Organic Synthesis: The Disconnection Approach
2nd Edition

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The first edition was written with the active participation of Denis Marrian who died in 2007. We dedicate this second edition to Denis Haigh Marrian, 1920–2007, a great teacher and friend.
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Preface

In the 26 years since Wiley published *Organic Synthesis: The Disconnection Approach* by Stuart Warren, this approach to the learning of synthesis has become widespread while the book itself is now dated in content and appearance. In 2007, Wiley published *Organic Synthesis: Strategy and Control* by Paul Wyatt and Stuart Warren. This much bigger book is designed as a sequel for fourth year undergraduates and research workers in universities and industry. The accompanying workbook was published in 2008. This new book made the old one look very dated in style and content and exposed gaps between what students were expected to understand in the 1980s and what they are expected to understand now. This second edition is intended to fill some of those gaps.

The plan of the original book is the same in the second edition. It alternates chapters presenting new concepts with strategy chapters that put the new work in the context of overall planning. The 40 chapters have the same titles: some chapters have hardly been changed while others have undergone a thorough revision with considerable amounts of new material. In most cases examples from recent years are included.

One source of new material is the courses that the authors give in the pharmaceutical industry. Our basic course is ‘The Disconnection Approach’ and the material we have gathered for this course has reinforced our attempts to give reasons for the synthesis of the various compounds which we believe enlivens the book and makes it more interesting for students. We hope to complete a second edition of the workbook shortly after the publication of the main text.

The first edition of the textbook was in fact the third in a series of books on organic chemistry published by Wiley. The first: *The Carbonyl Group: an Introduction to Organic Mechanisms*, published in 1974, is a programmed book asking for a degree of interaction with the reader who was expected to solve problems while reading. People rarely use programmed learning now as the method has been superseded by interactive programmes on computers. Paul Wyatt is writing an electronic book to replace *The Carbonyl Group* which will complete a package of an electronic book and books with associated workbooks in a uniform format that we hope will prove of progressive value as students of organic chemistry develop their careers.

Stuart Warren and Paul Wyatt
March 2008.
General References

Full details of important books referred to by abbreviated titles in the chapters to avoid repetition.

1

The Disconnection Approach

This book is about making molecules. Or rather it is to help you design your own syntheses by logical and sensible thinking. This is not a matter of guesswork but requires a way of thinking backwards that we call the disconnection approach.

When you plan the synthesis of a molecule, all you know for certain is the structure of the molecule you are trying to make. It is made of atoms but we don’t make molecules from atoms: we make them from smaller molecules. But how to choose which ones? If you wanted to make, say, a wooden joint, you would look in a do-it-yourself book on furniture and you would find an ‘exploded diagram’ showing which pieces you would need and how they would fit together.

The disconnection approach to the design of synthesis is essentially the same: we ‘explode’ the molecule into smaller starting materials on paper and then combine these by chemical reactions. It isn’t as easy as making wooden joints because we have to use logic based on our chemical knowledge to choose these starting materials. The first chemist to suggest the idea was Robert Robinson who published his famous tropinone synthesis in 1917. His term was ‘imaginary

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hydrolysis' and he put dashed lines across a tropinone structure.

*Tropinone: Robinson's Analysis*

This was a famous synthesis because it is so short and simple and also because it makes a natural product in a way that imitates nature. The reaction is carried out at pH 7 in water. In fact Robinson didn’t use acetone, as suggested by his ‘imaginary hydrolysis’, but acetone dicarboxylic acid. This procedure is an improved one invented by Schöpf in 1935.

*Tropinone: Synthesis*

Amazingly, nobody picked up the idea until the 1960s when E. J. Corey at Harvard was considering how to write a computer program to plan organic syntheses. He needed a systematic logic and he chose the disconnection approach, also called retrosynthetic analysis. All that is in this book owes its origin to his work. The computer program is called LHASA and the logic survives as a way of planning syntheses used by almost all organic chemists. It is more useful to humans than to machines.

**The Synthesis of Multistriatin**

Multistriatin 1 is a pheromone of the elm bark beetle. This beetle distributes the fungus responsible for Dutch elm disease and it was hoped that synthetic multistriatin might trap the beetle and prevent the spread of the disease. It is a cyclic compound with two oxygen atoms both joined to the same carbon atom (C-6 in 1) and we call such ethers acetals.

We know one good way to make acetals: the reliable acid-catalysed reaction between two alcohols or one diol and an aldehyde or ketone.

Intending to use this reliable reaction for our acetal we must disconnect the two C–O bonds to C–6 and reveal the starting material 2, drawn first in a similar way to 1, and then straightened
out to look more natural 2a. Numbering the carbon atoms helps to make sure 2 and 2a are the same.

We now have a continuous piece of carbon skeleton with two OH groups and a ketone. No doubt we shall make this by forming a C–C bond. But which one? We know that ketones can form nucleophilic enolates so disconnecting the bond between C–4 and C–5 is a good choice because one starting material 3 is symmetrical. As we plan to use an enolate we need to make 3 nucleophilic and therefore 4 must be electrophilic so we write plus and minus charges to show that.

Anion 3 can be made from the available ketone 5 but the only sensible way to make 4 electrophilic is to add a leaving group X, such as a halogen, deciding later exactly what to use.

Compound 6 has three functional groups. One is undefined but the other two must be alcohols and must be on adjacent carbon atoms. There is an excellent reaction to make such a combination: the dihydroxylation of an alkene with a hydroxylating agent such as OsO₄. A good starting material becomes the unsaturated alcohol 7a as that is known.

In one synthesis the alcohol 7a was made from the available acid 8 and the leaving group (X in 6) was chosen as tosylate (OTs; toluene- p-sulfonate).

The two pieces were joined together by making the enolate of 5 and reacting it with 7; X = OTs. The unsaturated ketone 9 was then oxidised with a peroxycacid to give the epoxide 10 and
cyclisation with the Lewis acid SnCl$_4$ gave the target molecule (TM) multistriatin 1.

You may have noticed that the synthesis does not exactly follow the analysis. We had planned to use the keto-diol 2b but in the event this was a less practical intermediate than the keto-epoxide 10. It often turns out that experience in the laboratory reveals alternatives that are better than the original plan. The basic idea—the strategy—remains the same.

**Summary: Routine for Designing a Synthesis**

1. Analysis
   (a) Recognise the functional groups in the target molecule.
   (b) Disconnect with known reliable reactions in mind.
   (c) Repeat as necessary to find available starting materials.

2. Synthesis
   (a) Write out the plan adding reagents and conditions.
   (b) Modify the plan according to unexpected failures or successes in the laboratory.

We shall develop and continue to use this routine throughout the book.

**What the Rest of the Book Contains**

The synthesis of multistriatin just described has one great fault: no attempt was made to control the stereochemistry at the four chiral centres (black blobs in 11). Only the natural stereoisomer attracts the beetle and stereoselective syntheses of multistriatin have now been developed.

![11; chiral centres in multistriatin](http://www.chem4all.vn)

We must add stereochemistry to the list of essential background knowledge an organic chemist must have to design syntheses effectively. That list is now:

1. An understanding of reaction mechanisms.
2. A working knowledge of reliable reactions.
3. An appreciation that some compounds are readily available.
4. An understanding of stereochemistry.

Don’t be concerned if you feel you are weak in any of these areas. The book will strengthen your understanding as you progress. Each chapter will build on whichever of the four points are relevant. If a chapter demands the understanding of some basic chemistry, there is a list of references at the start to chapters in Clayden *Organic Chemistry* to help you revise. Any other textbook of organic chemistry will have similar chapters.
The elm bark beetle pheromone contains three compounds: multistriatin, the alcohol 12 and \( \alpha \)-cubebene 13. At first we shall consider simple molecules like 12 but by the end of the book we shall have thought about molecules at least as complex as multistriatin and cubebene.

Multistriatin has been made many times by many different strategies. Synthesis is a creative science and there is no 'correct' synthesis for a molecule. We shall usually give only one synthesis for each target in this book: you may well be able to design shorter, more stereochemically controlled, higher yielding, more versatile—in short better—syntheses than those already published. If so, you are using the book to advantage.

References

Basic Principles: Synthons and Reagents
Synthesis of Aromatic Compounds

Background Needed for this Chapter

Synthesis of Aromatic Compounds
The benzene ring is a very stable structural unit. Making aromatic compounds usually means adding something(s) to a benzene ring. The disconnection is therefore almost always of a bond joining a side chain to the benzene ring. All we have to decide is when to make the disconnection and which reagents to use. You will meet the terms *synthon* and *functional group interconversion* (FGI) in this chapter.

Disconnection and FGI
You already know that disconnections are the reverse of known reliable reactions so you should not make a disconnection unless you have such a reaction in mind. In designing a synthesis for the local anaesthetic benzocaine 1, we see an ester group and know that esters are reliably made from some derivative of an acid (here 2) and an alcohol (here ethanol). We should disconnect the C–O ester bond. From now on we will usually write the reason for a disconnection or the name of the forward reaction above the arrow.

\[
\text{H}_2\text{N} \quad \text{Et} \quad \text{O} \quad \text{H} \\
\text{1; benzocaine} \quad \rightarrow \quad \text{H}_2\text{N} \quad \text{Et} \quad \text{O} \quad \text{H} \\
\text{1a} \quad \text{ester} \quad \rightarrow \quad \text{H}_2\text{N} \quad \text{EtOH} \\
\text{2} \quad \text{OH} \\
\]

The sign for a disconnection on a molecule is some sort of wiggly line across the bond being disconnected. You can draw this line in any way you like within reason. The 'reaction arrow' is the 'implies' arrow from logic. The argument is that the existence of any ester implies that it can be made from an acid and an alcohol.
We should now like to disconnect either the NH₂ or the CO₂H group but we know of no good reactions corresponding to those disconnections. We need to change both groups into some other groups that can be added to a benzene ring by a known reliable reaction. This process is called functional group interconversion or FGI for short and is an imaginary process, just like a disconnection. It is the reverse of a real reaction. Here we know that we can make amino groups by reduction of nitro groups and aryl carboxylic acids by oxidation of alkyl groups. The FGIs are the reverse of these reactions.

![Chemical structures](image)

We ‘oxidised’ the amino group first and ‘reduced’ the acid second. The order is unimportant but is something we come back to in the forward reaction. What matters is that we have found a starting material 4 that we know how to make. If we disconnect the nitro group 4a we shall be left with toluene 5 and toluene can be nitrated in the para-position with a mixture of nitric and sulfuric acids.

![Chemical structures](image)

Now we should write out the synthesis. You cannot of course predict exactly which reagents and conditions will be successful and no sensible organic chemist would attempt to do this without studying related published work. It is enough to make suggestions for the type of reagent needed. We shall usually give the reagents used in the published work and conditions where they seem to matter. Here it is important to nitrate first and oxidise second to get the right substitution pattern.¹

![Chemical structures](image)

**Synthons Illustrated by Friedel-Crafts Acylation**

The useful disconnection 6a corresponds to Friedel-Crafts acylation of aromatic rings and is the obvious one on the ketone 6 having the perfume of hawthorn blossom. Reaction² of ether 7 with MeCOCl and AlCl₃ gives 6 in 94–96% yield—a good reaction indeed.

![Chemical structures](image)
In both this reaction and the nitration of toluene we used to make benzocaine, the reagent is a cation: MeCO\(^+\) for the Friedel-Crafts and NO\(_2\)^+ for the nitration. Our first choice on disconnecting a bond to a benzene ring is to look for a cationic reagent so that we can use electrophilic aromatic substitution. We know not only which bond to break but also in which sense electronically to break it. In principle we could have chosen either polarity from the same disconnection: \(\text{a (we actually chose)}\) or \(\text{b (we did not)}\).

The four fragments 8–11 are 

"synthons" — that is idealised ions that may or may not be involved in the actual reaction but help us to work out which reagent to choose. As it happens, synthon 11 is a real intermediate but the others are not. For an anionic synthon like 10 the reagent is often the corresponding hydrocarbon as \(\text{H}^+\) is lost during the reaction. For a cationic synthon like 11 the reagent is often the corresponding halide as that will be lost as a leaving group during the reaction. It is a matter of personal choice in analysing a synthesis problem whether you draw the synthons or go direct to the reagents. As you become more proficient at retrosynthetic analysis, you will probably find that drawing the synthons becomes unnecessary and cumbersome.

**Synthons Illustrated by Friedel-Crafts Alkylation**

Friedel-Crafts alkylation is also useful though less reliable than acylation. With that in mind, we could disconnect BHT 13 ("Butylated Hydroxy-Toluene") at either bond \(\text{b}\) to remove the methyl group or bond \(\text{a}\) to remove both \(t\)-butyl groups. There are various reasons for preferring \(\text{a}\). para-Cresol 15 is available whereas 14 is not. The \(t\)-butyl cation is a much more stable intermediate than the methyl cation — and \(t\)-alkylations are among the most reliable. Finally the OH group is more powerfully ortho-directing than the methyl group.
We have a choice of reagents for the \( t \)-butyl cation: a halide with Lewis acid catalysis, and \( t \)-butanol or isobutene with protic acid catalysis. The least wasteful is the alkene as nothing is lost. Protonation gives the \( t \)-butyl cation and two \( t \)-butyl groups are added in one operation.\(^3\)

![Equation](http://www.chem4all.vn)

**Functional Group Addition Illustrated by Friedel-Crafts Alkylation**

Attempting Friedel-Crafts alkylation with primary halides often gives the ‘wrong’ product by rearrangement of the intermediate cation. If we want to make \( i \)-butylbenzene \( 16 \), it seems obvious that we should alkylate benzene with an \( i \)-butyl halide, e.g. \( 18 \) and \( \text{AlCl}_3 \).

![Equation](http://www.chem4all.vn)

This reaction gives two products \( 21 \) and \( 22 \) but neither contains the \( i \)-butyl group. Both contain instead the \( t \)-butyl group. The intermediate complex rearranges by hydride shift \( 19 \) into the \( t \)-butyl cation \( 20 \) as the primary cation \( 17 \) is too unstable.

![Equation](http://www.chem4all.vn)

Polyalkylation was an advantage in the synthesis of BHT \( 13 \): it is the rearrangement that is chiefly unacceptable here. Friedel-Crafts acylation avoids both problems. The acyl group does not rearrange and the product is deactivated towards further electrophilic attack by the electron-withdrawing carbonyl group. We have an extra step: reduction of the ketone to a \( \text{CH}_2 \) group. There are various ways to do this (see chapter 24)—here the Clemmensen reduction is satisfactory.\(^4\)

![Equation](http://www.chem4all.vn)

The preliminary to the corresponding disconnection is the ‘addition’ (imaginary) of a functional group where there was none. We call this FGA (functional group addition). The corresponding
known reliable reaction is the removal of the functional group. We could put the carboxyl group anywhere but we put it next to the benzene ring as it then allows us to do a reliable disconnection.

Reliable Reagents for Electrophilic Substitution

Table 2.1 summarises the various reagents we have mentioned (and some we haven’t). Full details of mechanisms, orientation and applications appear in Clayden chapter 22.

<table>
<thead>
<tr>
<th>Synthon</th>
<th>Reagent</th>
<th>Reaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>R⁺</td>
<td>RBr + AlCl₃</td>
<td>Friedel-Crafts alklylation⁵</td>
<td>good for t-alkyl OK for s-alkyl very general very vigorous other Lewis acids used too other Lewis acids used too may need fuming H₂SO₄ very vigorous product is Ar⁺N=NAr²</td>
</tr>
<tr>
<td>RCO⁺</td>
<td>RCOCI + AlCl₃</td>
<td>Friedel-Crafts acylation</td>
<td>nitration chlorination bromination sulfonation chloro-sulfonation diazo-coupling</td>
</tr>
<tr>
<td>NO₂⁺</td>
<td>HNO₃ + H₂SO₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl⁺</td>
<td>Cl₂ + FeCl₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br⁺</td>
<td>Br₂ + Fe (=FeBr₃)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO₂OH⁺</td>
<td>H₂SO₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO₂Cl⁺</td>
<td>CISO₂OH + H₂SO₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ArN₂⁺</td>
<td>ArNH₂ + HONO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changing the Polarity: Nucleophilic Aromatic Substitution

If we make the same disconnections as before 25 and 27 but change the polarity we need electrophilic aromatic rings and nucleophilic reagents. We shall need a leaving group X (might be a halogen) on the aromatic ring 26 and reagents such as alkoxides or amines.

The nucleophilic reagents are behaving normally for alcohols or amines but the aromatic electrophiles present a problem. Benzene rings are nucleophilic, if weakly, but are not electrophilic at all. There is no S₈N₂ reaction on an aryl halide. To get the reactions we want, we must have
ortho- or para-electron-withdrawing groups such as NO₂ or C=O to accept the electrons as the nucleophile adds 28 to form 29.

Fortunately, nitro groups go in the right positions (i.e. ortho and para but not meta) by direct nitration of, say, chlorobenzene. So we can be guided in our choice of polarity by the nature of the target molecule. The Lilly pre-emergent herbicide trifluralin B 31 has three electron-withdrawing groups: two nitro and one CF₃, ortho- and para- to the amine, ideal for nucleophilic substitution on 32. The nitro groups can be introduced by nitration as Cl directs ortho, para while CF₃ directs meta.

The synthesis is simplicity itself, as the synthesis of any agrochemical must be. The base in the second step is to remove the HCl produced in the reaction, not to deprotonate the amine.

Thinking Mechanistically

It is obvious that the choice between nucleophilic and electrophilic substitution must be mechanistically made but this is generally true of the choice of all disconnections, synths and reagents. The formation of 31 was easy because the aryl chloride was activated by three groups. In the synthesis of fluoxetine (Prozac), a rather widely taken anti-depressant, aryl ether 34 is an essential intermediate. Though disconnection b looks attractive, as a simple S_N2 reaction should work well, disconnection a was preferred because 34 must be a single enantiomer and enantiomerically pure alcohol 36 was available.
You should have been surprised to see fluoride as the leaving group. Fluoride is the worst leaving group among the halogens as the C–F bond is very strong; it is rare to see an S_N2 reaction with fluoride as the leaving group. Yet it is the best choice for nucleophilic aromatic substitution especially when the ring is only weakly activated as here with just one CF_3 group. In this two-step reaction, the difficult step is the addition of the nucleophile: aromaticity is destroyed and the intermediate is an unstable anion. The second step 38 is fast. Fluorine accelerates the first step as it is so electronegative and it doesn’t matter that it hinders the second step as that is fast anyway.

You may have noticed something else. The formation of trifuralin 31 shewed that amines are good nucleophiles for nucleophilic aromatic substitution and the nucleophile here is an amino-alcohol 36. Direct reaction with 36 might lead to the formation of an amine instead of an ether. To avoid this, 36 is first treated with NaH to make the oxyanion and then added to 35. The alcohol is less nucleophilic but the oxyanion is more nucleophilic than the amine. We hope you now see why an understanding of reaction mechanisms is an essential preliminary to the designing of syntheses.

**Changing the Polarity: Nucleophilic Aromatic Substitution by the S_N1 Mechanism**

Though the S_N2 mechanism is not available for aromatic nucleophilic substitutions, the S_N1 is providing we use the very best leaving group available. This is a molecule of nitrogen released from a diazonium salt 42 on gentle warming. A standard sequence is nitration of an aromatic compound 39 to give 40, reduction to the amine 41 and diazotisation with NaNO_2/HCl to give the diazonium salt 42. Nitrous acid HONO is the true reagent giving NO^+ that attacks at nitrogen.

The diazonium salt 42 is stable at 0–5 °C but decomposes to N_2 and an unstable aryl cation 43 on warming to room temperature. The empty orbital of 43 is in an sp^2 orbital in the plane of the aromatic ring, quite unlike the normal p orbital for cations like 20. Reaction occurs with any available nucleophile, even water, and this is a route to phenols 45.
This route is particularly valuable for substituents that cannot easily be added by electrophilic substitution such as OH or CN. Table 2.2 gives you a selection of reagents. For the addition of CN, Cl or Br, copper (I) derivatives usually give the best results. So the aryl nitrile 46 might come from amine 47 via a diazonium salt and routine disconnections lead us back to toluene.

The synthesis is straightforward. In the laboratory you would not have to carry out the first two steps as the amine 47 can be bought. Industry makes it on a large scale by this route. Notice that we do not draw the diazonium salt. You can if you want, but it is usual to show two steps carried out without isolation of the intermediate in this style: 1. reagent A, 2. reagent B. This makes it clear that all the reagents are not just mixed together. Another style is used in Table 2.2: the reactive intermediate is in square brackets. But it is helpful to show conditions for the diazotisation as temperature control is important.

![Diagram](http://www.chem4all.vn)

**TABLE 2.2** Reagents for aromatic nucleophilic substitution on ArN$_2^+$

<table>
<thead>
<tr>
<th>Synthon</th>
<th>Reagents</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OH</td>
<td>water</td>
<td>probably S$_N$1</td>
</tr>
<tr>
<td>-OR</td>
<td>alcohol ROH</td>
<td>probably S$_N$1</td>
</tr>
<tr>
<td>-CN</td>
<td>Cu(I)CN</td>
<td>may be a radical reaction</td>
</tr>
<tr>
<td>-Cl</td>
<td>Cu(I)Cl</td>
<td>may be a radical reaction</td>
</tr>
<tr>
<td>-Br</td>
<td>Cu(I)Br</td>
<td>may be a radical reaction</td>
</tr>
<tr>
<td>-I</td>
<td>KI</td>
<td>best way to add iodine</td>
</tr>
<tr>
<td>-Ar</td>
<td>ArH</td>
<td>Friedel-Crafts arylation</td>
</tr>
<tr>
<td>-H</td>
<td>H$_3$PO$_2$ or EtOH/H$^+$</td>
<td>reduction of ArN$_2^+$</td>
</tr>
</tbody>
</table>

**ortho- and para- Product Mixtures**

We used the nitration of toluene to give both the para-nitro 4 and the ortho-nitro compounds 48. In fact the reaction gives a mixture. This is acceptable providing the compounds can be separated and especially so if industry does the job on a very large scale, as here. The synthesis
of the sweetener saccharine is a good example. Saccharine \(50\) is a cyclic imide: that is a double amide from one nitrogen atom and two acids. If we disconnect the C–N and S–N bonds the two acids—one carboxylic and one sulfonic—are revealed \(51\). Both groups are meta-directing so we must do FGI to convert one of them into an ortho,para-directing group and we can use the same oxidation reaction we met at the start of the chapter (4 to 3). Now \(52\) can be made by sulfonation.

In practice chloro-sulfonic acid is used as this gives the sulfonyl chloride directly. You may be surprised at this, thinking that Cl might be the best leaving group. But there is no Lewis acid here. Instead the very strong chloro-sulfonic acid protonates itself to provide a molecule of water as leaving group (see workbook).

