

CHEM202

Stereochemistry

Lecture 3

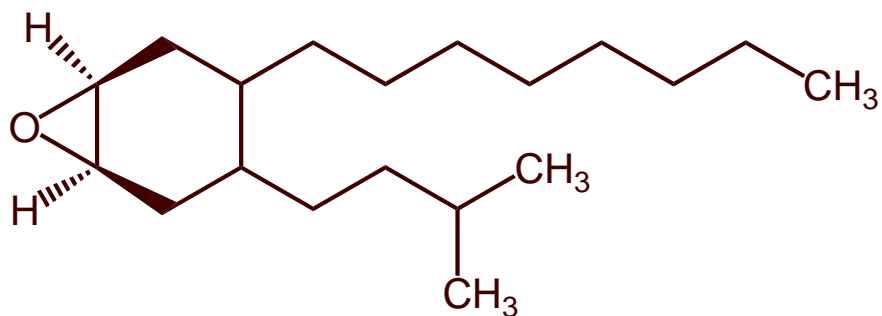
Cyclisation Reactions

Part 2

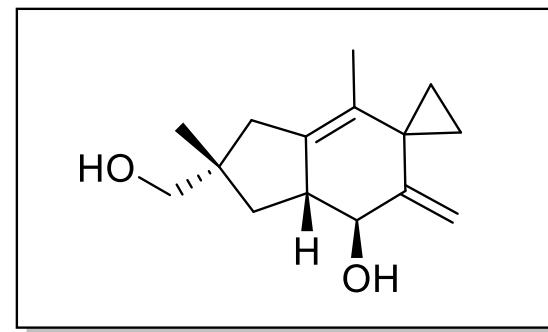


3-Membered Rings in Natural Products

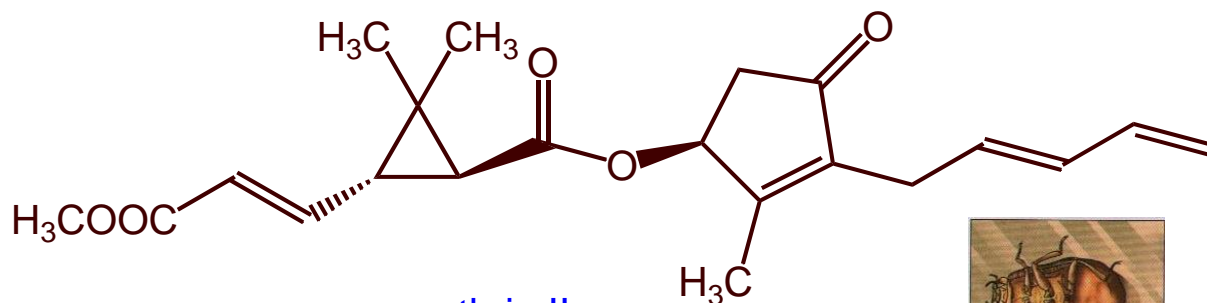
Despite the ring strain, compounds containing 3-membered rings are quite common in nature



disparlure
gypsy moth sex pheremone



Dalmatian Pyrethrum *Tanacetum cinerariifolium*

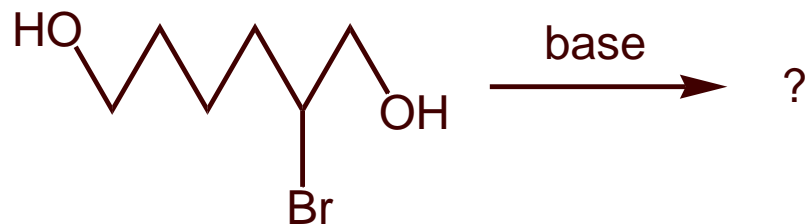


pyrethrin II
natural insecticide



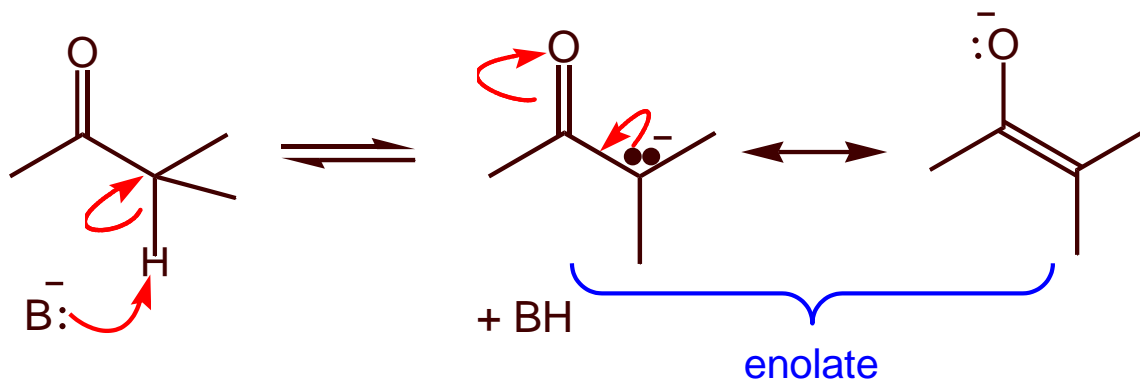
Lecture Problem

Predict the structure of the major product of the following:



Enolate Alkylation

- H atoms adjacent to C=O groupings are weakly acidic - can be removed by bases



- The resulting *enolate* species are good nucleophiles
- Reaction with alkyl halides in S_N reactions forms C-C bonds
- An example.....

