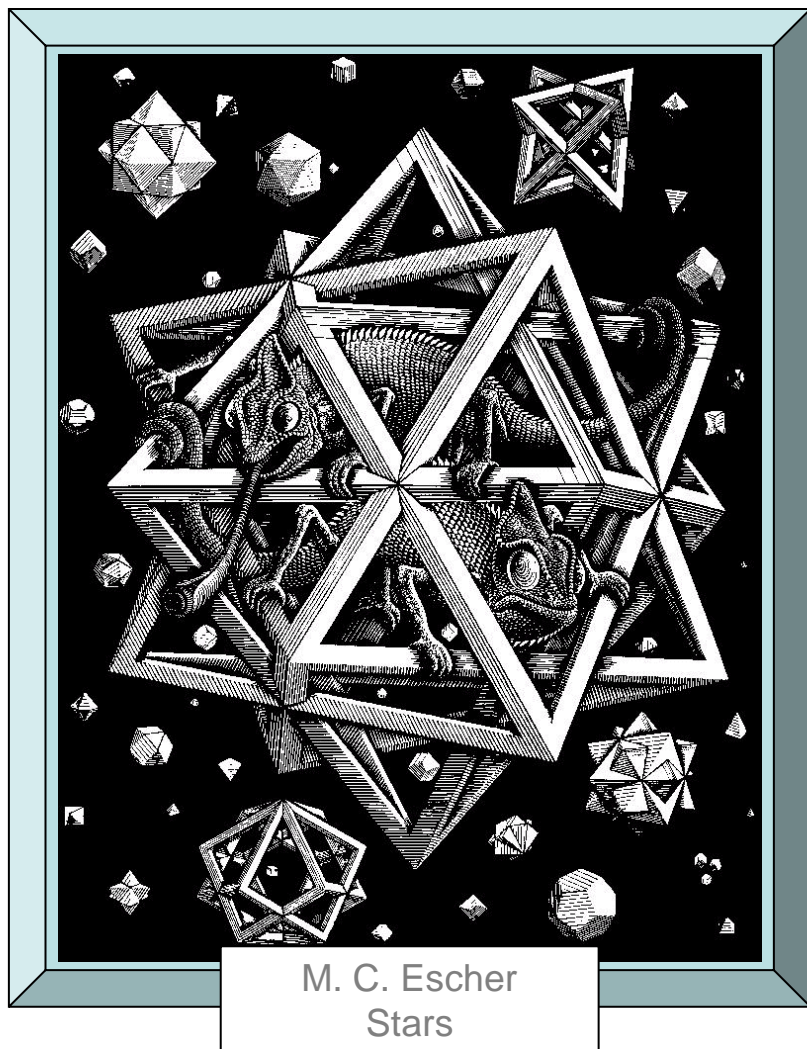


CHEM202

Stereochemistry

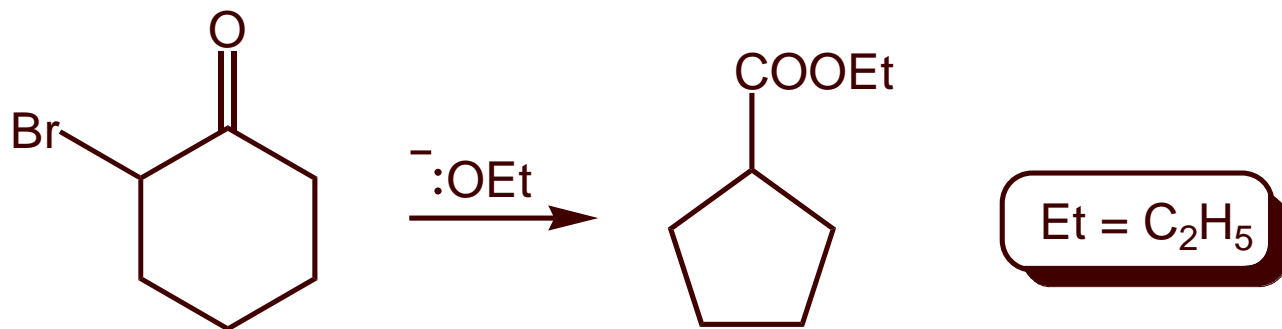
Lecture 4

Anchor Groups and Fused Ring Systems



Favorskii Rearrangement

Suggest a mechanism for the following reaction:

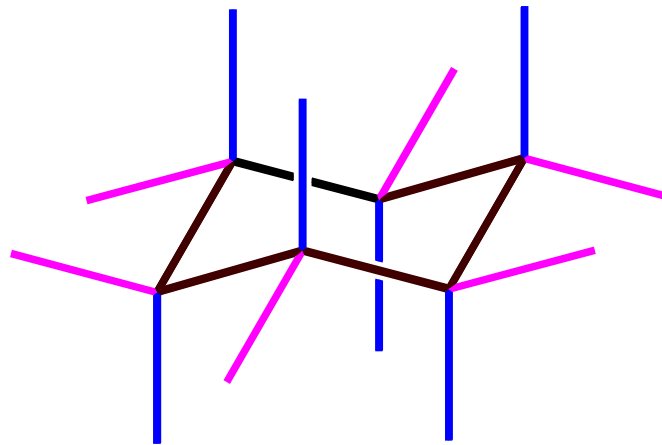


Cyclohexane

- Rapidly interconverting system
- 2 dominant chair conformations

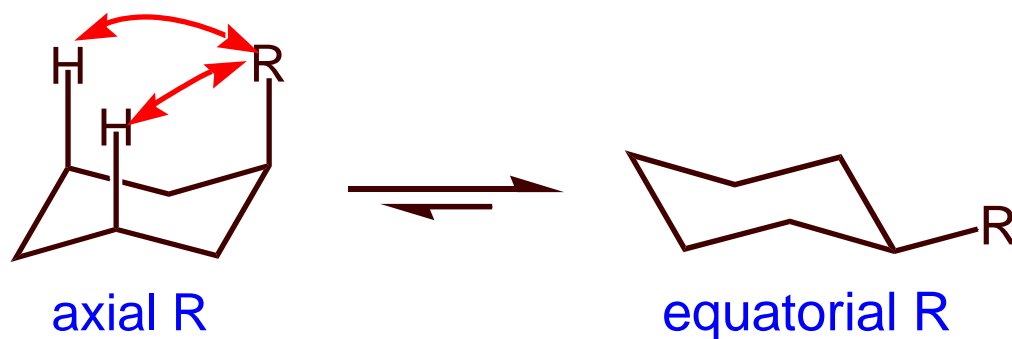


- Various boat and twist forms
- Each chair has two unique sets of C-H bonds:
 - axial
 - equatorial



Monosubstituted Cyclohexanes

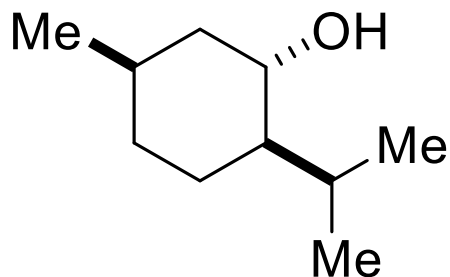
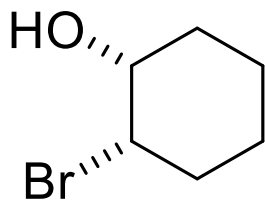
- The 2 chair forms can be distinguished
- That with the equatorial group has fewer steric interactions
- The system rapidly interconverts, with the equatorial form predominating



