Conformational Analysis and Stereoelectronics

Reading: *Lecture notes – Conformational Analysis and Stereoelectronics*
Clayden, Greaves, Wothers & Warren "Organic Chemistry" Chapters 18 & 33 (16 & 32 Ed 2)
Grossel "Alicyclic Chemistry," Oxford Chemistry (Primer 54)
Robinson "Organic Stereochemistry," Oxford Chemistry (Primer 88)
Kirby "Stereoelectronic Effects," Oxford Chemistry (Primer 36)

Topics for notes:

Acyclic Conformation: *The balance of steric, electronic, and stereoelectronic effects in governing conformation of acyclic systems. Looking for the best donor and acceptor orbitals and their effect on conformational control (e.g. anomeric effect). Effect of allylic strain on conformation.*

Ring Conformation: *Different types of strain in rings, conformational effects. Conformations of: 3, 4, 5, 6 membered rings: chair/boat and axial/equatorial relationships, cis and trans decalins; other systems as covered in the lectures. A–values and other conformational effects; Transannular interactions including 1,3-diaxial interactions.*

Conformation and Reactivity: Cyclic Systems: *(Almost all on 6-membered rings). Effects of axial and equatorial conformations on rates of reactions of ring substituents. Stereoselectivity of addition to C=O. Addition to C=C: Furst-Plattner rule in opening of cyclic (6-membered) epoxides and bromonium ions; Neighbouring group participation – net retention of configuration. Transannular reactions in medium rings. Fragmentations and other reactions in bicyclic rings. Non-classical carbocations.*

Stereoelectronic effects in Organic reactions: S_N2 / E2: *Stereoelectronic requirements; principle of microscopic reversibility; effects of neighbouring groups on transition states / reaction rates; Eliminations from alkenes to give alkynes; addition to alkynes.*

Carbonyls / Oxonium ions*: Addition to C=O (Bürgi-Dunitz), formation / hydrolysis of acetals; Felkin-Anh rule (and polar Felkin-Anh variant); Anomeric effect – carbohydrates; Double anomeric effect, conformational preference of spiroacetals; Addition to cyclic oxonium ions.*

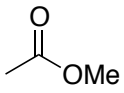
Aldol reactions*: Enolisation selectivity and Zimmermann-Traxler or Open transition states.*

Anchimeric assistance: *Neighbouring group participation (lone pair on adjacent atom, acetate groups); Prevost, Woodward, OsO_4 dihydroxylation methods; Consequences of orbital alignment in cyclic systems; Bredt's rule.*

Alkenes: *Addition to alkenes, allylic strain as a stereocontrolling element.*

Tutorial Problems

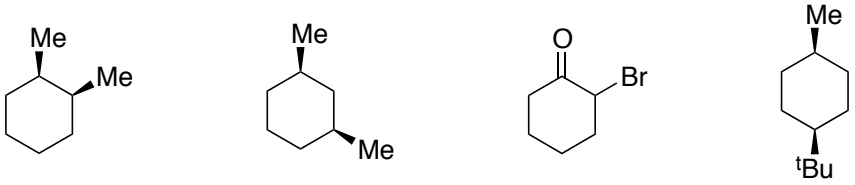
1) Indicate the preferred conformations of the following molecules, giving reasons (i.e. steric, electronic, and stereoelectronic arguments) for your choice.

$CH_3CH_2CH_2CH_3$ $MeOCH_2F$ FCH_2H_2F 

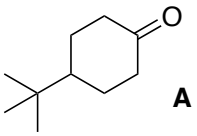
2) Comparison of the infra red spectrum, the bond angles and lengths of cyclopropane with those of ethane, ethene and ethyne, show that the bonding in cyclopropane is most similar to that of ethene. Explain.

3) The *cis*-isomer of methyl 3-methylcyclobutanecarboxylate is more stable that the *trans*-isomer. Explain.

4) Draw clear 3D representations of the following molecules. By consideration of their conformational equilibria, which form will predominate at equilibrium?

