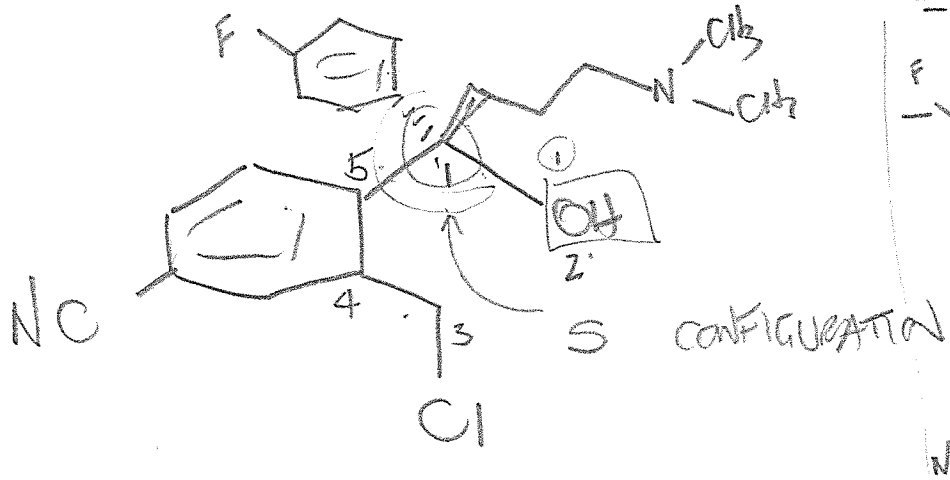
If ether is formed via C_3-O bond, C_3 would be the alkyl halide and O_2 the Nu!

17. (CONT'D)

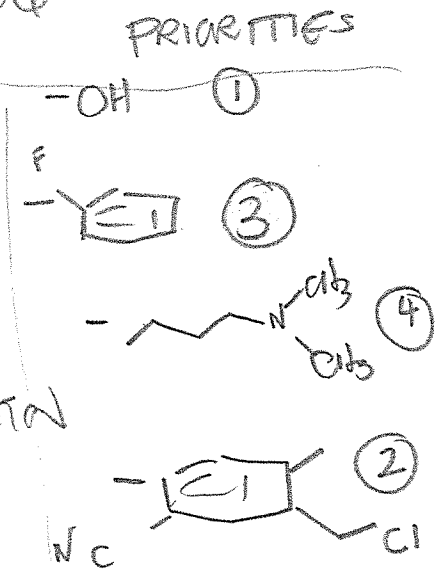


In SN2, alkoxide Nu: reacts w/ 1° alkyl halide. FAVORED IN SN2

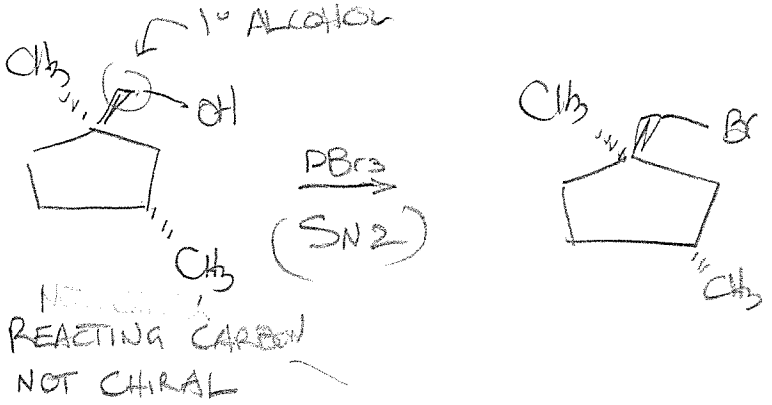
Must start w/ this alcohol and make sure that the C_1 carbon has the S- configuration. It does not change in the rxn w/ the 1° alkyl halide

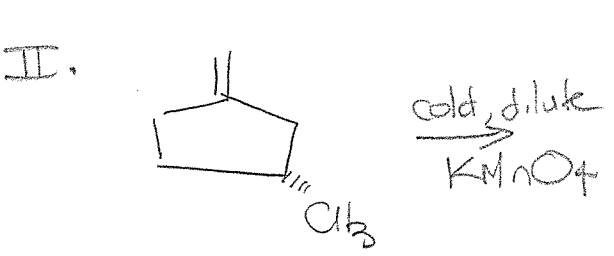


PRIORITIES



18.

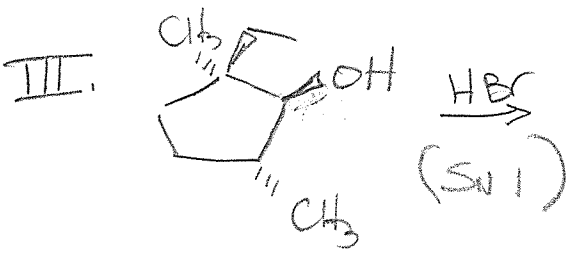
I. 

II. 

DIASTEREOMERS

C_1 inverted going from A → B

C_3 stays same.

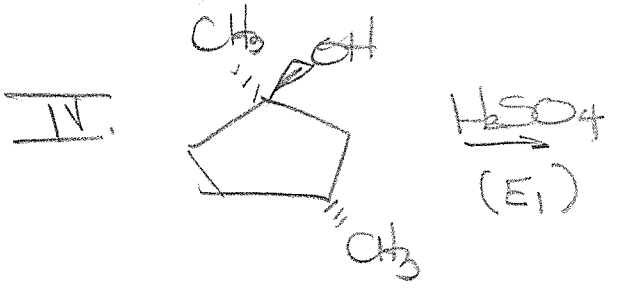
III. 

(B)

C_1, C_3 same in A & B

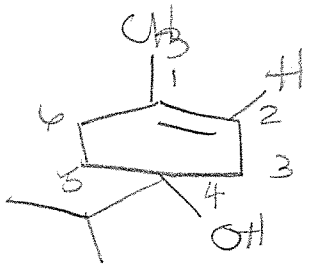
C_2 inverted going from A → B

DIASTEREOMERS

IV. 

POSITIONAL ISOMERS

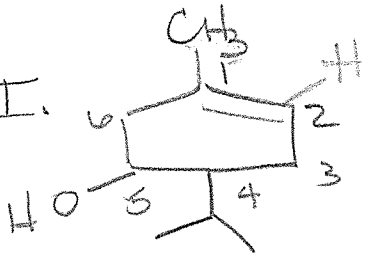
19.