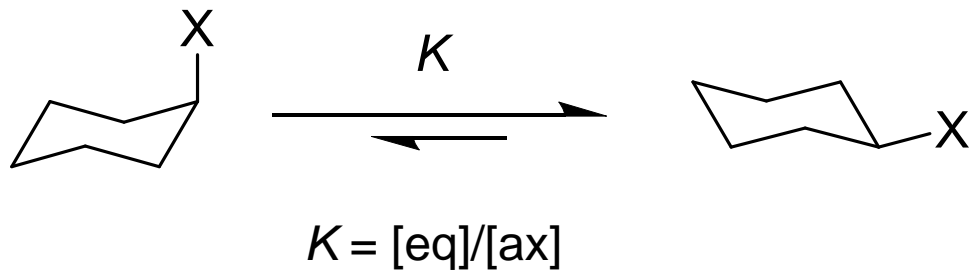
- Analysis of a chemical reaction on a changing system is very difficult - common to lock the conformation in some way:
 - use of anchor groups
 - fused ring systems

Anchor Groups

- An anchor group is a large substituent, such as a *tert*-butyl group, $-\text{C}(\text{CH}_3)_3$
- It restricts the system to the chair form with the big group equatorial
- When *tert*-butyl group is present another smaller group can be forced into an axial orientation



Axial Vs Equatorial (NEF)

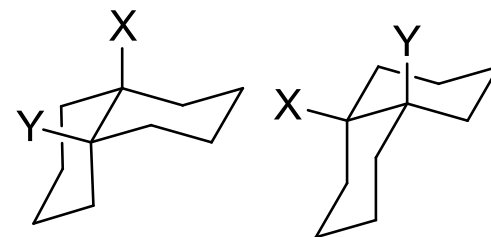


X	K	Energy diff. kJ/mol	% eq
H	1	0	50
OMe	2.7	2.5	73
Me	19	7.3	95
Et	20	7.5	95
<i>i</i> -Pr	42	9.3	98
<i>t</i> -Bu	>3000	>20	>99.9
Ph	110	11.7	99

Fused Cyclohexanes

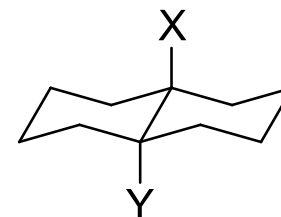
- 2 Rings are *fused* when they share a bond
- 2 Cyclohexane rings can be fused 2 ways – *i.e.* get 2 geometric isomers

- The *cis*-isomer can flip from chair to chair
- The *trans*-isomer cannot flip



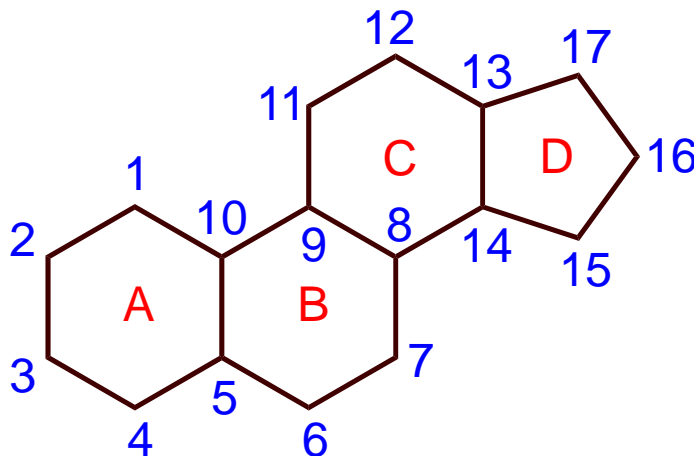
each ring constrains the other so that it cannot orient itself to have 2 bonds axial – the bonding linkage is too short to allow this