The reaction gives a mixture of the \textit{ortho}– \(53\) and \textit{para}– \(54\) products. The \textit{ortho}-compound is converted into saccharine by reaction with ammonia and oxidation and the \textit{para}-compound toluene-\(p\)-sulfonyl chloride \(54\), or tosyl chloride, is sold as a reagent for converting alcohols into leaving groups.

### References

3

Strategy I: The Order of Events

Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Electrophilic aromatic substitution; chapter 22. (Electrophilic Aromatic Substitution)

Alternating with instructional chapters, like the last one, will be strategy chapters, like this one, which discuss reasons for choosing one route rather than another: in other words the overall plan rather than the individual steps. In this chapter we shall examine the order of events, using the synthesis of aromatic compounds as examples. The details are specific but the guidelines general.

**Guideline 1:** Consider the effects of each functional group on the others. Add first (that is disconnect last) the one that will increase reactivity in a helpful way. So, for aromatic compounds, introduce first that group that helps, by reactivity or direction, the introduction of the others.

The analysis of the perfumery compound 1 could be tackled by two possible first disconnections. Friedel-Crafts alkylation a would work reasonably well with the secondary alkyl halide 2 but the ketone in 3 is meta-directing and would give the wrong product. Friedel-Crafts acylation b would give the right product as the alkyl group in 4 is ortho,para-directing. Further the alkyl group in 4 is activating while the ketone in 3 is deactivating.

**Analysis**

```
// Analysis

\[ \text{Friedel-Crafts alkylation} \]
```

The synthesis\(^\text{1}\) is straightforward providing we alkylate first and acylate second. The branched alkyl group in 4 ensures that the para-ketone 1 will be the main product by steric hindrance.

**Synthesis**

```
// Synthesis

\[ \text{benzene} \xrightarrow{\text{AlCl}_3} \text{4} \xrightarrow{\text{Cl}} \text{1; 86\% yield} \]
```

\(\text{Organic Synthesis: The Disconnection Approach, Second Edition}\)  
Stuart Warren and Paul Wyatt  
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Our next example emphasises one aspect of guideline 1. Some functional groups are so deactivating that it is difficult to do any further chemistry once they have been inserted. In other contexts it may be that they are so unstable that we would not wish to risk any further reactions. Musk ambrette 6 is a synthetic musk, essential in perfumes to enhance and retain the fragrance. It has five substituents round a benzene ring. Two of these, the nitro groups, are so deactivating that we want to add them last. So we disconnect them first.

Next we could disconnect either the methyl group 7a or the t-butyl group 7b with Friedel-Crafts alkylation in mind. There are many reasons for choosing 7b. The MeO group and the alkyl group in 8 and 9 are ortho,para-directing but the MeO group wins because it has a lone pair on oxygen that is delocalised into the aromatic system. So 9 will give the wrong product but 8 will give the right product. In addition, alkylation works well with a t-butyl group (SN1 mechanism) but badly with a methyl group. Our starting material 8 is the methyl ether of available meta-cresol 10 so is easily made by methylation of the phenol. Only experience would show that alkylation of 8 puts the t-butyl group ortho and not para to the MeO group.²

**Guideline 2:** Changing one functional group into another may alter reactivity dramatically. Changing an alcohol or phenol to a t-Bu ether increases steric hindrance. Alcohols and aldehydes or ketones are easily interconverted by redox reactions. The carbonyl compounds are electron-withdrawing, alcohols weakly electron-donating. Most dramatically for aromatic compounds, the nitro group is powerfully electron-withdrawing, deactivating and meta-directing while the amino group, often made by reduction of a nitro group, is strongly electron-donating, activating and ortho,para-directing. In an analysis featuring FGI, it may pay to consider at which stage to carry out some other reaction.

A simple example is the tetrachlorocompound 11 clearly made from toluene by some form(s) of chlorination. In fact we must change the meta-directing CCl₃ group into a ortho,para-directing methyl group before we disconnect the Ar-Cl bond.

This compound 11 was actually used³ to make the trifluorocompound 13. The chlorination of toluene with Lewis acid catalysis gives mostly 12 and chlorine and PCl₅ does the, probably radical, chlorination of the methyl group.
Guideline 3: Some substituents are difficult to add so it is best to start with them already present. It is not necessary to start all syntheses of aromatic compounds from benzene: a glance at any supplier’s catalogue will show the great range of aromatic compounds available. The chief examples of such substituents are phenols and the ethers derived from them as there is no simple reagent for electrophilic oxygen. But a methyl group and primary alkyl groups in general, are also difficult to add as Friedel-Crafts alkylation with primary alkyl halides leads to rearranged products.\(^4\)

The trisubstituted benzene 14 was used by Woodward as a starting material for his synthesis of the natural product reserpine.\(^5\) It too has to be made. We shall not add the MeO group but buy anisole (methoxybenzene) as starting material. Both nitrogens will be added by nitration but in which order?

Guideline 3: we prefer not to add this substituent

\[
\begin{align*}
\begin{array}{c}
\text{NH}_2 \\
\frac{\text{MeO}}{\text{NO}_2}
\end{array}
\end{align*}
\]

The MeO group is \textit{ortho,para}-directing so nitration of anisole 15 will give mostly the \textit{para} product 16 (steric hindrance). Nitric acid alone is needed: a mixture of nitric and sulfuric acids gives 2,4-dinitroanisole as the MeO group is activating.\(^6\) This also shows that a second nitrogen cannot be introduced in the right place from 16. However, reduction to the amine 17—many reagents could be used but Ti(III) gives good results—gives a more powerful activating group that might direct nitration to the right position (Guideline 2).

In practice, there is too much activation in 17 and attempted nitration oxidised the molecule. The amine must be acetylated first and then, without isolation of 18, can be nitrated (with nitric acid alone) to give 19. Hydrolysis of the amide gives 14 in excellent yield.\(^8\)

Guideline 4: Some disubstituted compounds are also readily available and they may contain a relationship (especially \textit{ortho}) that is difficult to achieve by electrophilic substitution. Here is a selection: a supplier’s catalogue will reveal more.
A good example is 21 needed for the synthesis of the GSK anti-asthma drug salbutamol 20. This ketone 21 could be made by a Friedel-Crafts acylation of 22, which turns out to be salicylic acid, with acetyl chloride.

This synthesis is easier than it may seem as the free phenol, rather than interfering, can be acylated to give the ester 23 which rearranges with AlCl₃ to give 21 directly. Even the intermediate 23 is available and cheap—it is aspirin.

**Guideline 5:** Some groups can be added to the ring by nucleophilic substitution. This is mechanistically more difficult than electrophilic substitution and requires an electron-withdrawing activating group such as nitro or carbonyl ortho or para to a normal leaving group such as a halide (chapter 2). Fortunately nitration or Friedel-Crafts acylation of halocompounds puts the activating group in the right position for nucleophilic substitution. So Friedel-Crafts acylation of fluorobenzene 24 gives the ketone 25 and displacement of fluoride by the addition–elimination mechanism gives the amine 26.

If this kind of activation is not available, nitrogen can be displaced from diazonium salts by the $S_{N}1$ mechanism. The acid 27 was needed at Hull University in work on liquid crystals.
The skeleton is diphenyl (Guideline 4) which reacts in the para-positions with electrophiles. The chlorination is difficult therefore and we need to replace the CO$_2$H group with a group more electron-donating than the phenyl ring. An amine is the answer 28 and that soon takes us back to diphenyl.

\[ \text{CO}_2\text{H} \xrightarrow{\text{FGI}} \text{NH}_2 \xrightarrow{\text{S}_4\text{Ar via diazonium salt}} \text{NH}_2 \xrightarrow{\text{C-Cl reduction}} \text{NO}_2 \xrightarrow{\text{FGI nitratio}} \text{diphenyl} \]

The nucleophile to introduce the CO$_2$H group is cyanide ion, used as its Cu(I) salt, and the amine in 29 must be acylated to prevent over-chlorination (compare 18).

\[ \text{diphenyl} \xrightarrow{\text{HNO}_3} \text{Ph} \xrightarrow{1. \text{H}_2 \text{Pd/C, 2. Ac}_2\text{O}} \text{Ph} \xrightarrow{1. \text{Cl}_2 \text{HCl, H}_2\text{O}} \text{28} \xrightarrow{1. \text{NaNO}_2 \text{HCl, Cu(I)CN, 2. NaOH}} \text{32} \]

**Guideline 6**: If a series of reactions must be carried out, start with one that gives a single product unambiguously and not one that would give a mixture. With aromatic compounds if you need to add both ortho and para substituents, putting in the para substituent first may be less ambiguous than the reverse.

Compound 33 was needed to make some antimalarial drugs. We prefer not to disconnect the OEt group (Guideline 3) and there are good reactions—nitration and chloromethylation—that would go in the right position (ortho or para) to the activating OEt group. Either disconnection a or b could be tried first.

\[ \text{O}_2\text{N} \xrightarrow{\text{Cl}} \text{34} \xrightarrow{\text{C-C}} \text{36} \]

We expect the para product to be the major product from either reaction on ether 36 (steric hindrance) so it makes sense to nitrate first. There is also a danger that nitration of 34 might oxidise the CH$_2$Cl group to CHO or even CO$_2$H. The synthesis works well if nitrination is carried out first.
It should be obvious that not all of these six guidelines will be relevant in every synthesis—indeed some may even contradict others. It is a matter for judgement and then laboratory trial to select a good route. As always, several different strategies may be successful.

References

One-Group C–X Disconnections

**Background Needed for this Chapter** References to Clayden, *Organic Chemistry*:
Chapter 12: Nucleophilic Substitution at the Carboxyl (C=O) Group.
Chapter 17: Nucleophilic Substitution at Saturated Carbon.

We started with aromatic compounds in chapters 2 and 3 because the position of disconnection needed no decision. We continue with ethers, amides and the like because the position of disconnection is again easily decided: we disconnect a bond joining the heteroatom (X) to the rest of the molecule: a C–O, C–N or C–S disconnection. We call this a 'one-group' C–X disconnection because we need to recognise only one functional group (ester, ether, amide etc.) to know that we can make the disconnection.

The corresponding reactions are mostly ionic involving nucleophilic displacement by $S_N1$, $S_N2$ or carboxyl substitution with amines, alcohols and thiols on carbon electrophiles. The normal polarity of the disconnection 1 will be a cationic carbon synthon 2 and an anionic heteroatom synthon 3 represented by acyl or alkyl halides 4 as electrophiles and amines, alcohol or thiols 5 as nucleophiles.

\[
\begin{align*}
R^+X &\rightarrow C-X \\
1 &\rightarrow 2 & 3 &\rightarrow RHal + HX \quad 4 & 5
\end{align*}
\]

It is possible to use the reverse polarity with a nucleophilic carbon synthon 6 and an electrophilic heteroatom synthon 7 but only with second or third row elements such as S, Si, P and Se. These synthons are represented by organometallic compounds 8 or 9 and compounds 10 such as RSCI, Me₃SiCl and Ph₂PCl and we shall consider these later.

\[
\begin{align*}
R'X &\rightarrow C-X \\
1 &\rightarrow 6 & 7 &\rightarrow RLi or RMgBr + X-Cl \quad 8 & 9 & 10
\end{align*}
\]

**Carbonyl Derivatives RCO.X**

We start with acid derivatives since we almost always choose to disconnect the bond between the heteroatom and the carbonyl group. So we make esters 11 and amides 13 from acid (acyl) chlorides 12 and alcohols or amines.

