Suggested solutions for Chapter 36

**PROBLEM 1**
Rearrangements by numbers: just draw a mechanism for each reaction.

![Chemical reactions and mechanisms](image)

**Purpose of the problem**
This problem is just to help you acquire the skill of tracking down rearrangements by numbering (arbitrarily) the atoms in the starting material and working out where they've gone in the product.

**Suggested solution**
The first reaction is the preparation of Corey's 'OBO' protecting group for carboxylic acids. The Lewis acid complexes one of the oxygen atoms and all the atoms of the starting material survive in the product. Atoms 3 and 5 are easy to identify in the product and it doesn't much matter which of the CH₂ groups you label 1, 2, and 4. Of course you may use a completely different numbering system and that's fine. The dotted lines show which new bonds are made and which old bonds are broken.
There is more than one reasonable mechanism: here are two possibilities, the second being perhaps the better.

The second reaction is even easier to work out. Atoms 2 and 3 are easy to find and they identify 1 and 4 in the product.

As the compounds are acetals we must use oxonium ions and not $S_N2$ reactions. Loss of BF$_3$ and rotation of the last intermediate gives the product.

The third reaction involves a cyclization. Atoms 1 and 7 clearly make the new bond and the rest of the atoms fit into place except that the bromine has gone and the alkene has moved from 7/8 to 8/9. Zinc inserts oxidatively into the C–Br bond and the mechanism follows from the nucleophilic nature of the organometallic compound.
PROBLEM 2

Explain this series of reactions.

Purpose of the problem

Working out the stereochemistry and mechanism of the Beckmann rearrangement.

Suggested solution

The first reaction forms the oxime by the usual mechanism (chapter 11). This reaction is under thermodynamic control so the OH group will bend away from the aryl substituent. Then we have the Beckmann rearrangement itself (p.958). The group anti to the OH group migrates from C to N and that gives the product after rehydration and adjustment of protons.

PROBLEM 3
Draw mechanisms for the reactions and structures for the intermediates. Explain the stereochemistry, especially of the reactions involving boron. Why was 9-BBN chosen as the hydroborating agent?

![Mechanisms and structures for the reactions and intermediates.](image)

Purpose of the problem
Rearrangements involving boron and a ring-closing rearrangement of sorts plus stereochemistry.

Suggested solution
The starting material is symmetrical so it doesn’t matter which face of which alkene you attack. The only important things are that boron binds to the more nucleophilic end of the alkene and that R₂B and H are added cis. Alkaline H₂O₂ makes the hydroperoxide anion (HOO⁻) which attacks boron.

The mesylate cyclises in aqueous base. The more nucleophilic end of the remaining alkene displaces the mesylate with inversion to make the cis ring junction much preferred by the 5,5 fused system. Water adds to the tertiary cation to give the next intermediate.
Elimination of the alcohol (E1 of course as it is tertiary) gives the alkene and a repeat of the hydroboration from the outside (convex face) of the folded molecule gives the final alcohol with five new stereogenic centres.

9-BBN was chosen because it is very large and reinforces the natural electronic preference of boron to bind to the less substituted end of the alkene with an extra steric effect. It also has bridgehead atoms bound to boron and they make poor migrating groups, forcing the migration of the third B substituent.

**PROBLEM 4**
It is very difficult to prepare three-membered lactones. One attempted preparation, by the epoxidation of di-\(t\)-butyl ketone, gave an unstable compound with an IR stretch at 1900 cm\(^{-1}\). This compound decomposed rapidly to a four-membered ring lactone that could be securely identified. Do you think they made the three-membered ring?

**Purpose of the problem**
Rearrangements as a proof of structure?
Suggested solution

The expected three-membered lactone would have a very high carbonyl stretching frequency because of ring strain. Three-membered cyclic ketones have carbonyl stretches at about 1815 cm⁻¹ and lactones have higher frequencies than ketones. So it might be the lactone. If it is, we should find a mechanism for the ring expansion to the four-membered lactone isolated. There is a good mechanism involving migration of a methyl group from one of the t-butyl groups. The general conclusion is that R. Wheeland and P. D. Bartlett did indeed make the first α-lactone.

PROBLEM 5
Suggest a mechanism for this rearrangement.

Purpose of the problem
Working out the mechanism of a new rearrangement.

Suggested solution
The starting material is an enamine and will react with bromine in the manner of an enol. Addition of hydroxide gives the starting material for the rearrangement. Notice that the nitrogen atom migrates rather than the carbon atom and this suggests that it does so by participation. If you numbered the atoms you would have found that the gem-dimethyl group and the nitrogen atom give the answer away immediately.
**PROBLEM 6**

A single enantiomer of the epoxide below rearranges with Lewis acid catalysis to give a single enantiomer of the product. Suggest a mechanism and comment on the stereochemistry.