- *Trans*-fusion is common in the steroids



Steroids

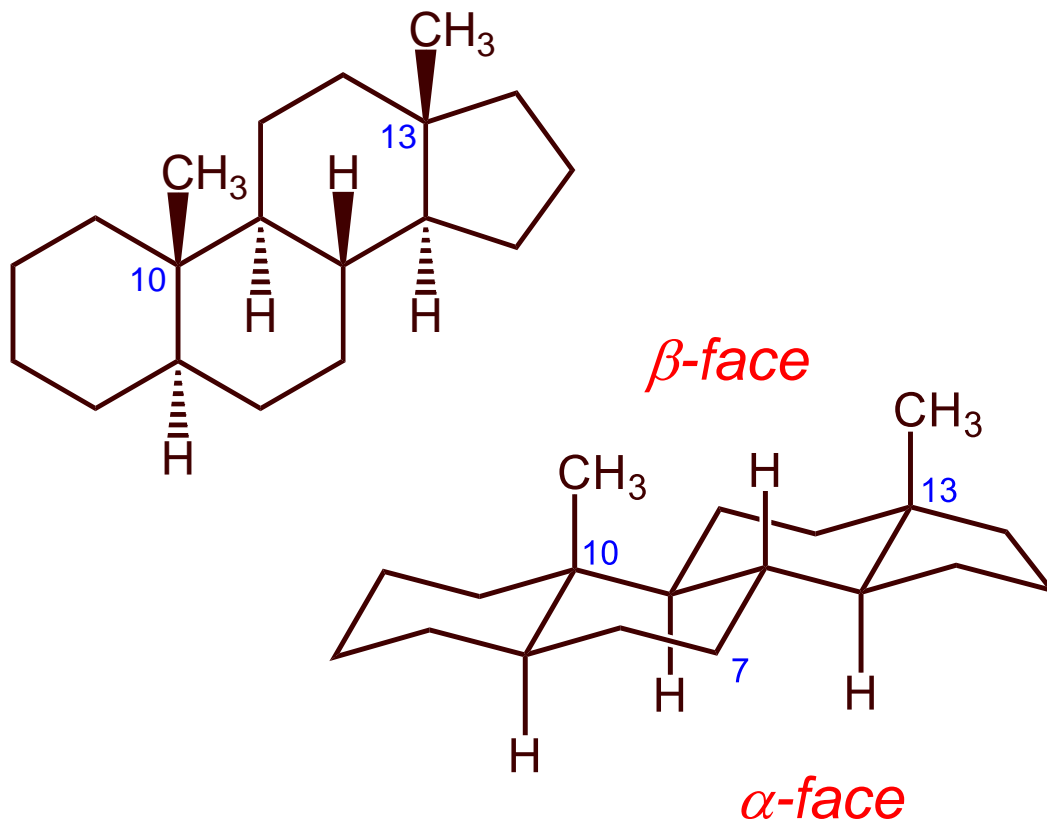
Fused system with 3 x 6-membered rings and 1 x 5-membered ring:



Note:

- Rings are labelled *A*, *B*, *C*, and *D*
- Carbons are labelled by *position numbers*
- Usually have:
 - *trans*-fused rings
 - methyl groupings at C-10 and C-13

Androstane Skeleton



Note:

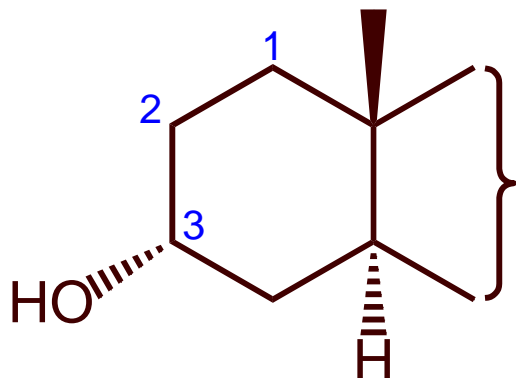
- The ring system is relatively flat
- The side to which methyls point is called the β -face
- The other side is the α -face