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The ester 14, used both as an insect repellent and as a solvent for perfumery, is easily made this way. The analysis reveals two available compounds: benzyl alcohol 15 and benzoyl chloride 16. Combining the two with pyridine as solvent and catalyst gives the ester 14.

Acid chlorides are often used in these syntheses because they are the most electrophilic of all acid derivatives and because they can be made from the acids themselves with PCl₅ or SOCl₂. The other important acid derivatives can all be made from acid chlorides or from any compound above them in the chart of reactivity. So you can make amides from acid chlorides, anhydrides or esters but it is very difficult to make any other derivatives from amides. All derivatives except amides can easily be made from the acids themselves.

A simple example is the weedkiller propanil 17 used on rice fields. Amide disconnection gives the amine 18 obviously made from o-dichlorobenzene 20 by nitration and reduction. All positions around the ring in 20 are about the same electronically but steric hindrance will lead to 19 being the major product.

The synthesis is very simple.¹ The only point worth noting is the use of catalytic hydrogenation for the reduction rather than the very messy tin and HCl. Industry greatly prefers catalytic methods with no toxic by-products.
4 The Synthesis of Ethers

The alternative disconnection, between the alkyl group and the heteroatom 21, is also acceptable but it would require an S_N2 reaction between the anion of the acid 22 and an alkyl halide. Reactions at carbonyl groups are much more reliable than S_N2 reactions and are usually preferred. Only if the S_N2 reaction is exceptionally good, as it would be to make the ester 23, is this route preferred.

\[
\begin{align*}
\text{ester} & \quad \text{ester} \\
21 & \quad 22 + 23
\end{align*}
\]

The Synthesis of Ethers

This same question of which bond to disconnect can be much more significant in the synthesis of ethers. With many ethers, like the gardenia perfume compound 24, it doesn’t matter much. The starting materials will be an alcohol 26 or 27 and an alkyl halide, say 25 or 28.

The reaction will be carried out by treating the alcohol with a base strong enough to form the anion—sodium hydride is a favourite as the hydride ion (H^-) is extremely hard and acts only as a base, never as a nucleophile. Either alcohol is available, either would give a nucleophilic anion. Either chloride is available, both react well in S_N2 reactions. We prefer route a as benzyl chloride 25 is more reactive and cannot undergo elimination while 28 just might.²

Choosing a Route Mechanistically

In other cases, the choice can be made because only one of the two S_N2 reactions will work well. The allyl phenyl ether 32 can be disconnected to bromobenzene 30 and the allylic alcohol 31 or to phenol 33 and the allylic bromide 34.
We might prefer route b because phenol is much more acidic (pK\textsubscript{a} 10) than an alcohol such as 31 (pK\textsubscript{a} about 15) and so a weaker base such as NaOH can be used. But the main reason to prefer route b is that route a will not work. Nucleophilic substitutions on bromobenzene do not work\textsuperscript{3} while those on allylic halides such as 34 work very well indeed\textsuperscript{4} (chapters 2 and 3).

\[ \text{phenol} \xrightarrow{\text{NaOH}} \text{phenolate} \xrightarrow{34} \text{product} \]

Notice that a disconnection we did not consider for a moment would come from reversal of polarity (in either C–O bond). Trying to improve disconnection a, we might suggest a nucleophilic phenyl species such as 36—perfectly all right—and an electrophilic oxygen reagent such as the hypochlorite 37—definitely not all right. If 37 existed it would be dangerously explosive.

Since alkyl halides are made from alcohols by treatment with reagents such as PBr\textsubscript{3} or HCl and a Lewis acid, it may make sense in designing the synthesis of ethers to write the two alcohols as starting materials and decide later which to convert into an electrophile. For ether 24 the two alcohols would be 27 and 26.

Either could be converted into the corresponding chloride or bromide. Benzyl chloride 25 is easy to make as both S\textsubscript{N}1 and S\textsubscript{N}2 reactions work well at a benzyl group. Formation of the primary alkyl bromide 38 needs more vigorous conditions but gives 83\% yield.\textsuperscript{5} In practice either compound can be bought cheaply.

If the ether is symmetrical, ROR, it is enough to treat the alcohol ROH with acid. Note that this applies only to symmetrical ethers. You would not get a good yield if you treated the mixture of 27 and 26 with acid: as well as the cross product, each alcohol would dimerise and there would be three products that would be very difficult to separate. This sort of question is considered in the next chapter.
The Synthesis of Sulfides

Unsymmetrical sulfides 39 need the same disconnection we have just used for ethers. The anion 41 of a thiol 42 will combine with an alkyl halide 40 to make a new C–S bond. The reaction is much easier with sulfur. Thiols are more acidic than alcohols, just as H₂S is more acidic than water. Sulfide anions 41 are more nucleophilic towards saturated carbon than are alkoxides and the risk of elimination is much less.

\[
\text{R}^1\text{S}^2 \text{R}^2 \xrightarrow{\text{C–S}} \text{R}^1\text{Hal} + \text{S}^2 \text{R}^2 \xrightarrow{\text{sulfide}} \text{HS} \text{R}^2
\]

The scaricide (kills mice and ticks) chlorbenside 43 is disconnected to give an acidic thiophenol 44 and a reactive alkyl halide 25. The synthesis merely combines these two in ethanol with NaOEt as base.⁶

\[
\begin{align*}
\text{Cl} & \xrightarrow{\text{C–S}} \text{Cl} \\
43 & \xrightarrow{\text{sulfide}} 44 + 25
\end{align*}
\]

Symmetrical sulfides can be made from the alkyl halide and Na₂S as the product from the first step is the monoanion needed to make the second C–S bond. The synthesis⁷ is just to combine the alkyl bromide with Na₂S in ethanol: dipropyl sulfide (R = Et) is formed in 91% yield from the bromide while dibenzyl sulfide (R = Ph) is made in 83% yield from benzyl chloride 25.

\[
\begin{align*}
\text{R} & \xrightarrow{\text{C–S}} \text{R} \\
45 & \xrightarrow{\text{sulfide}} 46 + 46
\end{align*}
\]

Summary of Compounds Made from Alcohols

Many nucleophiles we haven’t mentioned can be used in these reactions. In every case a nucleophilic heteroatom displaces a leaving group from a compound derived from an alcohol.
We have focussed on alkyl halides but tosylates from TsCl and mesylates from MsCl can be used too. The conversion of alcohols to chlorides and bromides is discussed earlier in this chapter and the combination of reagents used to make thiols is discussed in the next chapter.

\[
\text{TsCl = toluene-\(p\)-sulfonyl chloride} \\
\text{MsCl = methane sulfonyl chloride}
\]

References

Strategy II: Chemoselectivity

Background Needed for this Chapter References to Clayden, *Organic Chemistry*:
Chapter 8: Acidity, Basicity, and $pK_a$.
Chapter 24: Chemoselectivity: Selective Reactions and Protection.

If a molecule has two reactive groups and we want to react one of them and not the other we need chemoselectivity. Under this heading we can consider:

1. The relative reactivity of two different functional groups, such as $\text{NH}_2$ and OH.

   ![Reaction 1](image)

2. The reaction of one of two identical groups: we might want to make the *mono*ether 5.

   ![Reaction 2](image)

3. The reaction of a group once when it might react twice as in thiol synthesis.

   ![Reaction 3](image)

**Guideline 1:** If two groups have *unequal* reactivity, the *more* reactive can be made to react alone.

The amide 2 is paracetamol, the popular analgesic. Amines are much more nucleophilic than phenols (compare the basicities of ammonia and water) so reaction with acetic anhydride gives
the amide we want without any of the ester 3. The aminophenol 1 can be made by methods explained in chapter 2.

\[
\begin{align*}
\text{HO} & \quad \text{amide} & \quad \text{C-N} & \quad \text{FGI} & \quad \text{HO} & \quad \text{C-N} \\
\text{2} & & & & \text{10} & \quad \text{nitration} & \quad \text{11; phenol} \\
\end{align*}
\]

The synthesis is straightforward. Nitration of phenol needs only dilute nitric acid and the reduction is best carried out catalytically.\(^1\)

\[
\begin{align*}
\text{HO} & \quad \text{HNO}_3 & \quad \text{HO} & \quad \text{H}_2 & \quad \text{Ac}_2\text{O} \\
\text{11; phenol} & \quad \text{dilute} & \quad \text{10} & \quad \text{Pd/C} & \quad \text{TM2} \\
& & & & \quad \text{79\% yield} \\
\end{align*}
\]

The Synthesis of Cyclomethycaine

Selectivity between two oxygen nucleophiles might sound more difficult but when one is an alcohol and the other a carboxylic acid, there is no problem. The local anaesthetic cyclomethycaine 12 is obviously made from the carboxylic acid 13 and an amino-alcohol. The acid 13 is our concern. We disconnect the ether linkage 13a on the alkyl side so that the S\(_{N}\)2 reaction works. Chemoselectivity now arises as 15 has OH and CO\(_2\)H functional groups. Which will act as a nucleophile?

\[
\begin{align*}
\text{O} & \quad \text{NR}_2 & \quad \text{C-O} & \quad \text{ester} & \quad \text{HO(CH}_2\text{)}_3\text{NR}_2 \\
\text{12; cyclomethycaine} & & & & \text{an amino-} \\
& & & & \text{alcohol} \\
\text{O} & \quad \text{C-O} & \quad \text{ether} & \quad \text{X} & \quad \text{HO} & \quad \text{CO}_2\text{H} \\
\text{13a} & & & & \text{14} & \quad \text{15} \\
\end{align*}
\]

The answer is that it depends on the pH. Below about pH 5 15 is a neutral compound. The OH group is more nucleophilic than the delocalised CO\(_2\)H group but is not nucleophilic enough to react with an alkyl halide. We can increase its reactivity by adding base and, between about pHs 5 and 10, it exists as the carboxylate anion 16. We don’t want this as it will react at CO\(_2^-\) rather than at OH. But at pHs above about 10 it exists as the dianion 17 and now at last ArO\(^-\) is more nucleophilic than CO\(_2^-\).
All we need to do is to use two equivalents of a strong enough base with a suitable alkyl halide and we shall make our ether. As 14 is a rather unreactive secondary alkyl halide, we need a good leaving group such as iodide.  

**Guideline 2:** If one functional group can react twice, the product of the first reaction will compete with the reagent. The reaction will stop cleanly after one reaction only if the starting material is more reactive than the product.

So the reaction of an alkyl halide with NaSH or Na2S cannot usually be made to stop after one alkylation as the anion of the first product is at least as nucleophilic as HS− or S2−. This is obvious in reactions with Na2S. Less obviously with NaSH the first reaction 18 gives the thiol 19 but this is in equilibrium with RS− and a second displacement 20 gives the sulfide 21. We shall see shortly how to get round this problem. A more important example—the failure of the alkylation of ammonia to give a useful amine synthesis—has chapter 8 to itself.

But some reactions of this sort are successful. The synthesis of chloroformates from alcohols and phosgene (or a phosgene equivalent) is a useful example. We shall need benzyl chloroformate 21 in the next section to introduce an important protecting group. As it is an ester, disconnection to benzyl alcohol 22 and phosgene 23 looks good. But the product 21 is itself also an acid chloride and looks as though it might react again to form dibenzyl carbonate. But in this case there is delocalisation 24a in the product that is not present in phosgene and the carbonyl group of 21 is much less electrophilic than that of phosgene. The synthesis is successful. The halogenation of ketones in acid solution (chapter 7) is another example where a reaction occurs only once.

**Guideline 3:** Problems from guidelines 1 and 2 may be solved by protecting groups.

If we want to react the less reactive of two functional groups we protect the more reactive. If we want a reagent to react once when it could react twice we protect the reagent. A protecting group is something added to a functional group that reduces or eliminates unwanted reactivity. It must be easy to add and easy to remove as we are adding two steps to our synthesis. In an ideal world, no protecting groups would be needed but just look at any recently published synthesis of any moderately complex molecule and you will see several protecting groups. Protecting groups have chapter 9 to themselves.

A classic case is amino acid chemistry. The amine is more nucleophilic than the carboxyl group so, if we want to use the carboxyl group as a nucleophile, we must protect the amino group. Benzyl chloroformate 22 is often used in this way. It cleanly acylates the amino group to give the carbamate 26 whose nitrogen atom is much less nucleophilic because of further conjugation 27. If you compare 23, 22, and 26 you will see the carbonyl group becoming less
and less electrophilic. The anion of 26 will now react at oxygen (CO$_2^-$ in basic solution) with electrophiles.

\[
\begin{align*}
\text{Ph} & \text{O} \quad \text{O} \quad \text{CO}_2 \text{H} & + & \text{H}_2\text{N} \quad \text{CO}_2 \text{H} & \rightarrow & \text{Ph} & \text{O} \quad \text{N} \quad \text{CO}_2 \text{H} \\
\text{22} & & & \text{25} & & & \text{26} \\
\text{R} & \text{O} \quad \text{N} \quad \text{CO}_2 \text{H} & \leftarrow & \text{R} \quad \text{O} \quad \text{NH} \quad \text{CO}_2 \text{H} & \rightarrow & \text{R} & \text{O} \quad \text{N} \quad \text{CO}_2 \text{H} \\
\text{27} & & & & & \text{27}
\end{align*}
\]

The synthesis of thiols 19 is well managed if thiourea 28 is used instead of NaSH or Na$_2$S as the nucleophile. Thiourea is itself highly delocalised but it is still a good nucleophile for saturated carbon through the sulfur atom 29. The product is a thiouronium salt 30 and is not nucleophilic at all, being a cation. Hydrolysis with aqueous base liberates urea 31 and the thiol 19.

\[
\begin{align*}
\text{NH}_2 & \quad \text{S} \quad \text{NH}_2 & \text{Br} & \text{R} & \text{S} \quad \text{NH}_2 & \rightarrow & \text{R} & \text{S} \quad \text{NH}_2 & \overset{\text{NaOH}}{\xrightarrow{\text{H}_2\text{O}}} & \text{RSH} & + & \text{O} \quad \text{NH}_2 \\
28; \text{thiourea} & & 29 & & 30 & & 19 & & 31; \text{urea}
\end{align*}
\]

The sedative and tranquilliser captodiamine 32 contains two sulfides and four C–S bonds. Disconnection next to the more central sulfur atom 32 could be of either C–S bond. The one chosen leads to an available (but unpleasant) amine 34 and a thiol 33.

\[
\begin{align*}
\text{Ph} & \quad \text{S} \quad \text{NH}_2 & \xrightarrow{\text{C–S}} & \text{BuS} & \quad \text{SH} & + & \text{Cl} & \quad \text{NMMe}_2 \\
32; \text{captodiamine} & & & 33 & & & 34
\end{align*}
\]

Thiol 33 was made by the thiourea method from 35 and further disconnection by the methods from previous chapters takes us back to available benzene thiol 39.

\[
\begin{align*}
\text{BuS} & \quad \text{Ph} & \quad \text{Cl} & \xrightarrow{\text{C–S}} & \text{BuS} & \quad \text{OH} & \xrightarrow{\text{FGI}} & \text{BuS} & \quad \text{Cl} \\
33 & & \text{thiourea} & & \text{method} & & \text{35} & & \text{36} & & \text{37}
\end{align*}
\]

The first sulfide needs only a weak base as benzene thiol is acidic and the electron-donating BuS group directs para. The rest is straightforward.$^4$

\[
\begin{align*}
\text{PhSH} & \quad \text{BuCl} & \quad \text{Na}_2\text{CO}_3 & \quad \text{PhS} & \quad \text{BuCOCI} & \quad \text{AlCl}_3 & \quad \text{37} & \quad \text{1. NaBH}_4 & \quad \text{35} & \quad \text{34} & \quad \text{TM32} \\
39 & & & & & & & & & & \text{34}
\end{align*}
\]
Guideline 4: One of two identical groups may give a reasonable yield by a number of methods.

(a) In the same way as guideline 2, if the product from the first reaction is less reactive than the starting material, double reaction may be avoided.

Partial reduction of meta-dinitrobenzene is an example. Nitration of nitrobenzene 40 is difficult but succeeds with fuming nitric acid (about 90% HNO₃) in sulfuric acid and gives only the meta product 41 as expected from the deactivating nitro group.⁵ Reduction with NaHS cleanly gives \( m \)-nitroaniline by reduction of just one nitro group.⁶ The reason is that reduction is electron donation and the very electron-withdrawing nitro group encourages this. So the product 42 is less easily reduced than the starting material 41.

\[ \text{O}_2\text{N} \quad \xrightarrow{\text{fuming} \ HNO_3} \quad \text{O}_2\text{N} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{O}_2\text{N} \quad \xrightarrow{\text{NaHS} \ \text{MeOH}} \quad \text{O}_2\text{N} \quad \xrightarrow{\text{NH}_2} \quad \text{O}_2\text{N} \]

(b) If the starting material and the mono-reacted product are of roughly equal reactivity, reaction with one equivalent of reagent may give a moderate yield by the statistical method.

Treatment of the symmetrical diol 43 with strong base gives a mixture of monoanion 44, starting material 43 and the dianion. If the mixture were perfectly statistical, and each species equally nucleophilic, we should expect 50% 44 and 25% each of 43 and the dianion. It turns out that the starting material does not react with EtBr and there is evidently less of the dianion, presumably because the two anions are near enough to destabilise each other. The yield of the monoether 45, used in a synthesis⁷ of vitamin E, is 65%, substantially higher than 50%.

\[ \text{HO} \quad \xrightarrow{\text{Na}} \quad \text{HO} \quad \xrightarrow{\text{EtBr}} \quad \text{HO} \quad \xrightarrow{\text{EtO}} \]

(c) The best method is to combine the two identical functional groups into one functional group that reacts once to give a product of much lower reactivity than the starting material. This cannot always be arranged but cyclic anhydrides such as 48 are very useful reagents. If either 47 or 48 are combined with methanol in acidic solution, the diester 46 is formed. But in basic solution the anion of the monoester 49 is the product and the remaining acid group can be transformed into, say, the acid chloride 50 so that each carboxylic acid has been activated in a different way.

\[ \text{CO}_2\text{Me} \quad \xrightarrow{\text{MeOH} \ \text{acid}} \quad \text{CO}_2\text{H} \quad \xrightarrow{\text{Ac}_2\text{O}} \quad \text{CO}_2\text{Me} \quad \xrightarrow{\text{MeO}} \quad \text{CO}_2\text{H} \quad \xrightarrow{\text{SOCl}_2} \quad \text{CO}_2\text{Me} \]

The method works because methoxide attacks either carbonyl group 51 displacing the carboxylate anion. The product under the reaction conditions is 52 and methoxide will not attack another anion to make the diester. Neutralisation gives the half ester ⁸ 49.
The cyclic anhydride can also be used in Friedel-Crafts reactions. Note the position of acylation on 53-para to the chlorine and not to the methyl group—and that acylation has occurred only once. The product 54 was used in the synthesis of fungicidal compounds.9

These methods, particularly (a) and (b), depend on efficient separation of the starting material and the products from mono- and di-reaction. If separation cannot be achieved then a very good method is needed.

A Warning

If two groups are nearly but not quite identical, do not attempt to react one and not the other. Examples include the diols 55 and 56 where one extra methyl group is not enough to make a significant difference in reactivity. Attempts to make a specific monoether from either are doomed.

References

6 Two-Group C–X Disconnections

Background Needed for this Chapter References to Clayden, *Organic Chemistry*:
Chapter 10: Conjugate Addition.
Chapter 21: Formation and Reaction of Enols and Enolates.

One-Group and Two-Group C–X Disconnections

As you make the sulfi de 1 you would not hesitate to disconnect a C–S bond, choosing the one between the sulfur and the aliphatic part of the molecule to ensure a good $S_N2$ reaction. There is only one functional group in the target molecule 1 so you have to choose a one-group C–X disconnection.

\[
\begin{align*}
\text{PhS} & \xrightarrow{\text{C–S}} \text{sulfide} \quad \text{PhS}^\ominus \quad + \quad \text{Br} \\
1 & \quad 2 & \quad 3
\end{align*}
\]

If you were asked to make the sulfi de 4 you might very reasonably take the same decisions, proposing the same sulfur compound 2 as nucleophile and the alkyl bromide 5 as electrophile.

\[
\begin{align*}
\text{PhS} & \xrightarrow{\text{C–S}} \text{sulfide} \quad \text{PhS}^\ominus \quad + \quad \text{Br} \\
4 & \quad 2 & \quad 5
\end{align*}
\]

There is nothing wrong with this suggestion except that it ignores the other functional group—the ketone—in the target molecule 4 and so misses an opportunity for a two-group disconnection. Our message in this chapter is going to be that two-group disconnections are better than one-group disconnections. Reverting to synths for a moment, the sulfur synthon 2 is the same as the reagent but the carbon synthon 6 might make you think of a different reagent.
The idea with two-group disconnections is that we recruit the other functional group to help us discover a better reagent. Here the carbonyl group can make the cationic centre in 6 electrophilic if we simply add a double bond to the structure.

\[
\text{PhS} \quad \text{4} \quad \overset{\text{C-S}}{\text{sulfide}} \quad \text{PhS}^+ \quad \overset{\text{2}}{\text{+}} \quad \text{6; synthon} \quad \implies \quad \text{7; reagent}
\]

The reaction is conjugate addition of the thiolate anion 2 to the enone 7 making an enolate intermediate that captures a proton from PhSH 8 to give the target molecule 4 and regenerate the nucleophile 2.

This route using 7 is better than the first suggestion using 5 for several reasons.

1. There is no need to waste an atom of bromine to provide a leaving group: the enone 7 is naturally electrophilic at the right carbon atom.
2. The two functional groups in the target molecule co-operate in making the new C–S bond.
3. No strong acids, bases or high temperatures are needed as the enolate intermediate regenerates the reagent 2 so only catalytic weak base is needed.
4. The bromide 5 is likely to eliminate under the reaction conditions to give 7 anyway.

**Recognising a Two-Group C–X Disconnection**

The key step is recognising the relationship between the two functional groups. To do this, number the carbon atoms bearing the functional groups. It doesn’t matter which you call 1 —only the relationship matters. Here we see 4a that we have a 1,3-diX relationship. That means that the two functionalised carbon atoms have a 1,3-relationship. Knowing that, we can choose conjugate addition as our reaction and do the disconnection 4b we have already done and reveal 2 and 7 as our reagents.