![Chemical structure](image)

**Purpose of the problem**

An unusual group migrates and stereochemistry gives a clue to mechanism.

**Suggested solution**

The mechanism for the reaction must involve Lewis acid complexation of the epoxide oxygen atom, cation formation, and migration of CO$_2$Et. This last point may surprise you but inspection of the product shows that CO$_2$Et is indeed bonded to the other carbon of what was the epoxide.

![Mechanism](image)

Although something like this must happen, our mechanism raises as many questions as it answers:

- Why does that bond of the epoxide open? *Answer.* Because the tertiary benzylic cation is much more stable than a secondary cation with a CO$_2$Et substituent.
- Why does CO$_2$Et migrate rather than the H atom? *Answer.* For the same reason! If the H atom migrates, the product would be
a cation (or at least a partial positive charge would appear in the transition state) next to the CO$_2$Et group.

- Surely the carbocation intermediate is planar and the product would be racemic? Answer. This was the purpose of the investigation. One chiral centre is lost in the reaction so only absolute stereochemistry is relevant. One explanation is that the cation is short-lived and that bond rotation is fast in the direction shown (the CO$_2$Et group is already down and has to rotate by only 30° to get to the right position for migration). The other is that migration is concerted with epoxide opening. This looks unlikely as the overlap is poor.

![Reaction Mechanism]

**PROBLEM 7**
The ‘pinacol’ dimer of cyclobutanone rearranges with expansion of one of the rings in acid solution to give a cyclopentanone fused spiro to the remaining four-membered ring. Draw a mechanism for this reaction. Reduction of the ketone gives an alcohol that rearranges to a bicyclic alkene also in acid. Suggest a mechanism for this reaction and suggest why the rearrangements happen.

![Problem 7 Mechanism]

**Purpose of the problem**
An illustration of the easy rearrangement of four-membered rings to form five-membered rings.

**Suggested solution**
The first reaction is a simple pinacol rearrangement. The diol is symmetrical so protonation of either alcohol and migration of either C–C bond give the product.
Reduction to the alcohol is trivial and then acid treatment allows the loss of water and ring expansion of the remaining four-membered ring. You may well have drawn this as a stepwise process. Elimination gives the most substituted alkene. Both rearrangements occur very easily because of the relief of strain in going from a four- to a five-membered ring.

**PROBLEM 8**
Give the products of Baeyer-Villiger rearrangements on these compounds, with reasons.

**Purpose of the problem**
Prediction in rearrangements is as important as elsewhere and the Baeyer-Villiger is one of the more predictable rearrangements.

**Suggested solution**
There are a few minor traps here that we’re sure you’ve avoided. The first compound has two carbonyl groups but esters don’t do the Baeyer-Villiger rearrangement so only the ketone reacts. The more substituted carbon migrates with retention of configuration. The aldehyde rearranges with migration of the benzene ring in preference to the hydrogen atom. The last compound is $C_2$ symmetric so it doesn’t matter which group you migrate as long as you ensure retention of configuration. Take care when drawing the product as the migrating group has to be drawn the other way up.
**PROBLEM 9**

Suggest mechanisms for these rearrangements, explaining the stereochemistry in the second reaction.

**Purpose of the problem**

Unravelling one rearrangement after another with some stereochemistry.

**Suggested solution**

The first reaction is a simple ring expansion. The amine is not involved, presumably because it is fully protonated. The final loss of proton might be concerted with the migration as this would help explain the position of the alkene in the product.

The second reaction starts with bromination of the alkene and interception of the bromonium ion by the amine. Only when bromine adds to the opposite face of the alkene can the amine cyclize so this reaction resembles iodolactonization. Probably the bromination is reversible.
Finally, the weak base bicarbonate (HCO$_3^-$) is enough to remove a proton from the nitrogen atom and allow participation in nitrogen migration by displacement of bromide. This alkene is formed because the C–N$^+$ bond to tertiary carbon is broken preferentially.

PROBLEM 10
Give mechanisms for these reactions that explain any selectivity.

Purpose of the problem
To show that ring expansion from three- to four-membered rings and ring contraction the other way are about as easy.

Suggested solution
The first mechanism is a pinacol rearrangement and the compound is symmetrical so it doesn’t matter which alcohol is protonated. Both three- and four-membered rings are strained and the σ-bonds are more reactive than normal (they have a high energy HOMO). This makes ring contraction an easy reaction even though the strain is not relieved.
The second example looks at first to be a similar pinacol rearrangement. But the resulting ketone cannot easily be transformed into the product.

Breaking open one of the three-membered rings gets us off to a better start. This gives a hydroxy-ketone that can rearrange in a pinacol fashion with ring expansion of the remaining cyclopropane.

**PROBLEM 11**
Attempts to produce the acid chloride from this unusual amino acid by treatment with SOCl₂ gave instead a β-lactam. What has happened?

**Purpose of the problem**
To show that ring expansion in small rings is even easier in heterocycles because of participation.

**Suggested solution**
The formation of the acid chloride might go to completion or it might be that some intermediate on the way to the acid chloride rearranges. We shall use an intermediate. Whichever you use, it is participation by nitrogen that starts the ring expansion going, though the next intermediate is very unstable. When chloride attacks the bicyclic cation, it cleaves the most strained bond, the one common to two three-membered rings.
Solutions for Chapter 36 – Participation, Rearrangement, and Fragmentation

PROBLEM 12
Treatment of this hydroxy-ketone with base followed by acid gives the enone shown. What is the structure of intermediate A, how is it formed, and what is the mechanism of its conversion to the final product?

Purpose of the problem
Fragmentation may be followed by another reaction.

Suggested solution
Removal of the hydroxyl proton by the base promotes a fragmentation that is a reverse aldol reaction. It works because the C–C bond being broken is in a four-membered ring. Then an acid catalysed aldol reaction in the normal direction and elimination via the enol (E1cB) allows the formation of the much more stable six-membered ring.
PROBLEM 13
Just to check your skill at finding fragmentations by numbers, draw the mechanism for each of these one-step fragmentations in basic solution with acidic work-up.

![Mechanism diagrams](image)

**Purpose of the problem**
As the problem says, to help you unravel simple fragmentations.

**Suggested solution**
We can identify the six-membered ring in both compounds—the sequence 1-6 is clearly the same in both with a side chain at C3. The fragmentation is easy enough too—the OH proton is removed and the mesylate must be the leaving group so the groups doing the ‘pushing’ and ‘pulling’ are clear from the start.

![Mechanism diagrams](image)

The two CO₂H groups in the second product might cause a moment’s concern but one is on a –CH₂–CH₂– side chain and the other is at a branch point and we can soon fill in the rest of the numbers.
Clearly the OH proton is removed and one of the carboxyls is a leaving group. The stereochemistry disappears in the fragmentation but it is important, as the conformational drawing shows. One lone pair on the O, the bond being fragmented, and the bond to the leaving group are all parallel (shown in thick lines).

PROBLEM 14

Explain why both these tricyclic ketones fragment to the same diastereoisomer of the same cyclo-octane.

Purpose of the problem

Fragmentations linked to ester hydrolysis.

Suggested solution

It is obvious from the reactions that two features have disappeared from the starting materials: an ester group (OAc) and a four-membered ring. The ester can be hydrolysed by KOH and the four-membered ring disappears in the fragmentation. As usual, draw the mechanism first and worry about the stereochemistry later. For the first compound, this sequence gives the enolate of a diketone and hence the diketone itself.
The second compound follows the same sequence and a different enolate emerges, but it is simply another enolate of the same ketone. Both compounds give the same basic structure.

But what about stereochemistry? We are not told the stereochemistry of the starting materials but know that 5,4 fused rings must have a cis ring junction. This junction survives in the first compound so the stereochemistry must have changed. The second compound gives us the clue as to how. When it tautomerizes to the ketone it will select the more stable trans 8,5 ring junction. In the same way, the enolate from the first sequence is in equilibrium under the reaction conditions with all the other enolates of the same ketone, including those at ring junctions. This is a stereoselective reaction.
**PROBLEM 15**

Suggest a mechanism for this fragmentation and explain the stereochemistry of the alkenes in the product. This is a tricky problem, but find the mechanism and the stereochemistry will follow.

![Chemical structure](image)

165 °C

**Purpose of the problem**

Probably the most beautiful application of fragmentation yet by a true genius of chemistry, Albert Eschenmoser.

**Suggested solution**

The tosylate is obviously the leaving group, the two oxygens in the ring must become the ester group, and the CO$_2$ must leave as CO$_2$. All that remains is to trace a pathway from CO$_2$ to OTs via one of the ring oxygens using parallel bonds. Though you could draw a mechanism for this double fragmentation, it is not convincing. The only electrons anti-parallel to the C–OTs bond are those in the ring junction bond and the equatorial lone pair on one of the ring oxygens. Marking these with heavy lines, we carry out the first fragmentation. We've also drawn in the hydrogen that ends up on the alkene so you can see clearly where the *trans* geometry comes from

![Chemical structure](image)

The second fragmentation is easier to see if we redraw the intermediate so that we can see which groups are antiparallel. A conformational drawing also reveals the correct alkene geometry.
**PROBLEM 16**

Suggest a mechanism for this reaction and explain why the molecule is prepared to abandon a stable six-membered ring for a larger ring.

**Purpose of the problem**

A simple example of fragmentation used to create a medium size (11-membered) ring.