I. 

B: α-TERPINEOL

C_4: 3° ALCOHOL

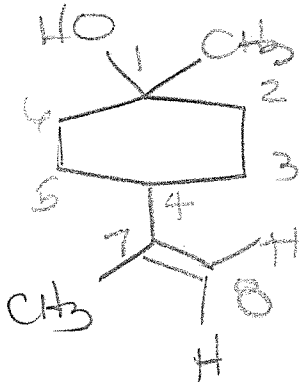
C_1-C_2 ALKENE: TRISUBSTITUTED

II. 

C_5: 2° ALCOHOL

C_1-C_2 ALKENE: TRISUBSTITUTED

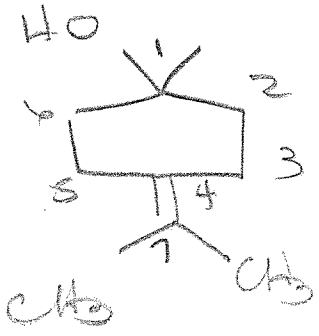
D: α-TERPINEOL

III. 

C_1: 3° ALCOHOL

C_7-C_8 ALKENE: DISUBSTITUTED

A: β-TERPINEOL

IV. 

C_1: 3° ALCOHOL

C_4-C_7 ALKENE: TETRASUBSTITUTED

C: γ-TERPINEOL

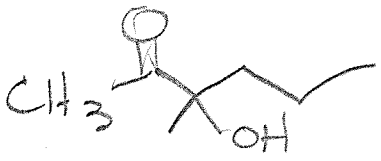
A = III B = I C = IV D = II

(B)

I = D II = A III = C IV = B

20.

I,



Jones	−
Iodoform	+
Br_2/H_2O	−
Lucas	+
$KMnO_4$	−

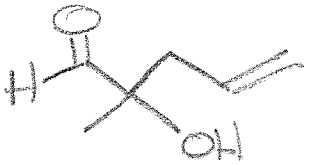
D

II,

Jones	+
Iodoform	−
Br_2/H_2O	−
Lucas	+
$KMnO_4$	−

A

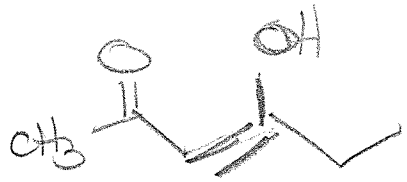
III,



Jones	+
Iodoform	−
Br_2/H_2O	+
Lucas	+
$KMnO_4$	+

C

IV



Jones	−
Iodoform	+
Br_2/H_2O	+
Lucas	−
$KMnO_4$	+

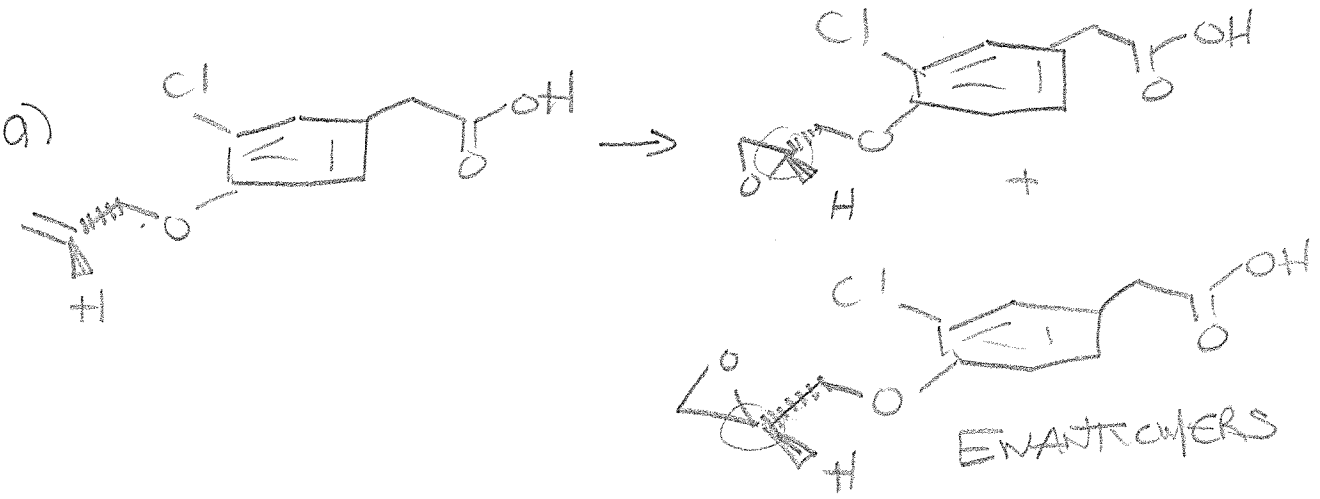
B

21. Reacts w/ $KMnO_4$, not PCC, Jones
- contains ALKENE
- no 1°, 2° Alcohols or aldehyde

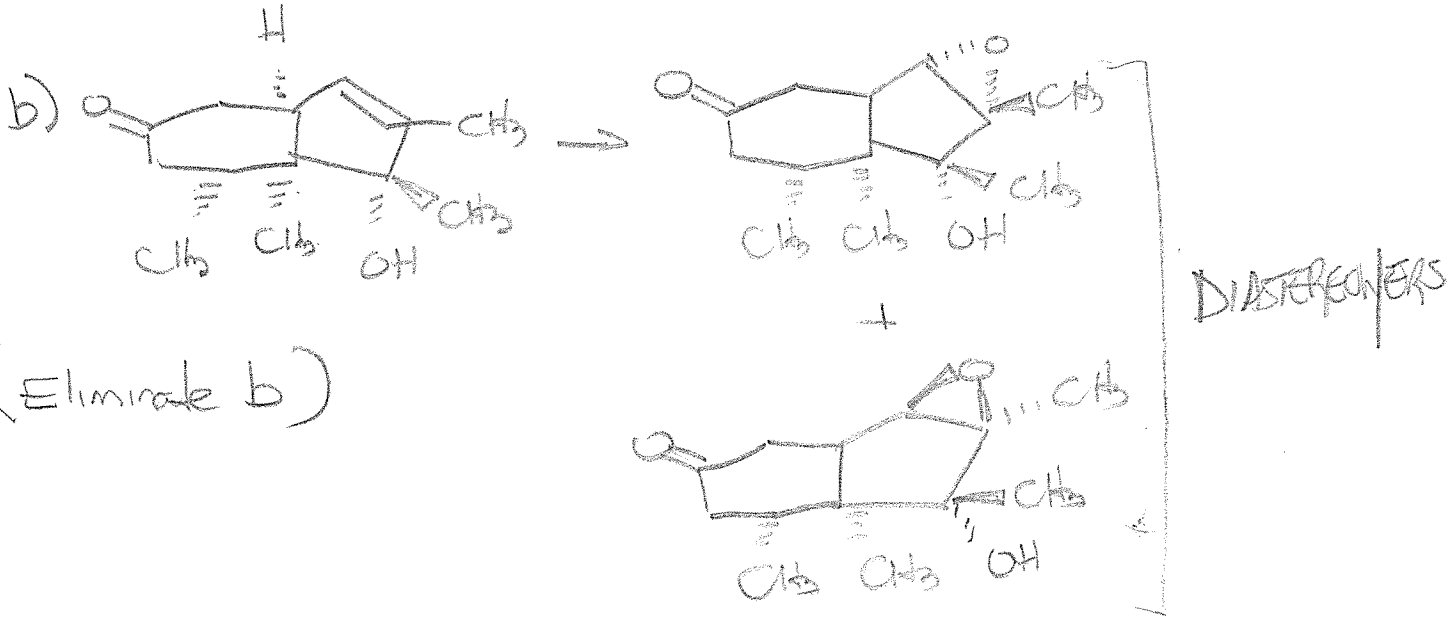
(Eliminate e)

Reaction w/ mCPBA gives mixture of enantiomers
- reaction must generate at least one chiral center
- no other chiral centers in the molecule

a)



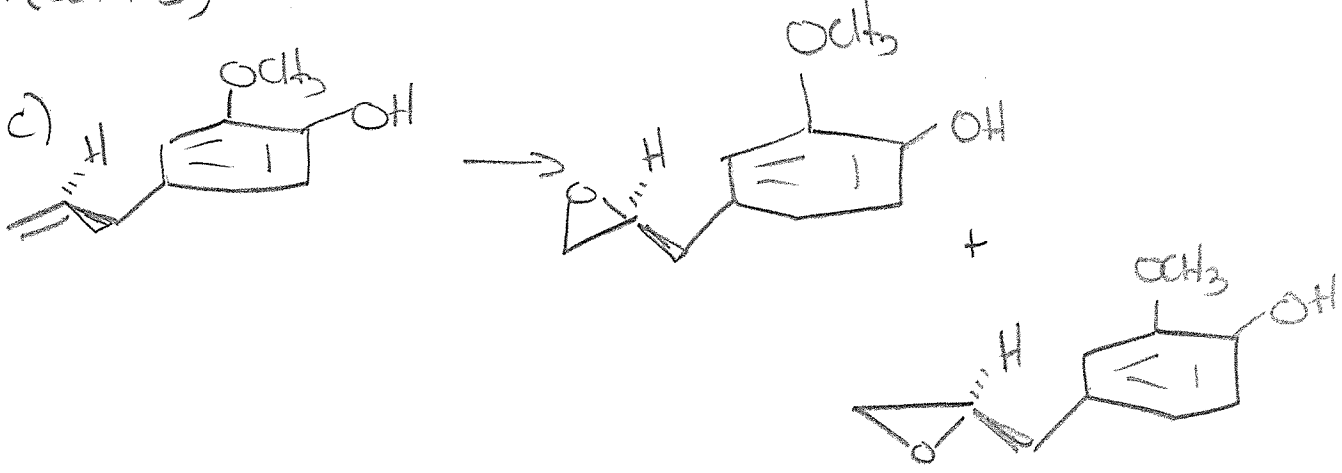
b)



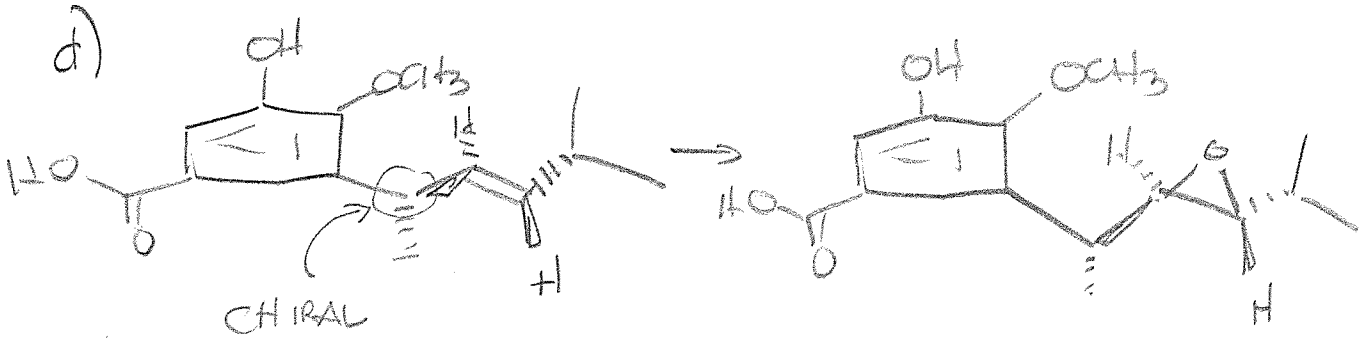
(Eliminate b)

21. (CONT'D)

c)

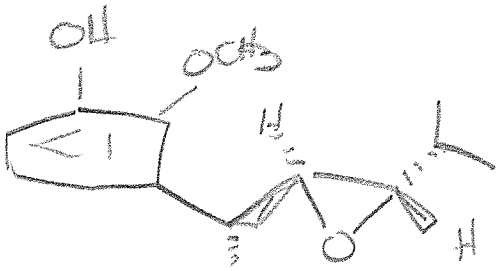


d)



(Eliminated)

DIASTEREOMERS



At pH = 7, intermolecular ion-dipole

- EG w/ pKa < 7 (i.e. carboxylic acid) is present, H ionizes and can then form ion-dipole interactions

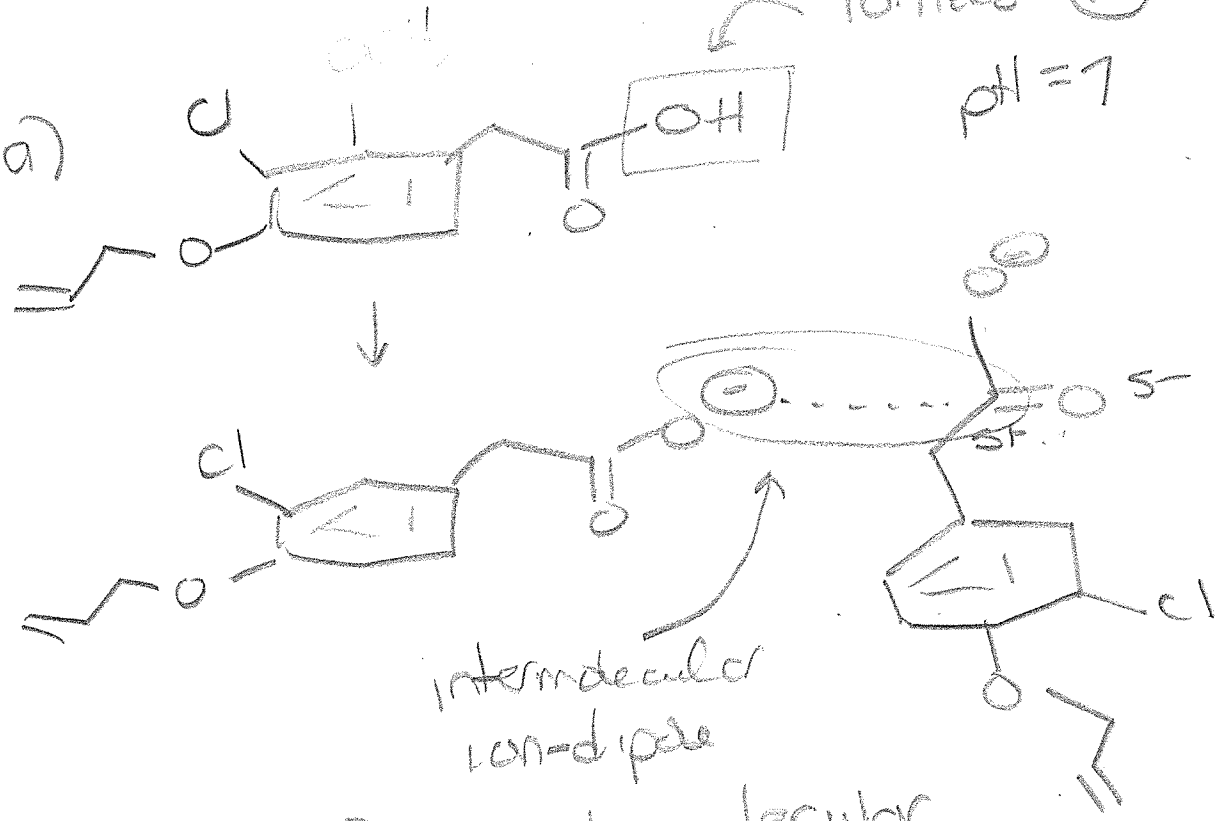
21. (CONT'D)

c)

NO IONIZATION @ pH = 7

(Eliminate c)

a)

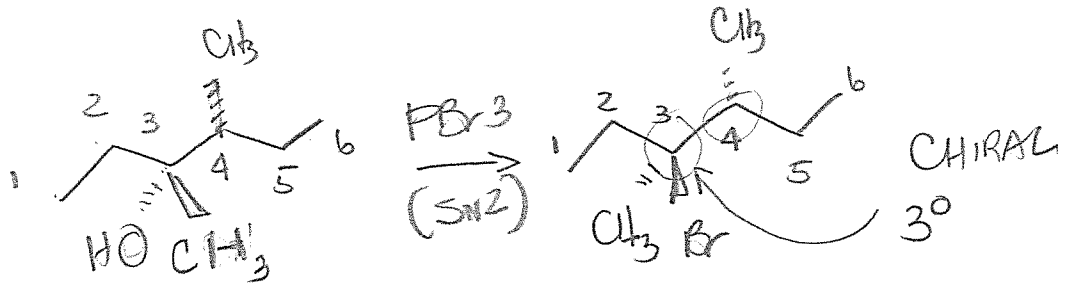


intermolecular ion-dipole

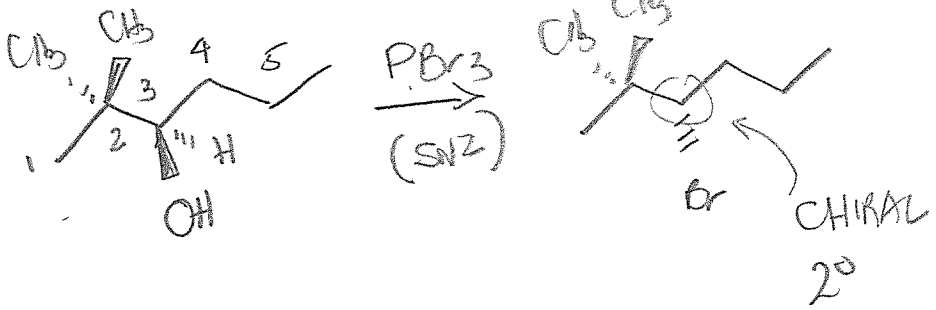
cannot form intramolecular since C=O of carboxylic acid cannot reach around to polar covalent bonds on ether or aryl halide

22.

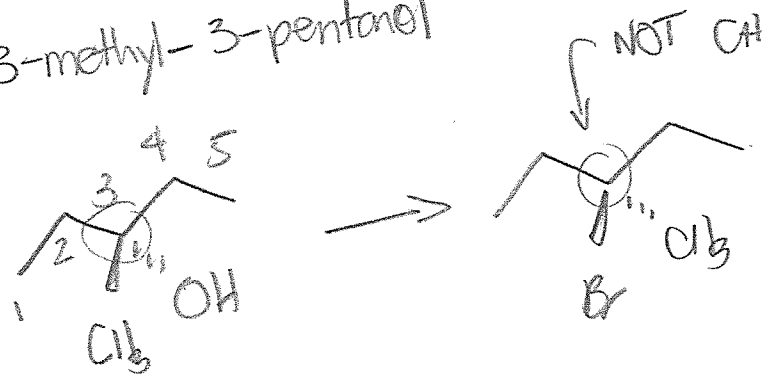
I. 3R,4S-3,4-dimethyl-3-hexanol



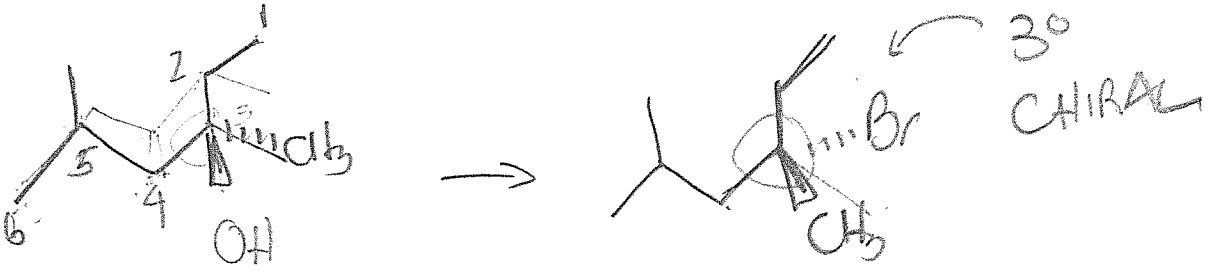
II. 3R-2,2-DIMETHYL-3-HEXANOL



III. 3-methyl-3-pentanol



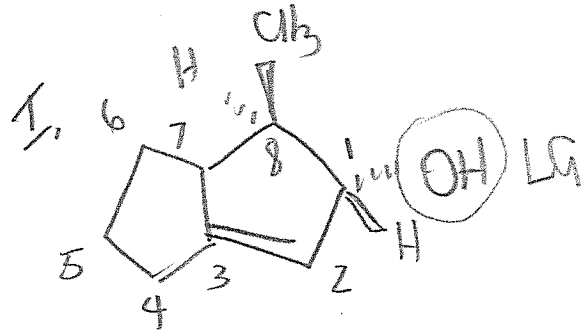
IV.



3S-3,5-DIMETHYL~~-3-~~HEXANOL

23. Reactions are E2.
Must have LG (i.e. OH) trans to adjacent H on sp^3C

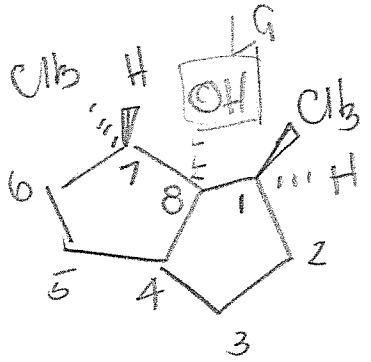
I.



NO E2

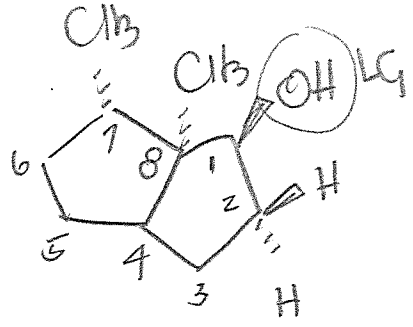
C_2 is sp^2, no C_1–C_2 alkene
C_8 H is cis to OH

II.



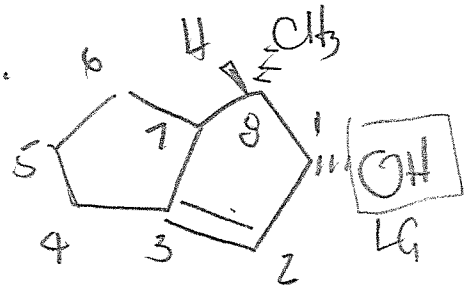
H @ C_7 is trans to OH
H @ C_1 is cus to OH
Alkene CAN form across C_7–C_8 bond

III.



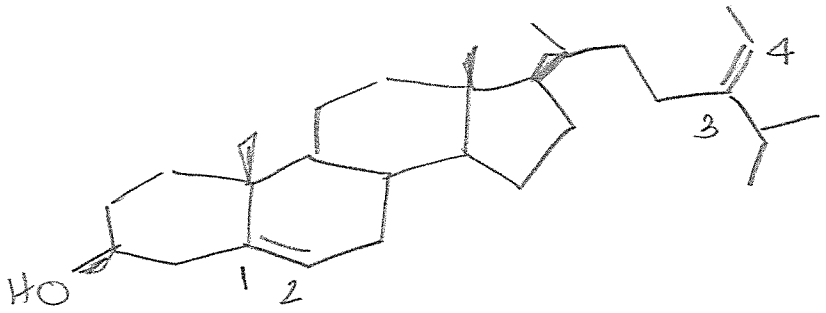
H @ C_2 is trans to OH
E2 CAN occur

IV.