Carbanion Cyclizations - 1

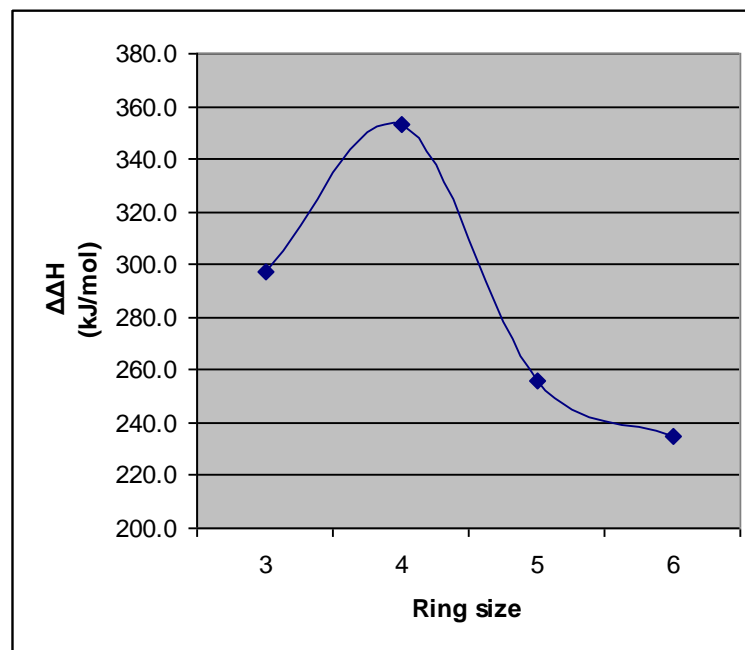
- Internal S_N reactions can be used to create rings of C atoms
- Halide nucleophiles are unable to cleave a C-C bond – *i.e.* the reactions are not reversible
- Data similar to those for formation of cyclic ethers (Lecture 2):

n =	Ring size	k_{rel}
1	3	>600000
2	4	1
3	5	6200
4	6	370

Carbanion Cyclizations - 2

- Difference in ΔH_f (ΔH_f (ring) - ΔH_f (acyclic)) calculated by molecular mechanics:

Ring Size	$\Delta\Delta H_f$ / kJ mol^{-1}
3	297.6
4	353.4
5	255.7
6	234.8



- Ring strain preference $6 > 5 > 3 > 4$ (observed $3 > 5 > 6 > 4$)
- Again, probability factors mean that smaller rings form faster than expected on the basis of ring strain

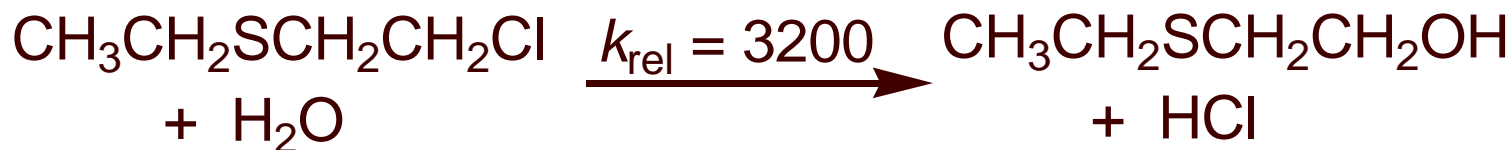
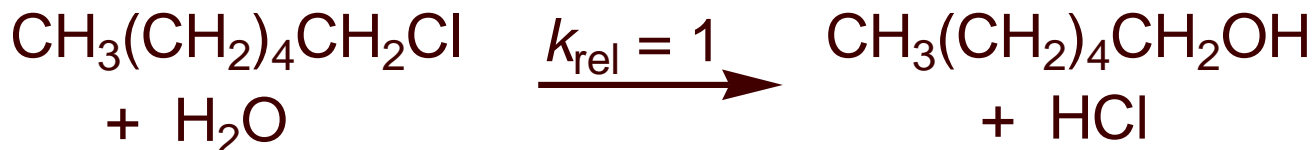
Neighbouring Group Participation

3-membered rings:

- Form very rapidly
- If formed non-reversibly they remain intact
- Do they form in reversible reactions?
 - Yes, but they re-open rapidly to relieve ring strain
 - Formation and re-opening of 3-membered rings can cause some unexpected effects

Rate Enhancement

- Consider 2 similar S_N reactions at 100 °C:



- The 1st is a simple S_N process – Cl[–] is displaced by H₂O
- The 2nd is very much faster - a different mechanism?
 - S atom is involved in internal displacement ⇒ 3-membered ring
 - This process is assisted by favourable probability factors
 - The strained 3-membered ring intermediate is highly susceptible to nucleophilic opening
 - The most abundant nucleophile is H₂O

Distinguishing Between the Two Mechanisms

Use $\text{CH}_3\text{-CH}_2\text{-S-CH}_2\text{-CD}_2\text{-Cl}$ – how?