**Suggested solution**

The strong base removes the proton from the OH group and the oxyanion attacks one of the carbonyl groups (they are the same). This intermediate might decompose back to starting materials but it can also fragment with the loss of an enolate. The product is then an ester, and protonation of the enolate completes the reaction. The eleven-membered ring is more stable than usual because of the benzene ring (see problem 2, chapter 34), and because the ester does not suffer from cross-ring interactions in its favoured s-trans conformation.
PROBLEM 17
Give mechanisms for these reactions, commenting on the fragmentation.

Purpose of the problem
Revision of conjugate addition of enols, another ring expansion with an enolate as leaving group and an interesting piece of stereochemistry.

Suggested solution
The first step is enamine formation and the second is conjugate addition. This appears to lead to a dead end as we cannot find a way to make the intermediate from the product.

The answer is to exchange the enamine of the ketone with the enamine of the aldehyde. Under the conditions, enamine formation is reversible and there are various ways you could draw details.
Cyclisation of this compound now gives the intermediate we are looking for.

The last two diagrams show where the stereochemistry comes from. The final product has a chair six-membered ring. The 1,3-bridge on the bottom of this ring must be diaxial or it cannot reach round. The pyrrolidine is equatorial and the five-membered ring must be cis fused. No doubt the stereochemistry as well as the intermediates are under thermodynamic control.

Finally the fragmentation itself. Methylation of the nitrogen makes it into a leaving group and addition of hydroxide to the ketone provides the electronic push. Notice that the C–N+ bond, the C–C bond being fragmented, and a lone pair on the O– group are all parallel. The stereochemistry is already there in the intermediate.

**PROBLEM 18**

Suggest mechanisms for these reactions, explaining the alkene geometry in the first case. Do you consider that they are fragmentations?
Purpose of the problem

Simple fragmentations involving the opening of three-membered rings.

Suggested solution

The first reaction is a fragmentation without any ‘push’ but that is all right because the bond that is being broken is in a three-membered ring. You may have drawn a concerted mechanism or a stepwise one with a cation as intermediate. Either may be correct. The stereochemistry of the alkene is thermodynamically controlled.

\[
\begin{align*}
\text{HO} & \quad \text{HBr} & \quad \text{Br} & \quad \text{H}_2\text{O} \\
\text{R} & \quad \text{R} & \quad \text{Br} & \quad \text{R} \\
\text{H}_2\text{O} & \quad \text{R} & \quad \text{Br} & \quad \text{R}
\end{align*}
\]

The second reaction is base-catalysed and starts with the hydrolysis of the ester by NaOH. This fragmentation also needs ‘push’, though only a three-membered ring is being broken, because the leaving group is an enolate, nowhere near as electron-withdrawing as the water molecule or the carbocation in the first example. Are they fragmentations? In both cases a C-C bond is being broken but we would understand if you felt the first was not strictly a fragmentation, particularly if it goes stepwise. Neither reaction breaks the molecule into three pieces and it the terminology is merely a matter of opinion.

\[
\begin{align*}
\text{O} & \quad \text{OAc} & \quad \text{NaOH} & \quad \text{O} & \quad \text{O} & \quad \text{H}_2\text{O} \\
\text{product}
\end{align*}
\]
PROBLEM 19

What steps would be necessary to carry out an Eschenmoser fragmentation on this ketone, and what products would be formed?

Purpose of the problem

Revision of an important and complex reaction involving fragmentation.

Suggested solution

The Eschenmoser fragmentation (p. 965) uses the tosyl hydrazone of an α,β-epoxy-ketone. The epoxide can be made with alkaline hydrogen peroxide and the tosylhydrazone needs just tosylhydrazine to form what is essentially an imine. Then the fun can begin. The stereochemistry doesn’t matter for once.

The fragmentation is initiated with base that removes the proton from the NHTs group. This anion fragments the molecule one way and then the oxyanion fragments it the other way with nitrogen gas and Ts− as leaving groups. The product is an acetylenic aldehyde or ketone.
**PROBLEM 20**

Revision content. Suggest mechanisms for these reactions to explain the stereochemistry.

![Reaction Diagram]

**Purpose of the problem**

Rearrangements and a fragmentation.

**Suggested solution**

The ring opening and the rearrangement cannot be concerted because the group on the ‘wrong’ side of the molecule migrates. There must be a cationic intermediate. In contrast, attack of bromide occurs stereospecifically from the side opposite the migrating group, so this is presumably concerted with the rearrangement.

![Mechanism Diagram]

The second reaction is a fragmentation. Silver(I) is an excellent Lewis acid for halogens and probably produces a secondary carbocation intermediate. Push from the OH group completes the fragmentation.

As it happens the starting epoxide is that of natural α-pinene so it and the product are single enantiomers. P. H. Boyle et al., *J. Chem. Soc., Chem. Commun.*, 1971, 395.