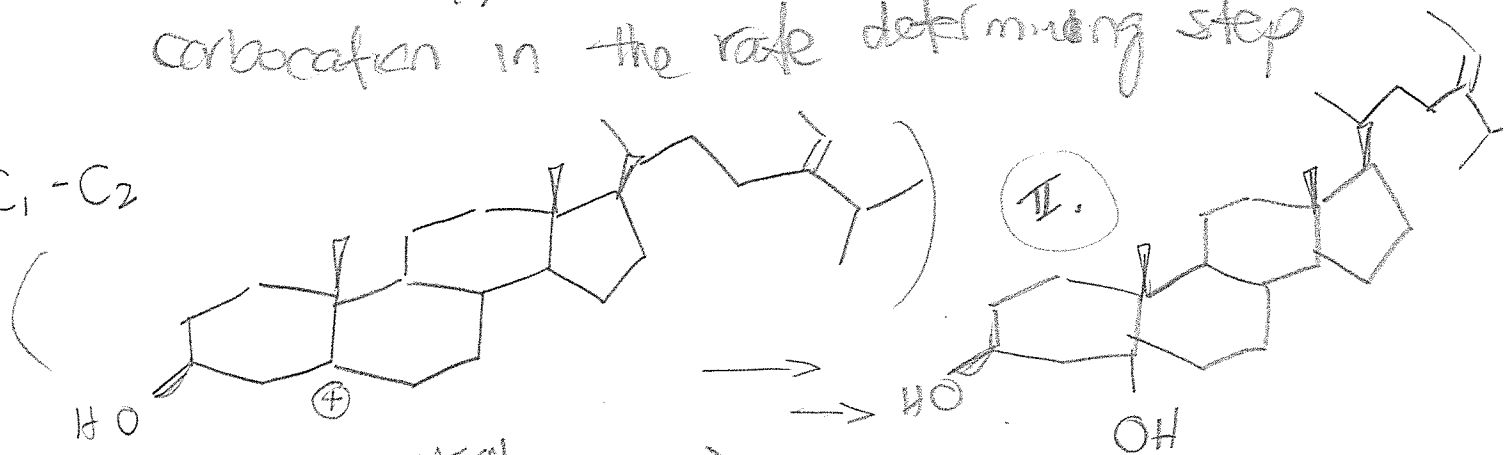
H @ C_8 is trans to OH
E2 CAN occur

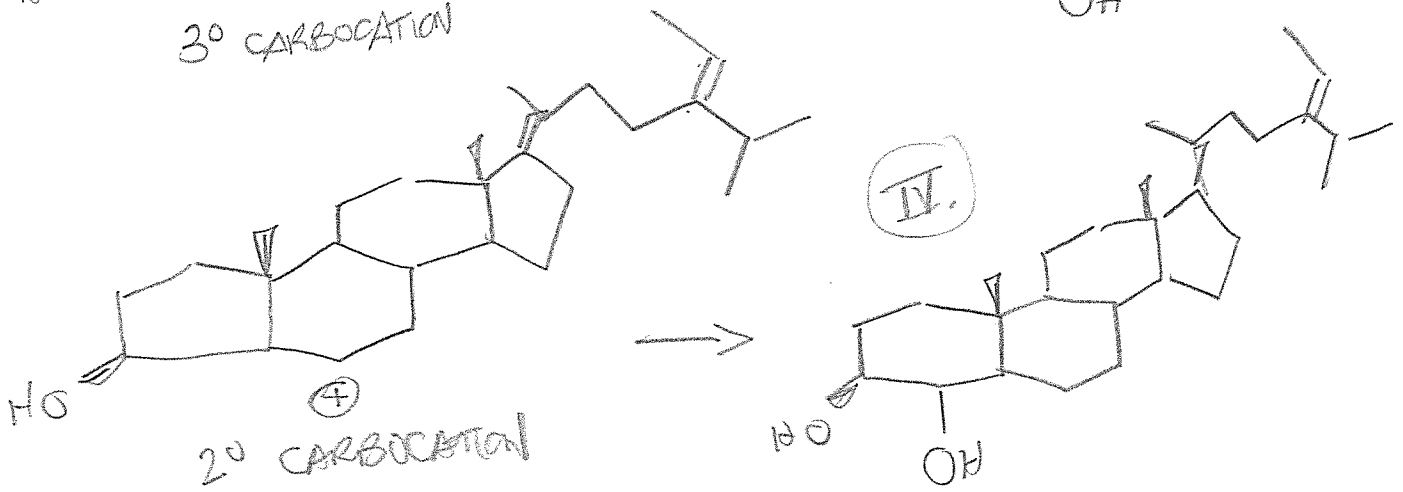
24.



Reaction of fucosterol w/ H_3O^+ is an electrophilic addition. With only one equivalent either the C_1-C_2 bond reacts, or C_3-C_4 bond reacts at a time. The bond(s) that react the fastest is the one(s) that form the most stable carbocation in the rate determining step