Analysis of the results by ^1H NMR

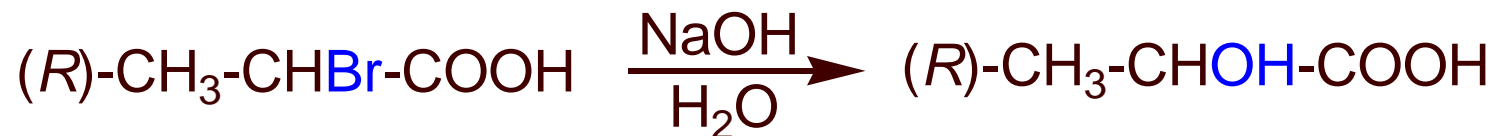
- Recall that ROH NMR signal disappears when sample is treated with D_2O

$\text{D} = ^2\text{H}$

<https://www.youtube.com/watch?v=lu48zS6ndtI>

Double Inversion

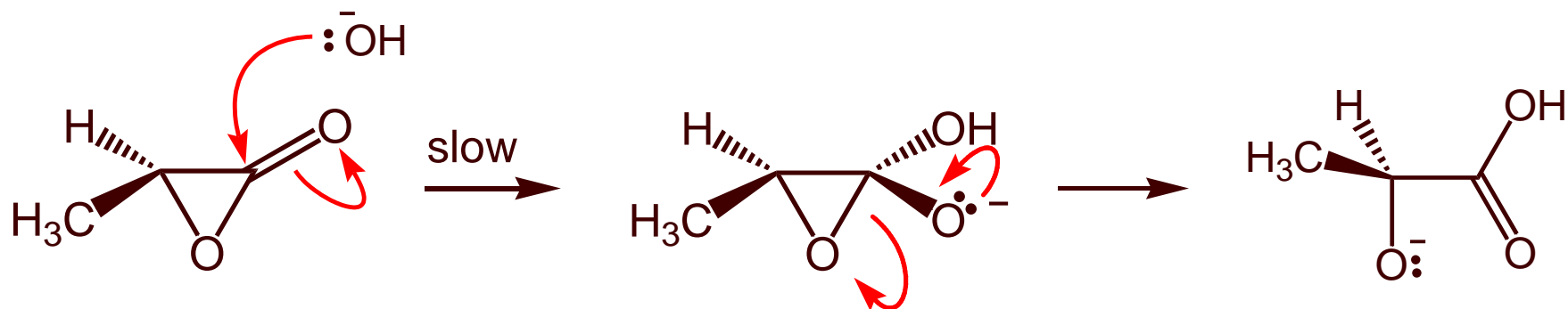
- A substitution reaction with overall retention of stereochemistry:



- S_N2 reaction would give the (*S*)-isomer (inversion)
- S_N1 reaction would give both the (*R*) and (*S*)-products (attack from either face of the planar carbocation)
- Explanation - 2 inversions involved - leads to overall retention
- 1st step - rapid formation of a 3-membered ring
inverts at the chiral carbon
 - 2nd step – the nucleophile opens the strained ring
the product has same bond arrangement as the original reactant

An Unusual Reaction for an Ester

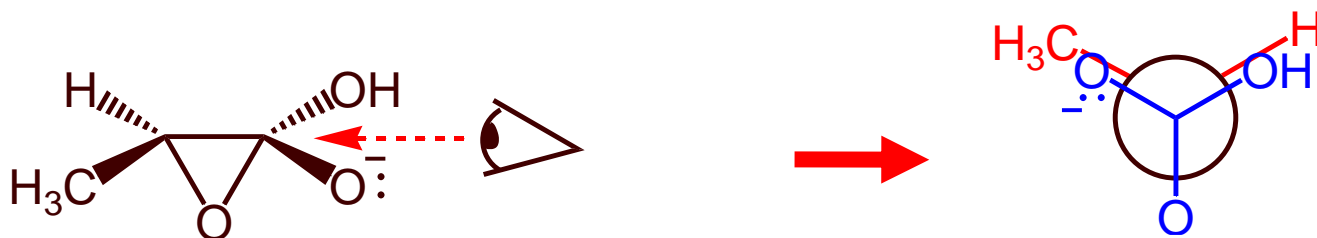
The intermediate is an ester which would normally react by OH^- attack at the $\text{C}=\text{O}$ (CHEM 191):



This would give the (*S*)-isomer.

Why does this not happen?

- The first step does not relieve the ring strain.
- The intermediate has bad eclipsing interactions:



Favorskii Rearrangement

Suggest a mechanism for the following reaction:

