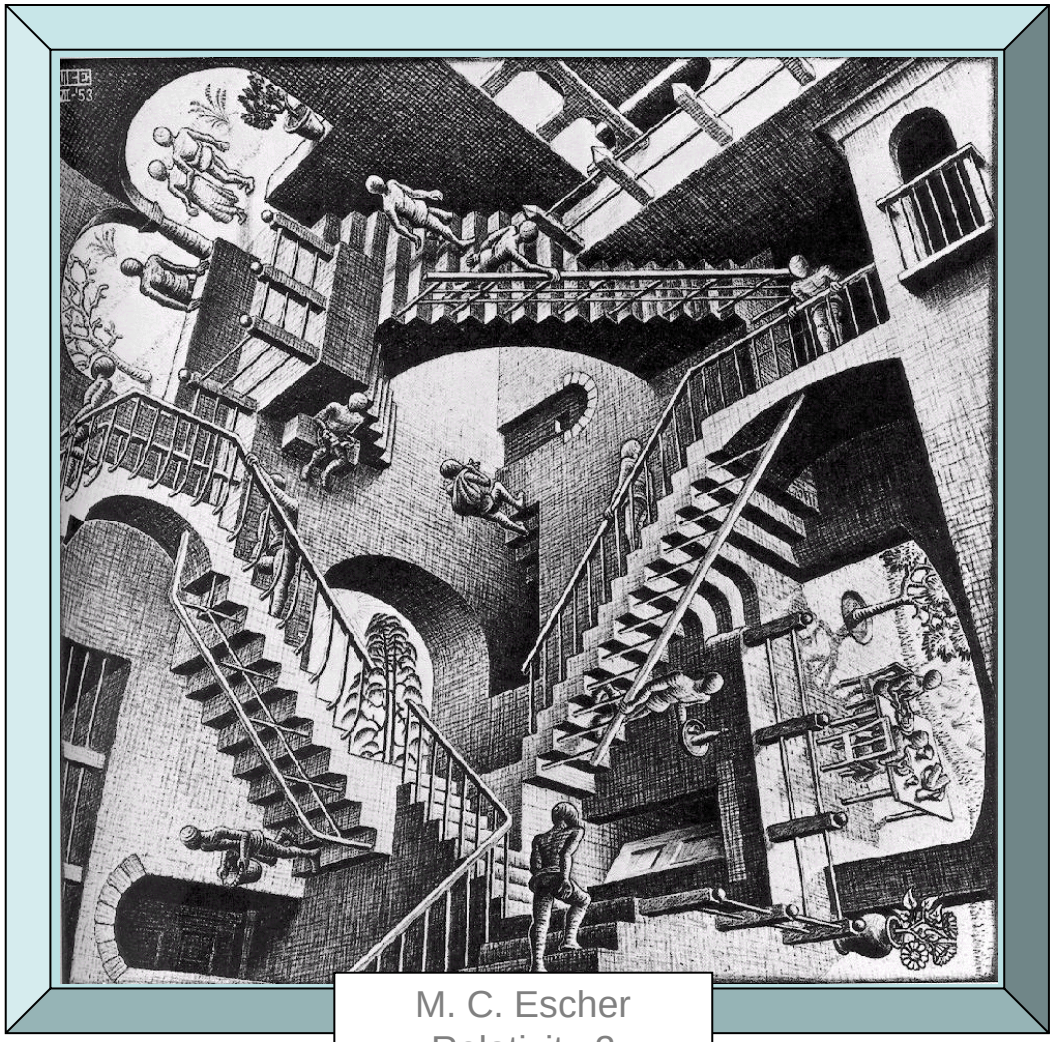
CHEM202

Stereochemistry



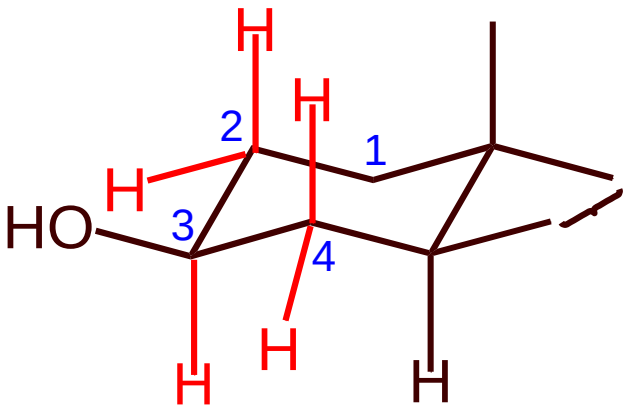
M. C. Escher
Relativity-2

Lecture 5

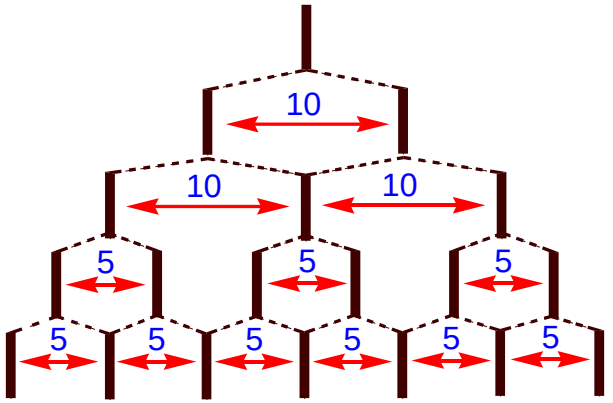
Rigid Transition States

Anti Addition to C=C

Androstan-3β-ol



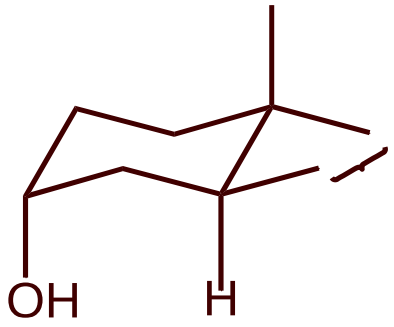
- The OH is equatorial so H-3α is axial
- Build a splitting tree by considering each coupling in turn
  - $J_{3\alpha,2\beta}$ - axial/axial (~10 Hz)
  - $J_{3\alpha,4\beta}$ - axial/axial (~10 Hz)
  - $J_{3\alpha,2\alpha}$ - axial/equatorial (~5 Hz)
  - $J_{3\alpha,4\alpha}$ - axial/equatorial (~5 Hz)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



Exercise – the 3a-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

From Last Lecture

Exercise – the 3a-epimer (of androstan-3b-ol) 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



Stereochemical Controls

Important roles in organic synthesis:

- routes to specific stereoisomers
- ability to perform selective manipulations of sets of identical functional groups

We look at 3 types of reaction:

- those with *rigid transition states* (Lectures 5 & 6)
- those controlled by *ease of access* (Lecture 7)
- those promoted by *steric acceleration* (Lecture 8)

Anti Addition - I

Introduces 2 new groups, one to each face of a double bond - *e.g.* addition of Br_2 (CHEM 191)

Note the formation of a three-membered ring which forms then is re-opened

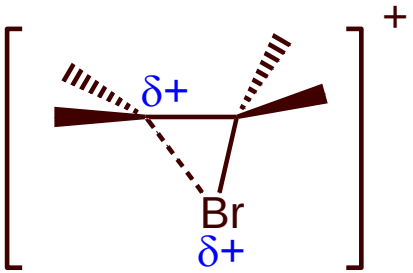
- *cf* example of neighbouring group participation involving S in Lecture 3)

Anti Addition - I I

3 scenarios for the intermediate:

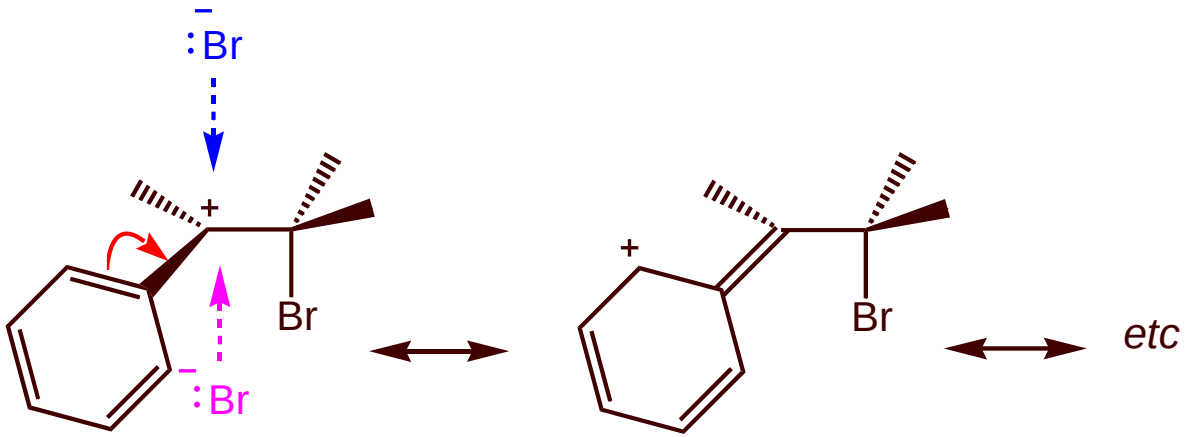
1. Usually has bonding between Br and the two C (*bromonium ion*)
   - the incoming Br:⁻ is forced to attack from other side (*anti*)

2. Sometimes unsymmetrical
   - the weaker bond is to the C that can best accommodate δ+
   - Br:⁻ usually attacks the more +ve C
   - however, attack may be the other way round if this C is sterically hindered
   - addition is still *anti*



Anti Addition - III

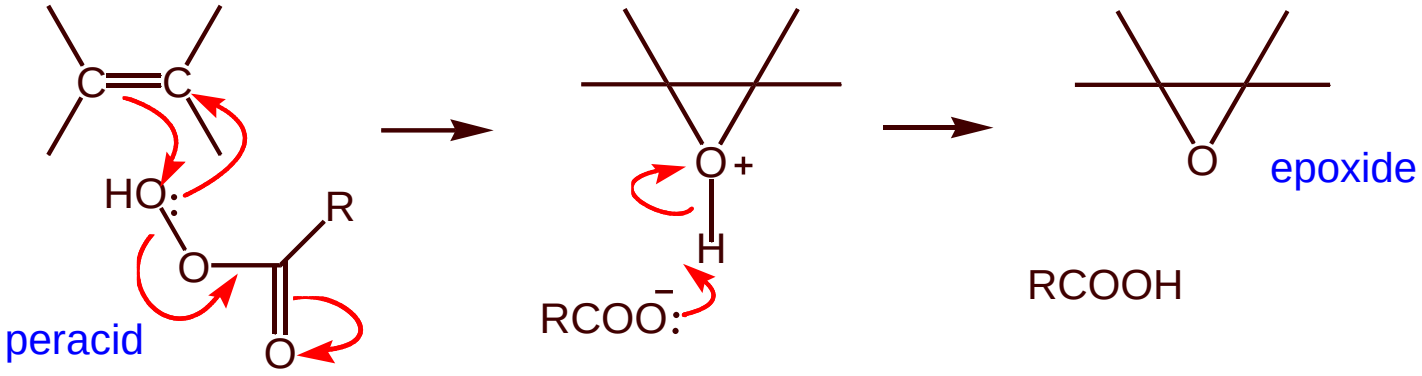
3. If the +ve centre is highly stabilised, the intermediate may be a true *carbocation*
   - this may be attacked from either side (*cf* S_N1) – *i.e.* no longer *anti*



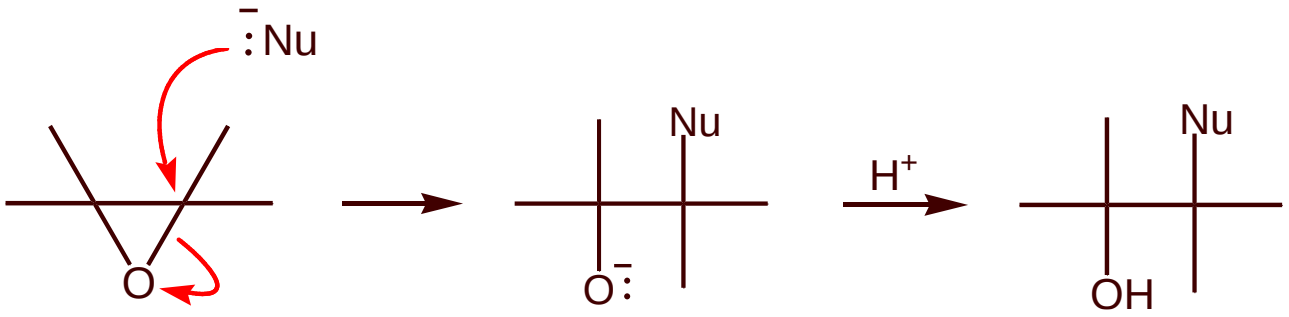
Epoxidation / Epoxide Opening

Epoxidation/opening sequence has same overall stereochemical consequences:

Step 1 - epoxidation:



Step 2 - nucleophilic opening:



Stereochemical Analysis

Anti additions proceed through two stages:

1. Formation of a 3-membered ring intermediate

2. Opening of the intermediate by a nucleophile

Three Questions:

A. In 1, is there preferential attack from one face of the C=C?

B. If both sides of the C=C are attacked, do the 2 routes give different stereoisomers?

C. In 2, the 3-membered ring has 2 sites for attack. Is one preferred?

A. In 1, is there preferential attack from one face of the C=C?

- Usually there is no distinction - products resulting from attack at either side are formed in equal amounts
- But, some molecules show *facial selectivity*. Steroidal alkenes give mainly α-face attack

B. If both sides of the C=C are attacked, do the 2 routes give different stereoisomers?

- There will be no stereoisomers if the intermediate has a plane of symmetry

C. In 2, the 3-membered ring has 2 sites for attack. Is one preferred?

- Openings may be S_N2 like:
  - The preferred site is the least sterically crowded – *i.e.* $1^o > 2^o > 3^o$
- If there is some degree of S_N1 character:
  - The preferred site is the one which best accommodates a +ve charge – *i.e.* $3^o > 2^o > 1^o$

Bromination of (*E*)-2-butene

A. No distinction between the 2 faces of the alkene - consider attack from both sides

B. The 3-membered ring intermediate has no plane of symmetry - 2 distinct stereoisomers

C. There is no difference between the 2 possible sites for nucleophilic attack in each intermediate

- Must explore attack at each
- All 4 attack routes are equally likely, but all lead to one isomer, the *meso* compound