![Diagram showing the recognition of a 1,3-diX relationship and the disconnection](image-url)

To start with you may like to draw the synthons and, by inspecting the carbon synthon, decide which electrophilic reagent to use. But as this chapter develops, you will see that there is a particular chemistry used to make each different relationship (e.g. a 1,3-relationship suggests conjugate addition) and you may soon not bother with the synthons but write the reagents directly. This is a matter for personal choice.
The 1,3-diX Relationship

Since we are using conjugate addition, it is essential to have an electron-withdrawing group, usually a carbonyl group but it could be CN for example, in the right position. The disconnection in general terms is this:

\[
\begin{align*}
\text{9: } & \quad \text{X} \quad \text{C-X} \quad \text{XH} \\
\text{10: } & \quad \text{R} \quad \text{O} \\
\text{11: } & \quad \text{synthon} \\
\text{12: } & \quad \text{reagent}
\end{align*}
\]

The nucleophilic reagent will depend on the heteroatom. If X=O or S, base will probably be necessary, but if X=N, the amine itself should be nucleophilic enough to do conjugate addition. An example would be the amino ester 13. Numbering the carbon atoms 13a reveals the 1,3-relationship and C-N disconnection gives the secondary amine 14 and ethyl acrylate as reagents.

\[
\text{13: } \quad \text{CO}_2\text{Et} \quad \longrightarrow \quad \text{number} \quad \text{13a: } \quad \text{CO}_2\text{Et} \\
\text{14: } \quad \text{NH} \quad + \quad \text{15: } \quad \text{CO}_2\text{Et}
\]

This is the time to reveal a potential problem. In this synthesis we want conjugate addition. But we might on another occasion want to make the amide 18 so how do we control whether the nucleophile adds direct to the carbonyl group or by conjugate addition 17? In general the reactivity of the electrophile is crucial. Very electrophilic compounds such as acid chlorides or aldehydes tend to prefer direct addition while less electrophilic compounds such as esters or ketones tend to do conjugate addition.

\[
\text{16: } \quad \text{CO}_2\text{R} \quad \text{conjugate} \quad \text{addition} \\
\text{17: } \quad \text{NH} \quad \text{HN} \quad \text{X} \quad \text{Cl} \quad \text{direct} \quad \text{addition} \\
\text{18: } \quad \text{NH}
\]

What if There Is No Carbonyl Group?

The amino alcohol 19 has a 1,3-diX relationship but no carbonyl group. So we introduce one by FGI. We could have an ester or an aldehyde. An aldehyde would be easier to reduce but there is a danger of direct addition. So we choose an ester (it doesn’t matter which).

\[
\text{19: } \quad \text{Ph} \quad \text{NH} \quad \text{OH} \quad \text{FGI} \quad \text{Ph} \quad \text{NH} \quad \text{1,3-diX} \\
\text{20: } \quad \text{3} \quad \text{2} \quad \text{1} \quad \text{CO}_2\text{Me} \quad \text{Ph} \quad \text{NH}_2 \quad + \quad \text{CO}_2\text{Me}
\]

The synthesis is straightforward and we shall need LiAlH₄ to reduce the ester.

\[
\text{21: } \quad \text{Ph} \quad \text{NH}_2 \quad + \quad \text{CO}_2\text{Me} \quad \longrightarrow \quad \text{22: } \quad \text{Ph} \quad \text{NH} \quad \text{CO}_2\text{Me} \quad \text{LiAlH}_4 \quad \text{TM19}
\]
Supposing there is no oxygen-based functionality at all, as in the diamine 23? It is not necessary to have a carbonyl group for conjugate addition, in fact a nitrile is much better. So we do FGI on the primary amine and disconnect the secondary amine Et$_2$NH from acrylonitrile 25. The synthesis is to mix those two and reduce 24 catalytically or with LiAlH$_4$.

Examples of 1,3-Difunctionalised Compounds

Enantiomerically pure chloro-ester 26 was needed for an investigation into the stereochemistry of the Friedel-Crafts reaction. Disconnecting the ester we reach the one piece of carbon skeleton and see that it has a 1,3-diX relationship 27. However we need a carbonyl group and an ester 28 should ensure conjugate addition of chloride to 29.

The acid itself was chosen for the conjugate addition as the intermediate can then be resolved by crystallisation of the quinine salt. Conjugate addition of HCl was successful and the acid was reduced to the alcohol with LiAlH$_4$ before esterification in the usual way.$^1$

The aminoether 30 containing a seven-membered ring has a 1,3-relatioaship but no carbonyl group. We could remove the seven-membered ring and put a carbonyl group at C-3 but a shorter synthesis comes from the nitrile 31 as we can add the alcohol 32 in one piece to acrylonitrile 25.

The synthesis is a simple two-stage process with catalytic hydrogenation used for reduction of the nitrile.$^2$
The 1,2-diX Relationship

The 1,2-diX relationship presents a different series of opportunities in which we use the second functionality to make the right carbon atom electrophilic. The amino, thio- and alkoxy-alcohols 33 to 35 all fit the pattern 36 and can be disconnected to the usual heteroatom nucleophile and the synthon 37.

If you don’t see at once what reagent will be used for the synthon 37, you are not alone. How can we use the other OH group at C-1 to make C-2 electrophilic? One way to visualise the answer is to imagine what would happen if you actually made the cation 37. It would instantly cyclise 38 to form a three-membered ring 39 that could lose a proton to give the epoxide 40. Epoxides are strained ethers and react with nucleophiles such as amines 41 to give 42 and hence the aminoalcohol 33.

It doesn’t matter which end of the symmetrical epoxide is attacked by the nucleophile—the same product 42 is formed. If there is a substituent at either end of the molecule 43 or 45 we can still make the 1,2-diX disconnection but the ‘two’ epoxides 44 are the same. This is clearly a problem. In fact the nucleophile will prefer to attack the less substituted end of the three-membered ring 46 so we can make 45 but not 43 this way.

The disconnection 47 gives a different synthon 48 at the carbonyl oxidation level and the best reagents are the α-halo carbonyl compounds 49. At first this looks like a one-group disconnection but there are two reasons why it isn’t. The presence of the carbonyl group makes the S_N2 displacement of halide enormously faster and the α-halo carbonyl compounds 49 are made from the ketone 51 by acid-catalysed halogenation of the enol 50.
Examples of 1,2-Difunctionalised Compounds

The ether 52 was needed to study the Claisen rearrangement and can be disconnected in 1,2-diX fashion as the epoxide 54 will be attacked at the less hindered end by the anion of 53.

The synthesis involves treating the allylic alcohol 53 with NaH to make the anion 55 and combining that with the epoxide 54 easily made from styrene.\(^3\)

Compounds like the ester 56 were briefly mentioned in chapter 4 and we can now show how they can be made by a two-group disconnection. The electrophile will be the α-halo carbonyl compound 57 and the nucleophile the anion of a carboxylic acid.

The bromide 57 is made by direct bromination of the ketone 59 and only the very weak base NaHCO\(_3\) is needed to make the anion of the carboxylic acid. This reaction shows just how electrophilic such α-halo carbonyl compounds must be as carboxylate anions are very weak nucleophiles. Compounds 56 are therefore derivatives of carboxylic acids. They are highly crystalline and can be used to characterise and purify such acids.\(^4\)

The Pfizer anti-fungal compound fluconazole 60 is a more advanced example of such disconnections.\(^5\) It has two identical 1,2-diX relationships between nitrogen and the OH group. You might think that we can make both the same way, but not so. The first disconnection is easy: we want the aromatic amine triazole 62 to combine with the epoxide 61 at its less substituted end.
But how are we to make the epoxide 61? The obvious route is by epoxidation of the alkene 63. The alkene 63 could be made by a Wittig reaction (chapter 15) on the ketone 64 or directly by sulfur ylid chemistry (chapter 30).

The ketone 64 still has a 1,2-diX relationship but at the carbonyl oxidation level, so we disconnect to another molecule of triazole 62 and the α-halo ketone 66 is easily made by a Friedel-Crafts reaction using available chloroacetyl chloride. This time we buy the 1,2-diX relationship in the form of chloroacetyl chloride.

The synthesis follows the analysis exactly giving fluconazole 60 in only 5 steps from available starting materials. This synthesis should demonstrate that important modern drugs are made by the style of reactions that you are meeting in this book.6

The 1,1-diX Relationship

The label ‘1,1-diX’ may look strange but all it means is that the two functional groups are joined to the same carbon atom. You already know how to make acetals 68: you combine an aldehyde 67 with an alcohol, say methanol, in acidic solution. The disconnection 68a is therefore of both C–O bonds. This reveals a valuable truth: two heteroatoms joined to the same carbon atom are at the carbonyl oxidation level (two C–O bonds to the same C atom in both 67 and 68) and the TM is probably made from a carbonyl compound.

Again you may think that we are not using the two groups in cooperation. But we are. The key step in acetal formation and hydrolysis is the expulsion of one OR group by the other. In the synthesis, protonation of the hemiacetal 69 is followed by expulsion of a molecule of water 70 and the addition of the second molecule of methanol 71 is possible because of the first. In the
hydrolysis, these steps happen in reverse. Acetals are not ‘just ethers’—they are more reactive compounds because of the two RO groups joined to the same carbon atom.

If the two heteroatoms are the same, it is usually best to disconnect both C–X bonds, choosing the ones to the same carbon atom, and write a carbonyl group at that atom. The heterocycle 72 has two C–N bonds to the same carbon atom. If we disconnect both, we get cyclohexanone and a very unstable looking imine 73. We know how to make imines: combine a carbonyl group with an amine so disconnecting both imines we end up with the diketone 74 and two molecules of ammonia.

Supposing you had not noticed the 1,1-diX relationship but had spotted the imines. Disconnection 72a takes us directly to the diketone 74 and a very unstable diamine 75. Now you can’t avoid the 1,1-diX disconnections 75 and we get the same starting materials whichever analysis we follow.

But what about the synthesis? When we are making stable 5- or 6-membered rings, syntheses are often very forgiving as you will discover in chapters 29 and 39. All you need to do is to mix together the two ketones with ammonium acetate, to provide both a source of ammonia and an acid catalyst, and TM72 is formed in good yield. If the heteroatoms are different and one of them is oxygen, it makes more sense to disconnect the other so that the oxygen of the carbonyl group remains. The phosphonate 76 is an example. The nucleophilic synthon is 77 and this can be made by deprotonation of 78.
As this chemistry may be unfamiliar, you may like to know that 78; R=Et, known as diethyl phosphite, is available and forms the anion 77, better drawn as 79, with bases and adds 80 to aldehydes to give the anion 81 of the TM.

\[
\begin{array}{c}
\text{base} \\
78 \quad \rightarrow \\
\overset{\text{H}}{\overset{\text{O}}{\overset{\text{P(OR)}_2}{\text{77}}} \quad \rightarrow \\
\overset{\text{R}}{\overset{\text{O}}{\overset{\text{P(OR)}_2}{\text{79}}} \quad \rightarrow \\
\overset{\text{R}}{\overset{\text{O}}{\overset{\text{P(OR)}_2}{\text{80}}} \quad \rightarrow \\
\overset{\text{R}}{\overset{\text{O}}{\overset{\text{P(OR)}_2}{\text{81}}} \quad \rightarrow \\
\end{array}
\]

A real life example is made from 82 and 78; R=Et with the weak base Et₃N. This produces some of the anion 79; R=Et and the ammonium salt protonates the anion of the TM to give 83 in excellent yield.

\[
\begin{array}{c}
\text{82} \\
\end{array}
\quad +
\begin{array}{c}
\text{O} \\
\text{H-P(OEt)}_2 \\
\text{78; } R = \text{Et} \\
\end{array}
\quad \rightarrow
\begin{array}{c}
\text{83; } \text{94% yield} \\
\text{Et₃N} \\
\end{array}
\]

Two-Group C–X Disconnections as a Preliminary to a Full Analysis

A brief inspection of the polycyclic cage structure of the natural product sarracenicin 84 makes it appear a formidable target for synthesis. As we move forward into the book, it will become more and more important to identify any continuous pieces of carbon skeleton and an essential preliminary for that is to disconnect any structural C–X bonds, preferably using two-group disconnections. That strategy works spectacularly well here. Sarracenicin 84 has several C–O bonds in its skeleton. One obvious 1,1-diO relationship is marked with a black blob in 84 showing where an acetal indicates a hidden carbonyl group. The black blob on 84 is the aldehyde in 85. Disconnecting the acetal gives 85 with two fewer rings.

Further into the skeleton is another hidden carbonyl group 85 masked as a hemiacetal rather than an acetal. Disconnection there shows up an enol 86 and conversion of the enol into the aldehyde gives the simplest structure we have yet seen 87 without any rings at all. Indeed if we redraw that structure in a more conventional way 88, we can see that it is one continuous piece.
of carbon skeleton. One published synthesis\(^8\) reconnects the two aldehydes on the right to give one alkene and the aldehyde and alcohol on the left to give another \(89\). This compound looks a great deal simpler than sarracenin but in fact has exactly the same number of carbon atoms. We shall meet the reconnection strategy in chapter 27.

References

Strategy III: Reversal of Polarity, Cyclisations, Summary of Strategy

This chapter considers in more depth two strategic points that emerged from the discussion of C–X disconnections in chapters 4–6.

Reversal of Polarity
Synthesis of Epoxides and α-Halo-Carbonyl Compounds

In chapter 6 we needed three types of synthon depending on the di-X relationship in the target molecule. For the 1,3-diX relationship we used just one synthon 2, for the 1,2-diX we used related synthons 5 and 8, and for the 1,1-diX two more 11 and 14. The synthons for the 1,3-diX and 1,1-diX relationships could be turned into reagents 3, 12 and 15 simply by using the natural electrophilic behaviour of the carbonyl group. The synthons 5 and 8 for the 1,2-diX relationship could not be turned into reagents so easily; reagent 6 does not resemble synthon 5 while synthon 8 looks very unstable and such intermediates cannot be made.

![Chemical structures](image)

We solved those problems by using an epoxide 6 for synthon 5 and an α-haloacetone 9 for 8: two apparently different devices that actually rely on the same principle—one that is the subject of this chapter. It is easy to see with the synthon 8: if we simply reverse the polarity to the anion
16 we discover a synthon that again uses the natural reactivity of the carbonyl group as an enol 17 (or enolate) in equilibrium with the ketone 18 by tautomerisation.\(^1\) Treatment of the ketone 18 with bromine in acidic solution gives the α-haloketone 9 with an electrophilic carbon atom in the right place.

![Chemical diagram](http://www.chem4all.vn)

The epoxide 6 is naturally electrophilic, but where does the epoxide come from? By far the most important method of epoxide synthesis is the treatment of alkenes 19 with peroxo acids RCO₂H 21. Alkenes are naturally nucleophilic:\(^2\) they react with bromine to give dibromides 20 and with electrophilic peroxyacids 21 to give epoxides. Again, these reactions convert nucleophilic alkenes into electrophilic derivatives. A very popular reagent for epoxidation is mCPBA (meta-chloro-perbenzoic acid) 21; R = 3-chlorophenyl but many other compounds are used.

![Chemical diagram](http://www.chem4all.vn)

The Halogenation of Ketones

The halogenation of ketones must be carried out in acid solution to avoid polyhalogenation.\(^1\) So the synthesis of reagent 22, used to make derivatives of carboxylic acids in chapter 6, is simple providing that we notice the directing effects of the two groups on the benzene ring in 23 and disconnect with Friedel-Crafts in mind.

![Chemical diagram](http://www.chem4all.vn)

The synthesis is very straightforward: no bromination occurs on the ring as would be expected in the absence of a Lewis acid. Enols react with bromine without the need of any catalysis.\(^3\)
This bromination was unambiguous as the ketone could enolise on one side only. In general the reaction is suitable only for ketones that are symmetrical (e.g. 25), blocked on one side (e.g. 23 or 27) or which enolise regio-selectively (e.g. 29).

Halogenation of Acids

There is no ambiguity in the halogenation of acids as they can of course enolise on one side only. Reliable methods are bromination with PCl₃ and bromine or red phosphorus and bromine. The acid is converted into the acyl chloride with PCl₃ or the acid bromide by PBr₃, formed in the reaction mixture from red phosphorus and bromine. Bromohexanoic acid 34 can be made in good yield if the reaction mixture is worked up with water.

If the reaction is quenched with an alcohol, only the acyl halide reacts and this is a simple way to make α-bromoesters 38. The alternative product 39 is not formed. Water and alcohols are poor nucleophiles in the SN2 reaction but better with carbonyl groups.

Many α-chloroacids are available commercially (chloro-acetic, propanoic, etc.) and chloroacetyl chloride 41 is made on a very large scale industrially. The α-chloro amide 40, needed to make some analeptic tetrazoles, is best disconnected as an amide as 41 is cheap.

It is better to acylate aniline before nitration to prevent oxidation or over-nitration and reduce the proportion of ortho-nitration. The yield of 45 is after separation from the ortho isomer. Notice that in the last step nitrogen, like oxygen, prefers to attack the acyl rather than the alkyl chloride.
Cyclisation Reactions

Generally intramolecular reactions are easier than intermolecular reactions: entropy being a major factor. If you want to make an acetal from a ketone (chapter 6) it is better to use a diol 47 rather than, say methanol. The equilibrium is in favour of the cyclic acetal 48 but not in favour of the methyl acetal 46. Two molecules—one of each—go into 48 but three—two alcohols and one ketone—go into 46. Entropy is a thermodynamic factor.

![NMR spectrum](http://www.chem4all.vn)

But the rates of cyclisations to form 3-, 5-, 6- and 7-membered rings are greater than the rates of corresponding bimolecular reactions. This is kinetics but the smaller loss of entropy (fewer degrees of freedom lost in the cyclisation) is also a factor. We should not expect a good yield in an acid-catalysed ether formation from two alcohols. If the reaction worked at all, we should get dimers of each alcohol as well as the mixed ether 51.

![NMR spectrum](http://www.chem4all.vn)

But if the reaction were a cyclisation of the diol then things would be very different. The rate of the cyclisation will be much greater so even this unpromising reaction should go well. And no regioselectivity problems would arise. If the side chains on nitrogen were different 52 we should still get the same product 53 regardless of which OH group were protonated and which acted as the nucleophile. The parent compound 54 is morpholines and this unit is present in many drugs such as the analgesic phenadoxone\(^{14}\) 55.

![NMR spectrum](http://www.chem4all.vn)

The necessary diol for such compounds comes, by two 1,2-
\textit{diX} disconnections 56, from the amine RNH\(_2\) and two molecules of ethylene oxide. Now we want the epoxide to react twice so an excess is used and the diol 56 cyclised in acid.\(^{12}\)

![NMR spectrum](http://www.chem4all.vn)

Choosing cyclisation reactions can make possible syntheses we should certainly reject if a bimolecular reaction were required. The ether disconnection 58 gives a perfectly reasonable...
dil 59 that would certainly cyclise as we wish. But making 59 would involve creating an ortho relationship with the unwanted para relationship probably preferred.

![Chemical structure diagram]

We should not normally consider the Friedel-Crafts alternative 58a as the intermediate 61 would be unstable. But what that means is that 61 will cyclise rapidly to 58. Indeed it is difficult to isolate13 61 as it gives 58 even at 35°C.

![Chemical reaction diagram]

A dramatic example occurs in the last stage of the production of sildenafil 63 the Pfizer treatment of male erectile dysfunction better known as Viagra™. The cyclisation of 62 must involve the attack of the nitrogen atom of one amide on the carbonyl atom of the other (arrows show first stage). This is an exceptionally difficult reaction: amides are very poor nucleophiles and very poor electrophiles. Yet this reaction goes in over 90% yield.14 It does so because it is intramolecular.

![Chemical reaction diagram]

The diamide 62 is heated under reflux for several hours in t-butanol with the base t-BuOK as catalyst so it may be that the anion of the nucleophilic amine is involved. Afterwards, dilution with water and neutralisation to pH 7.5 with HCl gives pure 63.

**Summary of Strategy**

In chapter 1 we gave the bare bones of synthetic strategy. We can now add life to those bones by adding the main points from chapters 2–7. There will be fuller outlines as the book progresses.
Analysis:

1. Recognise the functional groups in the target molecule.
2. Disconnect with known reliable reactions in mind, using FGI as needed to give the right FG. Disconnect:
   (a) Bonds joining an aromatic ring to the rest of the molecule, whether Ar−X or Ar−C (chapters 2 and 3);
   (b) Any C−X bond (chapter 4) especially:
       (i) Bonds next to carbonyl groups RCO−X (chapter 4);
       (ii) Using two-group disconnections (chapter 6);
       (iii) Bonds in saturated rings as cyclisations are so good (chapter 7).
3. Repeat as needed to reach available starting materials.

Synthesis:

1. Write out the plan in the forward direction adding reagents and conditions.
2. Check that a rational order of events has been chosen (chapter 3).
3. Check that chemoselectivity is favourable (chapter 5). Use protection if necessary (chapter 9).
4. Modify the plan from points 2 and 3 (and later from unexpected failures or successes in the laboratory).

Example: Salbutamol

The anti-asthma drug salbutamol 64, better known as GSK’s Ventolin™, is closely related to adrenaline 65. The extra carbon atom, marked with a black blob in 64, prevents dangerous side effects on the heart and the t-butyl group makes the drug longer lasting.

Salbutamol has three hydroxyl groups and an amine but the only two-group C−X disconnection is of the C−N bond 64a revealing the epoxide 66 as a starting material. This approach is successful but it involves chemistry we encounter in chapter 30 so we shall discuss it there.

An alternative is FGI back to the ketone 67 and hence the α-bromoketone 68 that can be made from the ketone 69 itself by methods discussed earlier in this chapter. The ketone 69 is clearly made by some sort of Friedel-Crafts acylation, but how are we to make the diol 70? In chapter 3 we said that a good strategy to make ortho-disubstituted aromatic compounds was to start with an
available compound with that relationship already present. Here the obvious candidate is salicylic acid 71.

Further consultation of chapter 3 reveals the synthesis of the related ketone 73 by a Friedel-Crafts style reaction on aspirin 72. As we have two reductions (of the acid and the ketone) it makes sense to do them both at the end. The plan is now:

Checking for chemoselectivity problems, we might suspect that the amine could be alkylated twice by the very reactive α-bromoketone 74 so it might be better to protect the nitrogen atom with a benzyl group. This can be removed by catalytic hydrogenation. In the laboratory, it proved better to brominate 73 in neutral rather than acidic solution so the final scheme becomes:

This synthesis is short and high yielding, makes good use of the strategic points used so far in this book and introduces the subjects of the next two chapters: amine synthesis and the use of protecting groups.
References

5. O. Widman and E. Wahlberg, *Ber.*, 44, 2065.
Amine Synthesis

**Background Needed for this Chapter** Reference to Clayden, *Organic Chemistry*: Chapter 14: Nucleophilic Substitution at C=O with Loss of Carbonyl Oxygen.

