Suggested solutions for Chapter 33

PROBLEM 1
How would you make each diastereoisomer of this product from the same alkene?

Purpose of the problem
A gentle introduction to stereochemical control in open-chain compounds.

Suggested solution
The compounds are acetals and can be made from the corresponding diols with no change in stereochemistry. The question really is: how do you make cis and trans diols from the alkene?

The cis diol is best made by dihydroxylation with OsO₄ as the reagent and a co-oxidant to regenerate it. The trans diol comes from the epoxide by nucleophilic attack with water.
PROBLEM 2

Explain the stereochemistry shown in this sequence of reactions.

Purpose of the problem

Chelation-controlled reduction is an important method for stereochemical control in open-chain compounds.

Suggested solution

In both reductions the zinc atom is coordinated to the oxygen of the nearer functional group (CO$_2$Bn in the first and OH in the second) and the oxygen of the ketone being reduced. This fixes the conformation of the molecule and the borohydride ion attacks from the less hindered side. Anti stereochemistry results in both cases.
**PROBLEM 3**

How is the relative stereochemistry of this product controlled? Why was this method chosen?

![Chemical structure]

**Purpose of the problem**

This may seem trivial but the principle is important.

**Suggested solution**

The relationship between the two chiral centres in the product is 1,5 and that is too remote for any realistic control. The only plan is to disconnect between the two centres and add a removable anion-stabilizing group to one side and a leaving group to the other. The starting materials must of course be single enantiomers—then only one diastereoisomer can be formed.

![Chemical structure]

**PROBLEM 4**

When this hydroxy-ester is treated with a two-fold excess of LDA and then alkylated, one diastereoisomer of the product predominates. Why?

![Chemical structure]

**Purpose of the problem**

Analysis of an apparently simple case where chelation has the last word.
Suggested solution

The first LDA molecule removes the OH proton and only the second gives the lithium enolate. The enolate is held in a ring by chelation to the first lithium atom so that the allyl group adds to the less hindered face – opposite the methyl group. We’ve rotated the right hand end of the product to compare the stereochemistry clearly with the structure in the problem: make sure you can see that there is no change at the ester-bearing centre when you do this.

PROBLEM 5
Explain the stereochemical control in this reaction, drawing all the intermediates.

Purpose of the problem

Aldols are versatile and important ways of controlling open-chain stereochemistry by way of a cyclic transitions state.

Suggested solution

The geometry of the enolate is all important (p. 868) and here the large \( t \)-butyl group will direct the formation of the \( Z \)-lithium enolate. Then the aldol reaction goes through a six-membered cyclic transition state (Zimmerman-Traxler) with the \( R \) group of the aldehyde taking up an equatorial position. This gives the \( \text{syn} \) aldol product.
**Problem 6**

Explain how the stereochemistry of this epoxide is controlled.

**Purpose of the problem**

An example of the important iodolactonization reaction.

**Suggested solution**

The bicarbonate (NaHCO₃) is a strong enough base to remove the proton from the carboxylic acid. Iodine attacks the alkene reversibly to give a mixture of diastereoisomers of the iodonium ion. If the I⁺ and Me groups are on the same side of the chain, the carboxylate group can attack the iodonium ion from the back and set up a *trans* iodolactone. The iodolactone is cleaved by methoxide and the oxyanion displaces iodide to give the epoxide.
PROBLEM 7
Explain how these reactions give different isomers of the same product.

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\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

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Purpose of the problem
Practice at the analysing stereochemical control using the Felkin-Anh model.

Suggested solution
In each case we have nucleophilic attack on a carbonyl group with a neighbouring chiral centre. The Felkin-Anh analysis tells us first to put the largest group perpendicular to the carbonyl group and then to bring the nucleophile in alongside the smaller substituent. This is best shown as a Newman projection. In the first case it is better to rotate the front atom in the product so that the two Ph groups are at 180° and we can then draw the structure in the same arrangement.
PROBLEM 8
Explain the stereoselectivity of this reaction. What isomer of the epoxide would be produced by treatment of the product with base?

Purpose of the problem
A stereoelectronically controlled Felkin-Anh analysis.

Suggested solution
In this case the chloro substituent dominates because it has an electronic interaction with the carbonyl group. The two alkyl chains come out opposite one another so it is easy to draw the product in a reasonable fashion by imagining yourself observing the Newman projection from the top right.

To draw the stereochemistry of the epoxide formation it is sensible to put the reacting groups in the plane of the paper and arranged so that the oxyanion can do an S_N2 displacement.
**PROBLEM 9**

How could this cyclic compound be used to produce the open-chain compound with correct relative stereochemistry?

![Cyclic Compound](image)

![Open-Chain Compound](image)

**Purpose of the problem**

Practice at relating the stereochemistry of cyclic and open-chain compounds.

**Suggested solution**

We should first discover which atoms in the cyclic compound provide which atoms in the product. Numbering the atoms is the easiest way and it shows little change except that C9 has gone and C8 has become an aldehyde.

![Numbered Cyclic Compound](image)

![Numbered Open-Chain Compound](image)

We need to hydrolyse the ester and the acetal and oxidize the 1,2-diol to cleave the C–C bond between the two OH groups. The stereochemistry at C3 and C7 is unchanged and neither is threatened by any of the reaction conditions.
**PROBLEM 10**

How would you transform this alkene stereoselectively into either of the diastereoisomers of the amino alcohol?

![Diagram of alkene transformation](image)

**Purpose of the problem**

A more difficult extension of problem 1.

**Suggested solution**

Opening the epoxide with a nitrogen nucleophile makes one isomer. At least the alkene is symmetrical so it doesn’t matter which end of the epoxide is attacked by the nucleophile. We have chosen azide ion as the nucleophile. You were not asked to make both diastereoisomers so we can stop there.

![Diagram of reaction](image)

**PROBLEM 11**

Explain the formation of essentially one stereoisomer in this reaction.

![Diagram of reaction](image)

**Purpose of the problem**

A more difficult extension of problem 4 with added Felkin-Anh considerations.

**Suggested solution**

The *syn* selectivity of the aldol reactions comes from the chair conformation of the cyclic (Zimmerman-Traxler) transition state.
Ignoring the stereochemistry of the aldehyde we have this simplified explanation. The transition state contains a chair in which the methyl group has no choice but to be axial while the aldehyde's R substituent chooses to be equatorial.

We have inevitably drawn the syn aldol product as one enantiomer but so far there we have no explanation for the control of absolute stereochemistry. The aldehyde itself is a single enantiomer so the two faces of the carbonyl group are diastereotopic and we might expect one would be chosen by the normal Felkin-Anh argument.

To our surprise this is not the preferred isomer. In fact the ‘anti-Felkin’ isomer predominates by about 3:1. The compound is entirely the syn aldol, as predicted, but attack has occurred on the aldehyde in the alternative conformation.

There is an important lesson to be learnt here. The principles we have been explaining are generally true but in any new individual case the result may not follow the principle. This is particularly true of Felkin-Anh control with aldehydes as the small size of the H atom allows other conformations to become relatively favourable.