Shorthand Conventions

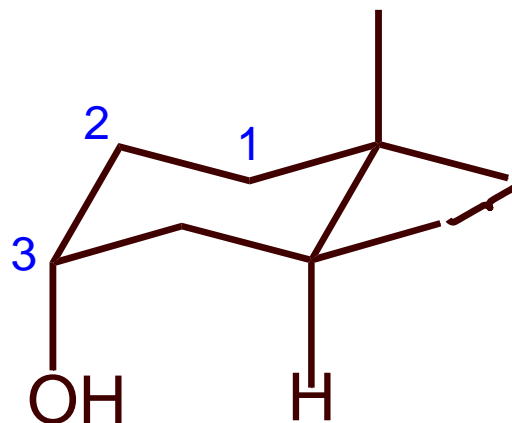
For simplicity, abbreviated structures are often drawn:

- CH_3 groups are represented as lines
- Focus is directed to the part of the molecule of interest by the use of partial structures

e.g. androstan-3 α -ol:

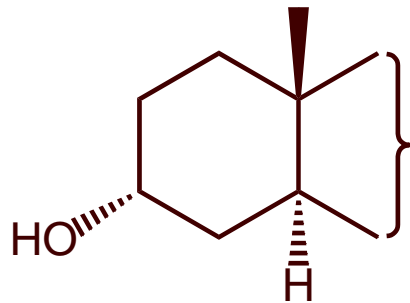


or

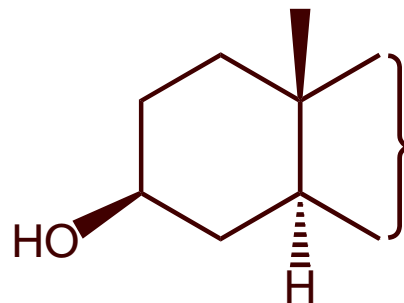


Epimers

- A typical steroid has several chiral carbons – carbons with each of the 4 bonds attached to something different
- *Epimers* are isomers that differ at only one of these chiral carbons
- *E.g.* the 3-epimer of androstan-3 α -ol is androstan-3 β -ol



androstan-3 α -ol

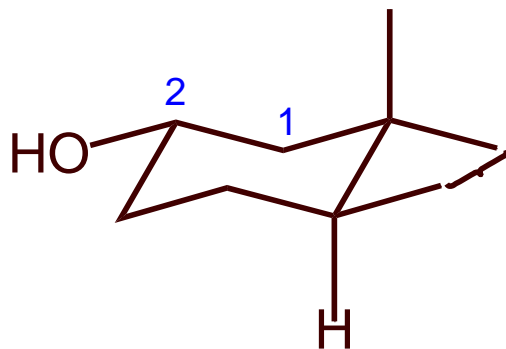


androstan-3 β -ol

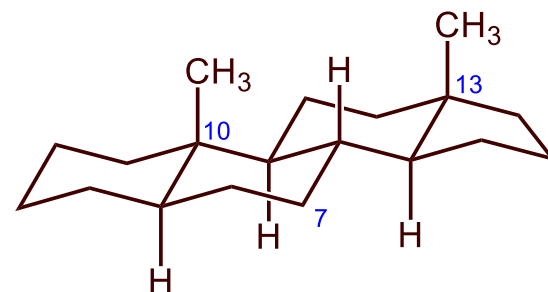
- Epimers are diastereoisomers
 - they are not related as mirror images
 - they have different physical properties

Important – *Trans*-fused Steroids Cannot Flip

- The 6-membered rings of a *trans*-fused steroid are fixed in one chair form
- Therefore it is possible to say with certainty whether an individual grouping is axial or equatorial
- *E.g.* androstan-2 α -ol must have an equatorial OH group



What about 7 α -bromoandrostandane?

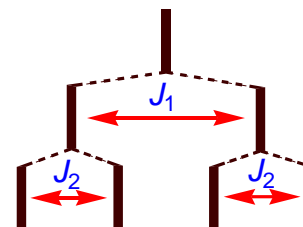


Use of NMR

Two of the features of NMR that provide useful information about the stereochemistry of groups are:

1. Analysis of coupling patterns

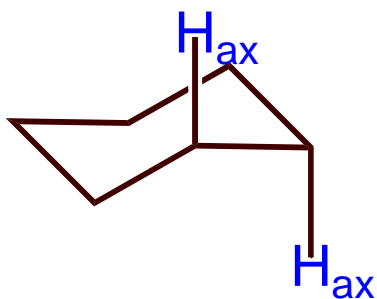
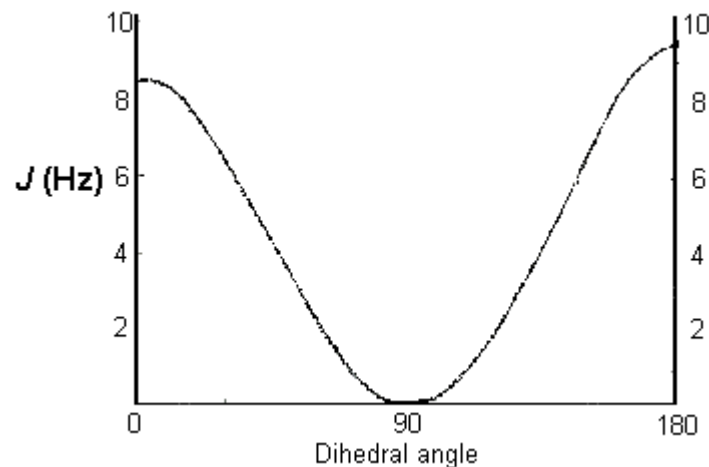
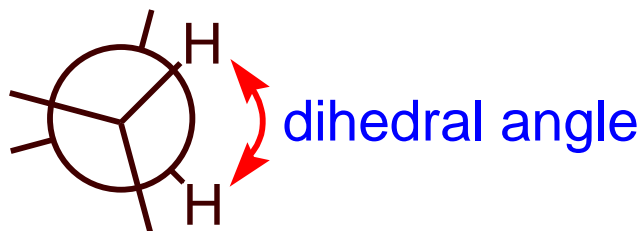
- Note $-\text{CH}(\text{red})-\text{CH}_2-$ gives a triplet in simple compounds ($n+1$ rule)
- In ring systems the two CH_2 signals are often non-equivalent and a double-doublet is observed:



2. Comparison of chemical shifts

1. Analysis of Coupling Patterns

Coupling constant, J , depends on the dihedral angle (**Karplus equation**)

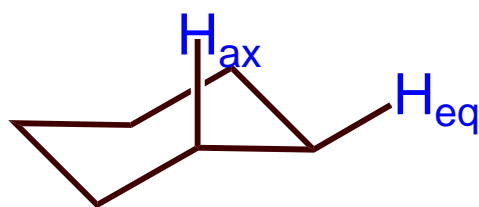


Dihedral angle

180°

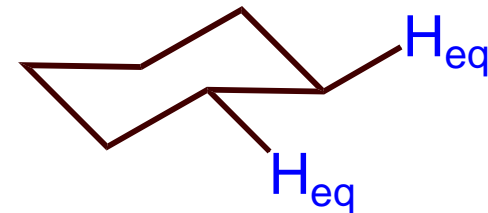
Typical J (Hz)