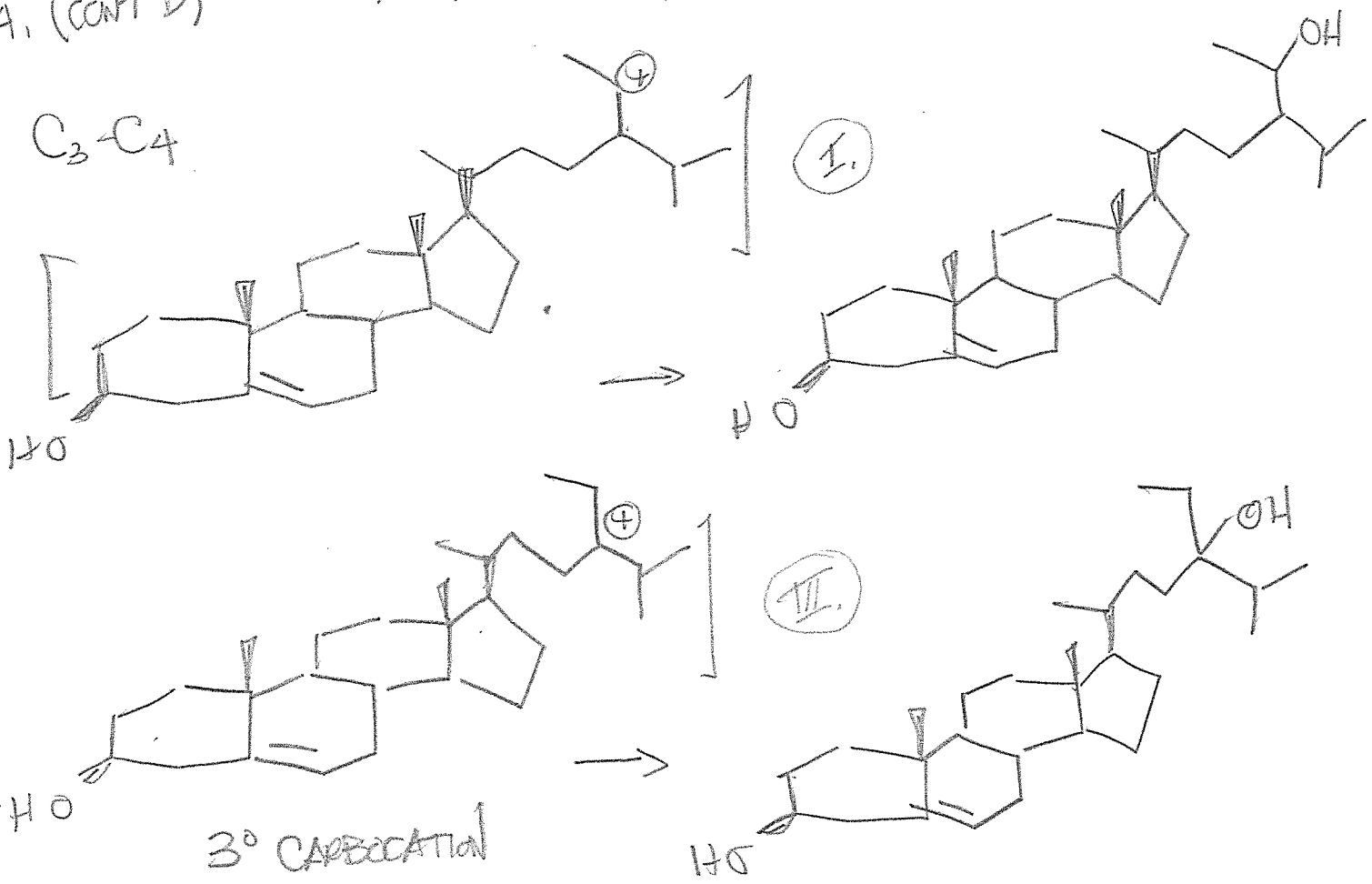
C_1-C_2





24. (CONT'D)

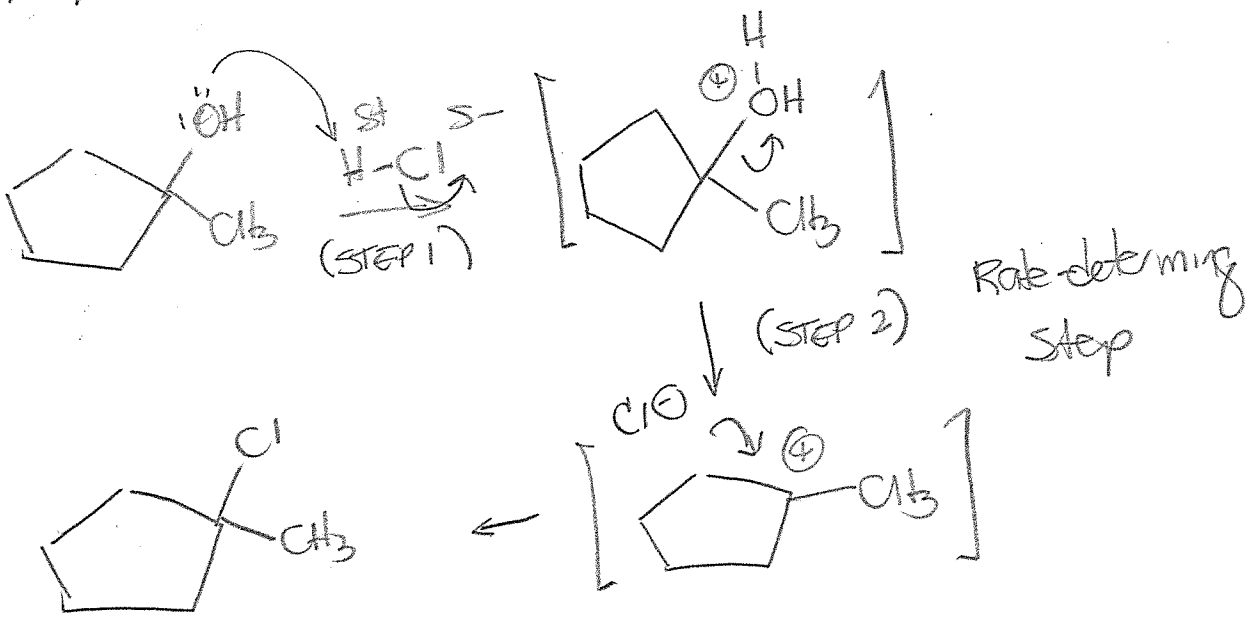
2° CARBOCATION

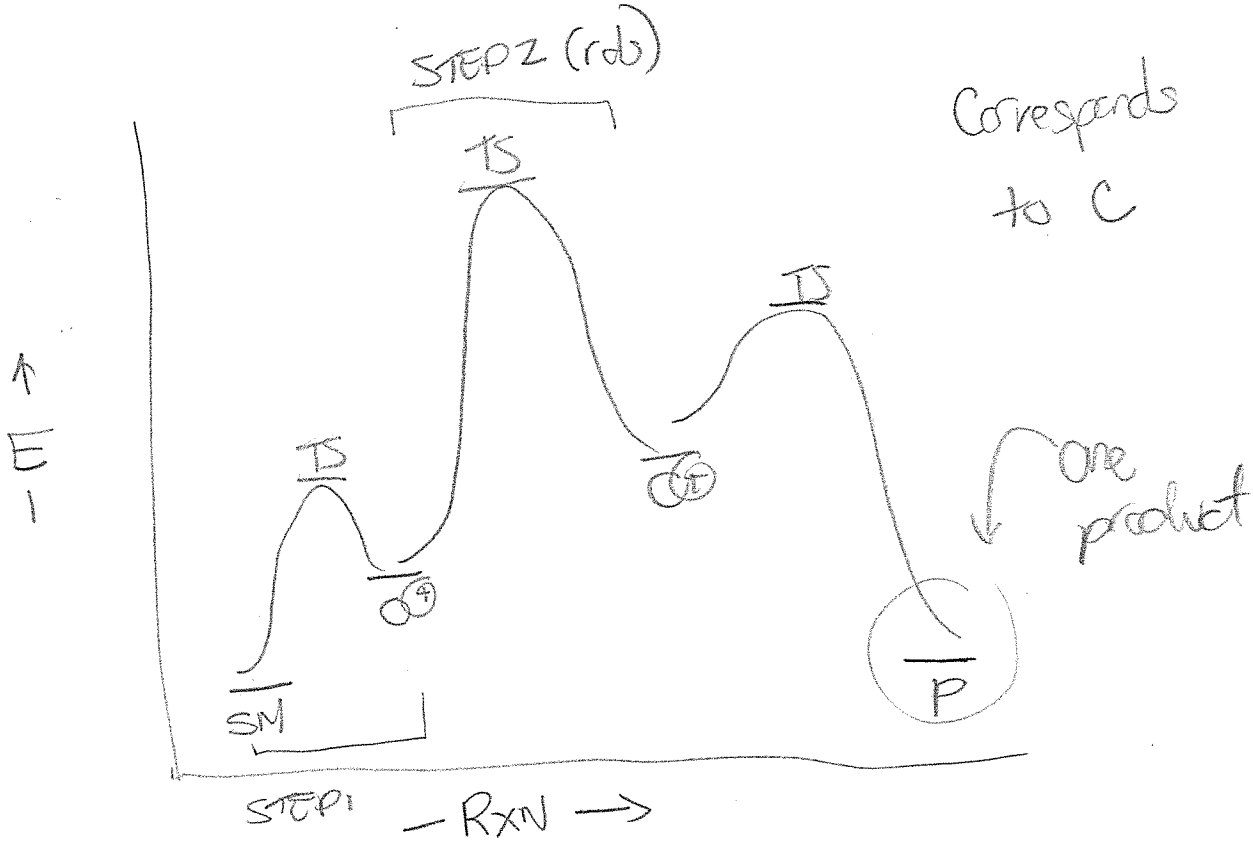


I & II are formed from most stable, equivalently stable 3° carbocations. Both are formed equally fast. (E)

25.

I. 1-METHYLCYCLOPENTANOL + HCl





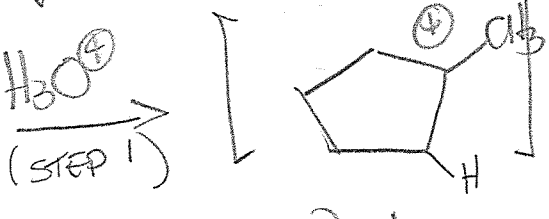
25. (CONT'D)

11.

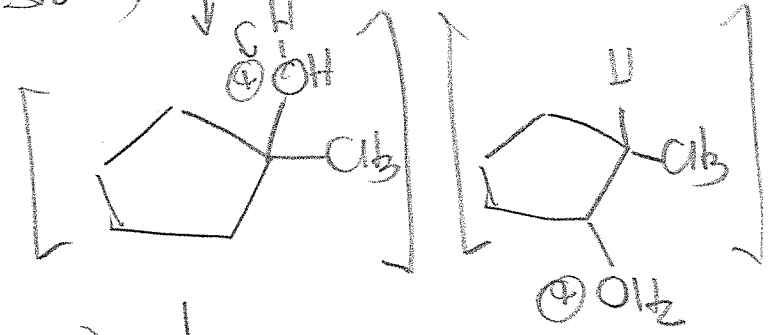
1-methyl cyclopentene

(Electrophilic addition)

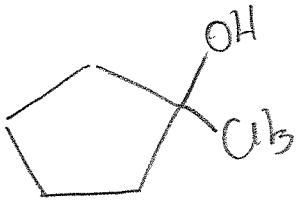
rate determining step

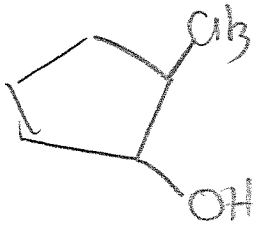


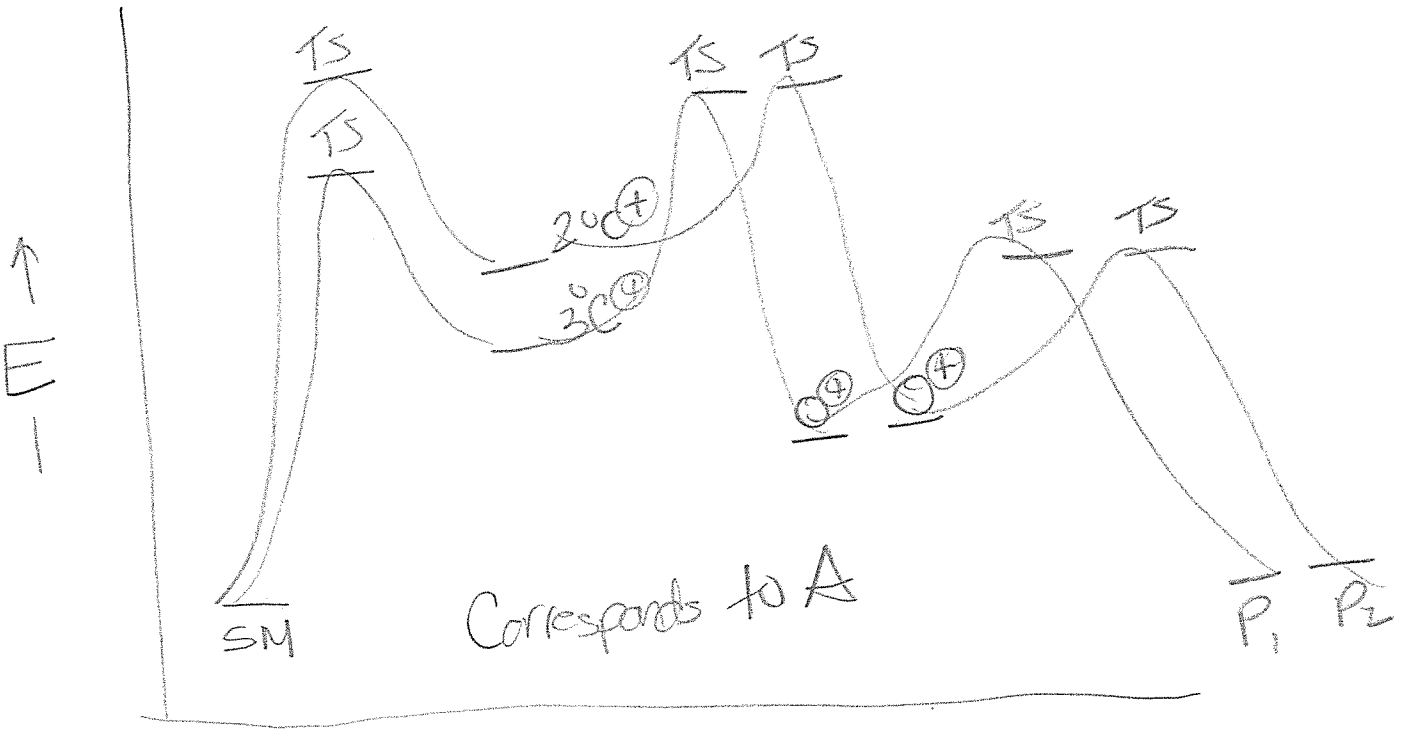
(STEP 2)



(STEP 3)







25. (CONT'D) A = II B = III C = I (E)