Bromination of (*Z*)-2-butene

A. Again, no distinction between the 2 faces of the alkene - consider attack from both sides

B. The 3-membered ring intermediate has a plane of symmetry. There is only one species for the nucleophile to attack

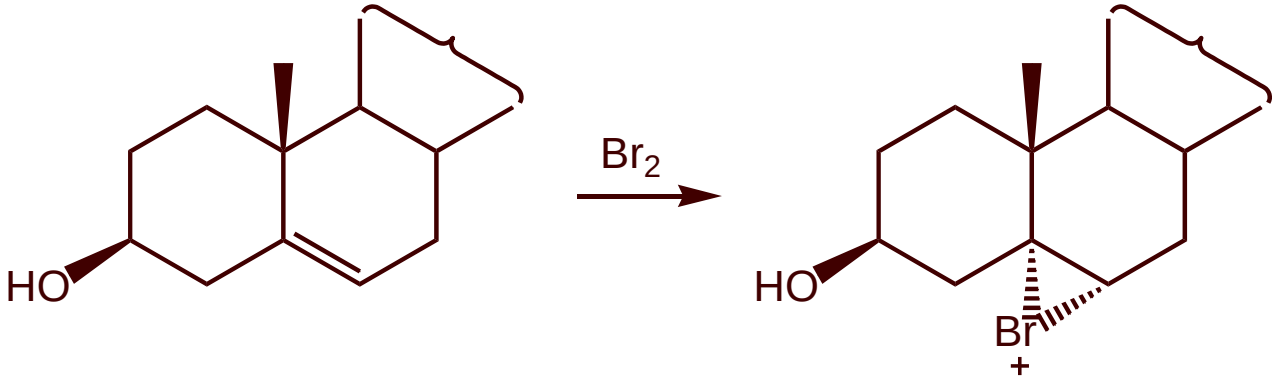
C. There is no difference between the 2 possible sites for nucleophilic attack in the intermediate

  – One attack leads to one compound, the other to its enantiomer - *i.e.* get a racemic mixture (Verify this for yourself)

Addition in Steroids

In a steroid:

- Have facial selectivity
- Initial attack is preferentially on the least hindered (α-face) of the molecule
- With cholesterol:



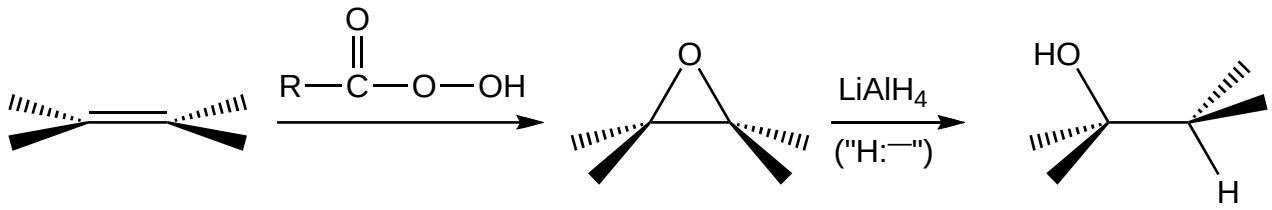
Question:

"Does Br:$^-$ attack at C-5, the centre which can best accommodate δ+ (S_N1 like), or does it attack at C-6, the centre which is less sterically hindered (S_N2 like)?"

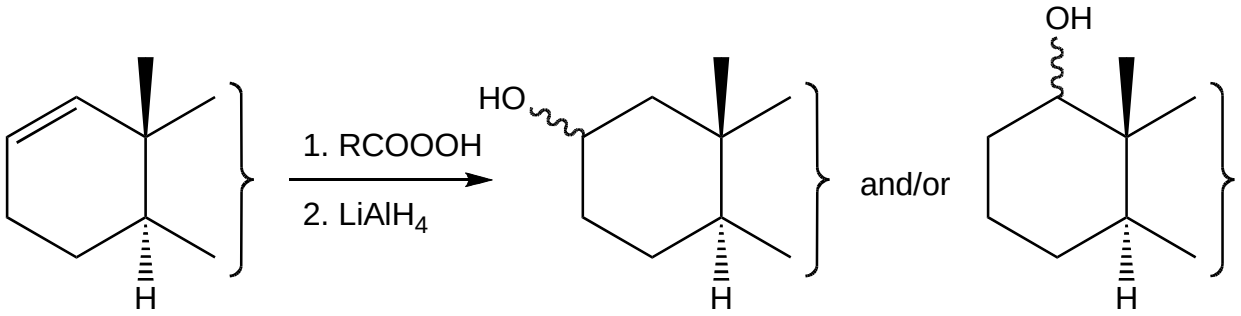
See Structure Elucidation Problem C

Lecture Problem

An alkene may be converted into an alcohol with overall *anti* addition of "H" and "OH":



With androst-1-ene, the possible alcohol products (stereochemistry not shown) are:



- Draw chair structures for the two possible alcohols showing the orientation of the OH in each case
- Explain how NMR could be used to distinguish these