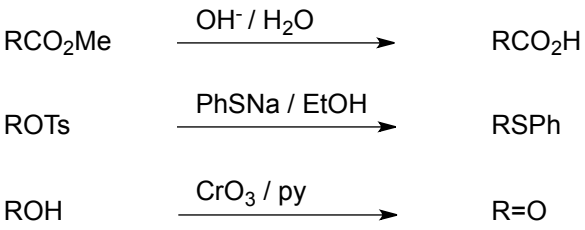


5) Predict and explain the major product of the reduction of the ketone **A** on treatment with: i) $LiB(s\text{-}Bu)_3H$? ii) $NaBH_4$? Iii) Under Meerwein-Ponndorf-Verley reduction conditions?



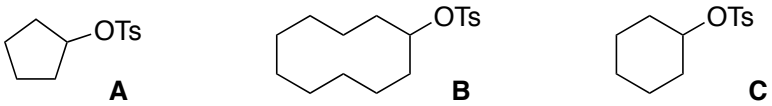
A

6) In the following reactions, R = *cis* or *trans*-4-*tert*-butylcyclohexyl. Indicate the stereochemical course of each reaction, and state which epimer you would expect to react faster.



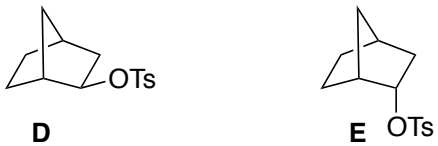
7) Explain the following observations:

a) When tosylates **A**, **B** and **C** are dissolved in acetic acid, **A** and **B** undergo solvolysis faster than **C**.



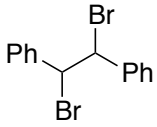
A **B** **C**

b) Acetolysis of **D** is far faster than that of isomer **E**.

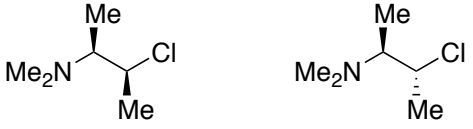


D **E**

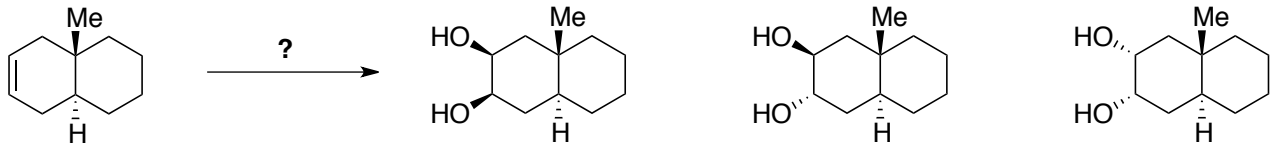
8) Why do the diastereomers of this bromide give different alkene products on treatment with base, and why are the rates of reaction different? Which is faster?



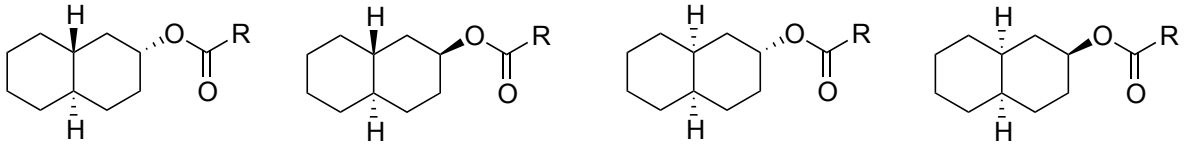
9) One of the following diastereomeric chlorides undergoes racemisation on heating whilst the other is returned unchanged. Explain.



10) How would you convert this alkene into each of the three illustrated diols? (three different reactions are required)



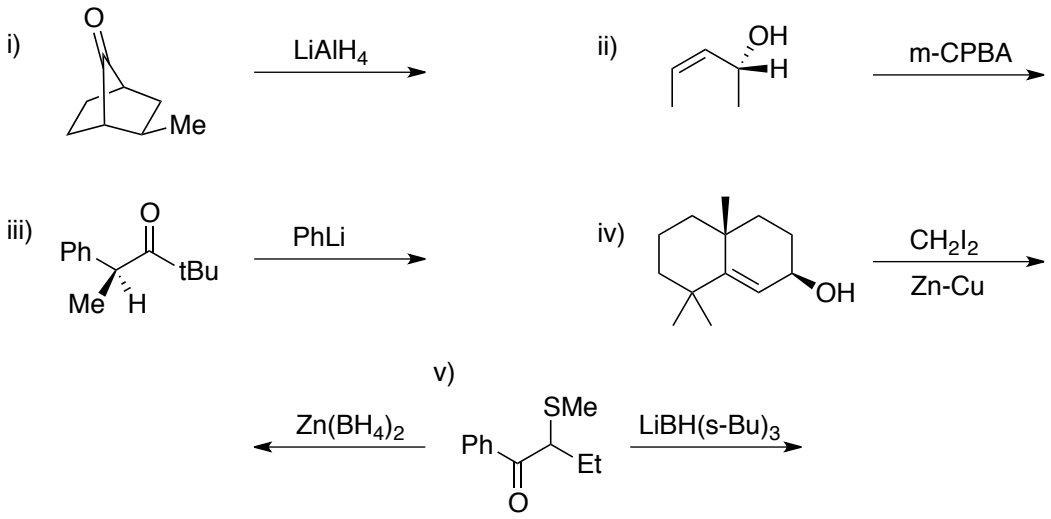
11) Ester **A** hydrolyses in aqueous sodium hydroxide 8 times faster than its epimer **B**. Under the same conditions ester **C** hydrolyses only 1.6 times faster than its epimer **D**. Isomers **A** and **C** hydrolyse at approximately the same rate. Explain these observations.



A **B** **C** **D**

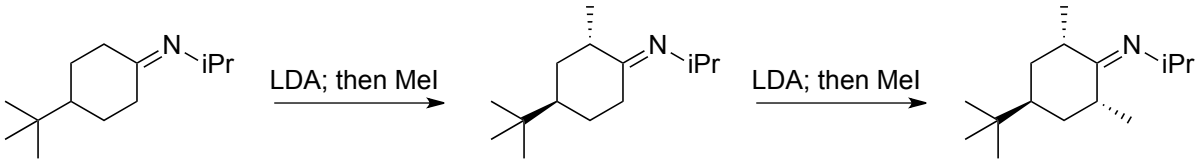
12) Explain, with illustrations, why medium-sized rings (i.e. 8-12) are the most difficult to prepare. and give examples of efficient methods for medium ring synthesis.

13) Predict the products of these reactions:



14) Account (concisely and clearly with mechanism / 3D pictures) for the stereochemical outcome of the following – consider all aspects where stereochemistry might be important!

i)



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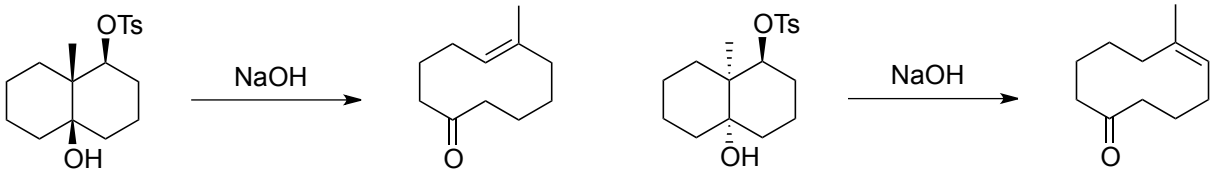

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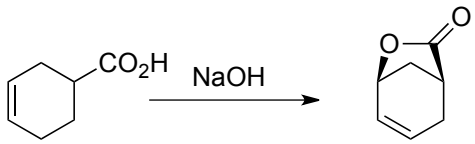

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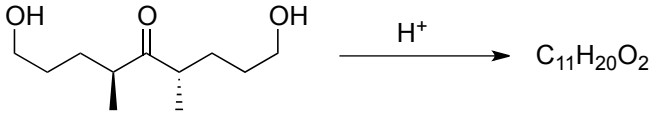
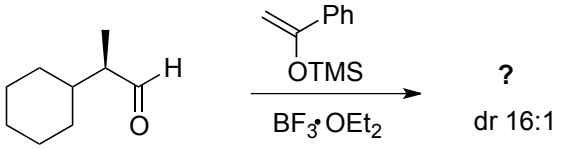


v)



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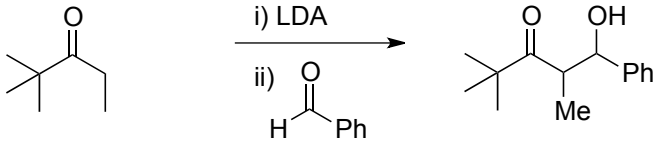

what is the major diastereomer?