~10



60°

3-5

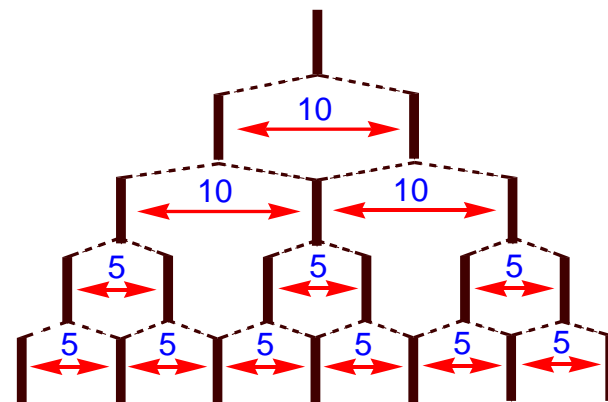
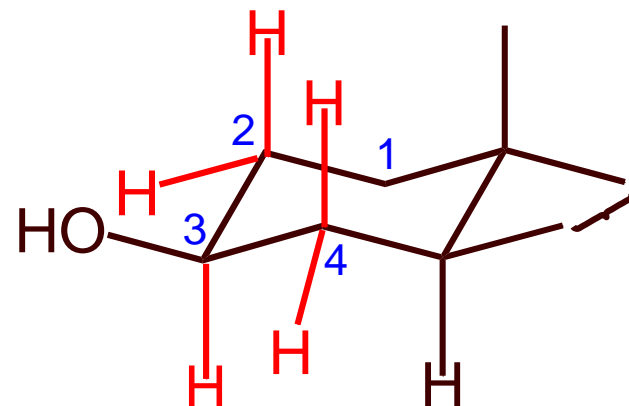


60°

3-5

Androstan-3 β -ol

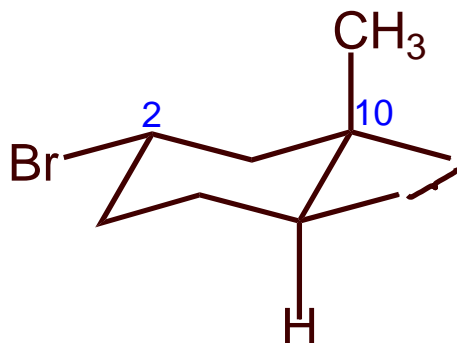
- The OH is equatorial so H-3 α is axial
- Build a splitting tree by considering each coupling in turn
 - $J_{3\alpha,2\beta}$ - axial/axial (~ 10 Hz)
 - $J_{3\alpha,4\beta}$ - axial/axial (~ 10 Hz)
 - $J_{3\alpha,2\alpha}$ - axial/equatorial (~ 5 Hz)
 - $J_{3\alpha,4\alpha}$ - axial/equatorial (~ 5 Hz)
- Predictions:
 - a 7 line pattern
 - a bandwidth ~ 30 Hz



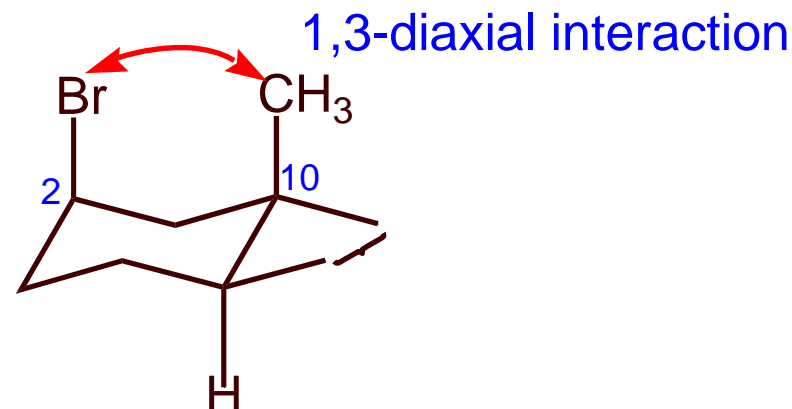
Exercise – the 3 α -epimer exhibits a 5 line pattern with band width ~ 20 Hz. Verify this using J values of 5 Hz for eq/eq and eq/ax couplings

2. Comparison of Chemical Shifts

- 1,3-diaxial interactions are deshielding - result in downfield shifts (away from TMS) - e.g. epimeric 2-bromoandrostanes



2 α -bromoandrostane



2 β -bromoandrostane

- | | |
|--|---|
| <ul style="list-style-type: none">equatorial BrCH₃ signal not deshielded | <ul style="list-style-type: none">axial BrCH₃ signal deshielded |
|--|---|