Amine synthesis needs a separate chapter because the C–X disconnection 1a used for ethers, sulfides and the like in chapter 4 is not suitable for amines. The problem is that the product of the first alkylation 2 is at least as nucleophilic as the starting material 1 (if not more so because of the electron-donating effect of each alkyl group) and further alkylation occurs giving the tertiary amine 3 or even the quaternary ammonium salt 4. It is no use adding just one equivalent of Mel as the first formed product 1 will compete with the starting material 2 for Mel.

![Chemical structure](image)

The simple alkylation of an amine with an alkyl halide can occasionally be used if the product is less nucleophilic than the starting material. This may be for electronic reasons: glycine 6 can be made by alkylation of ammonia with 5 as it exists mostly as the zwitterion 7 which no longer has a nucleophilic nitrogen. It may be for steric reasons: the alkylation of the α-bromoketone 8, mentioned at the end of chapter 7, with the sterically hindered amine 9 gives a good yield of the even more sterically hindered amine 10 and no quaternary salt is formed. If the reaction is a cyclisation (chapter 7) it may also work well.

![Chemical structure](image)
More general solutions come from the replacement of alkylation by reactions with carbonyl compounds. These generally occur once only and in many cases cannot occur twice as the products — amides 12 or imines 15 for example — are much less nucleophilic than the starting amine. The products are reduced to the target amines. The amide route is restricted to amines with a CH₂ group next to nitrogen 13 but the imine route is very general and is known as reductive amination.¹ It is the most important way to make amines and a recent survey showed that the majority of amines made in the pharmaceutical industry are made this way.

A preliminary FGI is needed before we apply the C–N disconnection. Amine 17 could be made from amide 18 or imine 21 and hence from two different primary amines 20 or 22 and two different carbonyl compounds 19 or 23. These methods are very versatile.

One published synthesis of this amine 17 is by reductive amination.² Note that it is not necessary, nor usually desirable, to isolate the rather unstable imine as reduction with NaB(CN)H₃ or NaB(OAc)₃H occurs under the conditions of imine formation.³ Since the imine is in equilibrium with the starting materials, slightly acidic conditions must be used so that the protonated imine is reduced more rapidly than the aldehyde or ketone. These two reducing agents are stable down to about pH 5.

An example that has been made by the amide route is the cyclic amine 24. Putting the carbonyl group on the side chain 25 allows us to use readily available piperidine 26 as a starting material. The synthesis⁴ uses catalytic reduction to give 24 in 92% yield from the amide 25.
Reductive Amination

This most versatile of amine syntheses can be used to make primary, secondary or tertiary amines providing only that an imine can be formed with an aldehyde or ketone. But tertiary carbon atoms cannot be joined to nitrogen by reductive amination as a tertiary carbon atom cannot have a carbonyl group. The method works by selective reduction of the imine 28 in the presence of the aldehyde 27 or ketone. Catalytic hydrogenation reduces the imine 28 preferentially as the C= N bond of the imine is weaker than the C=O bond of the aldehyde or ketone.

![Reductive Amination Reaction](image)

Normal nucleophilic reducing agents like NaBH₄ would reduce the more electrophilic aldehyde 27 in preference to the imine 28. They must be used in slightly acidic solution (pH 5–6) so that the more electrophilic imine salt 29 is reduced. But reducing agents like NaBH₄ are unstable in acidic solution, decomposing to hydrogen gas. That is why modified borohydrides [NaB(CN)H₃ or NaB(OAc)₃·H] are used. The electron-withdrawing CN or OAc groups reduce the nucleophilicity of the hydride(s) attached to boron, making it more selective towards the imine salt 29 and stabilising it in acid.

If the imine is stable enough to be isolated, as with diaryl imines 32 or crowded aliphatic amines such as 35, then NaBH₄ can be used for the reduction as there is no competition with unreacted aldehyde.

![Reductive Amination Reaction](image)

Primary Amines by Reductive Amination

The amine needed would be ammonia but unsubstituted imines 36 are very unstable. Ammonium acetate is usually used as the source of ammonia and to get the right pH for reductive amination with NaB(CN)H₃ or NaB(OAc)₃·H. Either aldehydes 37; R² = H or ketones 37 can be used.

![Reductive Amination Reaction](image)

Secondary Amines by Reductive Amination

Examples 17, 30 and 33 show how this works with aldehydes. Ketones give amines such as 40 and both can be discovered just by using the disconnections 28a and 41. If one of the two carbon atoms joined to nitrogen is tertiary, that must be R² in 30 or R³ in 40 as a tertiary centre cannot be set up by reduction.
Tertiary Amines by Reductive Amination

It may appear at first sight that tertiary amines cannot be made by reductive amination as an imine cannot be made. If a secondary amine such as piperidine 42 reacts with an aldehyde, the product is an enamine 44 not an imine. But reflect: the enamine 44 is formed by deprotonation of the imine salt 45 and that is the species we need for reaction with NaB(CN)H₃ or NaB(OAc)₃H to give the tertiary amine 46. So there is no problem.

The disconnections are straightforward: just draw the iminium salt 48 or 50 after FGI on the tertiary amine 47 or 49 and disconnect the C=N bond in the usual way. You will often have three choices as to which iminium salt you draw. Only if one of the substituents on nitrogen is tertiary is that option not available. We explore that problem soon.

Other Ways to Make Amines

Primary Amines by Alkylation with Alkyl Halides

There is one method of direct alkylation of a nitrogen nucleophile. Preliminary FGI (with reduction in mind again) to an alkyl azide 52 allows C–N disconnection to the alkyl halide and azide ion 54. This interesting species is linear and can slip into crowded molecules like a tiny dart. But there is a drawback: all azides are toxic and POTENTIALLY EXPLOSIVE.

A salt such as sodium azide is used and the reduction can be carried out catalytically, with NaBH₄ or with Ph₃P in protic solution. Simple amines such as octylamine 57 can be made this way.⁶ The azide 56 is not isolated but the whole reaction sequence carried out in the same aqueous solution to reduce the danger of an explosion.
A more deep-seated disconnection comes from a different FG1 (using reduction yet again) with the idea that cyanide ion 61 should be the nucleophile. This makes a C–C bond rather than a C–N bond but does at least disconnect two atoms. Cyanide is an interesting structure: it has to be linear and it has a lone pair on nitrogen and a negative charge on carbon making it one of the rare genuine carbonions. There is again a drawback: cyanides are very toxic.

This method is particularly useful if the SN2 reaction with cyanide is favourable as with benzyl bromide 62. The reduction can be carried out with a variety of reagents: here hydrogenation over Raney nickel gives a good result.7

**Joining Tertiary Carbon to Nitrogen**

One way to do this uses aliphatic nitro compounds and is discussed in chapter 22. One direct method is the Ritter reaction8 successful only for tertiary alkyl groups as it involves an SN1 reaction. The nitrogen nucleophile is a nitrile—a notoriously weak nucleophile that needs a carbocation for reaction. If t-butanol and acetonitrile are mixed in acidic solution, the tertiary cation is attacked by the nitrile 66 and the amide 69 is formed. Hydrolysis of the amide gives t-BuNH2 or reduction of the amide gives the secondary amine 70. The nitrile is chosen according to the other alkyl group needed.

**The Synthesis of Monomorine I**

We end with an example that includes methods from this chapter as well as some revision and a reminder of stereochemistry. Monomorine I 71 is the trail pheromone of Pharaoh's ant (*Monomorium pharaonis*). These ants are pests in hospitals as they spread infections and they follow a trail of monomorine as they go about their evil work. Synthetic monomorine might be
used to lure the ants to their doom. It is a bicyclic amine and disconnection at all the C–N bonds with reductive amination in mind reveals a linear triketone, drawn more clearly as 72a.

The chemists decided that reacting 72 with ammonia was asking a bit much so they selected the nitro compound 73 as their starting material. The idea is that the nitro group will provide the central nitrogen atom after reduction. As we shall see in chapters 22 and 24 nitro groups stabilise carbanions well and conjugate addition of such anions works well. Hence the disconnection of 73. Nitropentane 75 might be made by alkylation of the anion of nitropropane 75b or by the method chosen, an $S_N2$ reaction of nitrite anion on bromopentane 75a.

Now for the synthesis. The nitro compound 75 was made from bromopentane and a nitrite in DMSO, a good solvent for $S_N2$ reactions, and added to the enone 76, an acetal derived from the diketone 74 with the strong base tetramethyl guanidine 77 as catalyst to give the partly protected form 78 of 73. Now all is ready for the various reductions.

Catalytic reduction of the nitro group gives the amine 79 that cyclises instantly (chapter 7) to the imine 80 reduced in its turn to the cyclic amine 81. When the virtually planar five-membered ring of the imine settles on the surface of the Pd-charcoal catalyst it can choose between the side of the ring with a hydrogen atom or the side with the butyl group. It chooses the less hindered side and so the second hydrogen atom is $cis$ to the first and the stereochemistry is correct (compare 81 with 71).

Now the acetal is hydrolysed to reveal the ketone 82 which again cyclises spontaneously to the enamine 83 forming a stable six-membered ring. This cyclic enamine can be isolated and
treated with NaB(CN)H₃ in slightly acidic solution. The enamine is thus in equilibrium with the iminium salt (compare 44 and 45) and reduction again occurs on the less hindered side of the molecule, i.e. cis to the other two hydrogen atoms.

This elegant synthesis uses some of the methods of amine synthesis from this chapter and looks forward to the next chapter on protecting groups as well as later discussion of nitro group chemistry.

References

5. *Vogel*, page 783.
Strategy IV: Protecting Groups

**Background Needed for this Chapter** Reference to Clayden, *Organic Chemistry*: Chapter 24: Chemoselectivity: Selective Reactions and Protection.

Protecting groups have been mentioned occasionally in previous chapters: in this chapter the ideas behind their use are systematically presented and a collection of protecting groups suitable for a range of functional groups is tabulated. Protection allows us to overcome simple problems of chemoselectivity. It is easy to reduce the keto-ester 1 to the alcohol 2 with a nucleophilic reagent such as NaBH₄ that attacks only the more electrophilic ketone.

![Chemical structure](image)

Making alcohol 3 by reducing the *less* electrophilic ester is not so easy but protection of the ketone as an acetal 4—a functional group that does not react with nucleophiles—allows reduction of the ester with the more nucleophilic LiAlH₄.

![Chemical structure](image)

Another important function of protecting groups is to prevent a reagent from attacking itself. In the last chapter, when we discussed the synthesis of the bicyclic amine monmorine, we used the protected enone 12 but did not say how it was made. The chloroketone 9 is first made in 89–93% yield from the ketolactone 6 simply by reaction with HCl. Chloride displaces the protonated ester group 7 and the product 8 decarboxylates under the conditions of the reaction.

![Chemical structure](image)
Any attempt to make a Grignard reagent from 9 is doomed because the nucleophilic Grignard would immediately attack the ketone. We need to protect the ketone with an easily added group that is not attacked by Grignard reagents and the acetal 10 is the answer. Addition of the Grignard from 10 to acrolein (CH$_2$=CHCHO) gives the allylic alcohol 11 which is oxidised to the enone 12 with manganese dioxide.$^2$ If you look back to chapter 8 you will see that the acetal was retained until it was very easily removed almost at the end of the synthesis.

![Chemical Diagram]

**Qualities Needed in a Protecting Group**

1. It must be easy to put in.
2. It must be resistant to reagents that would attack the unprotected functional group.
3. It must be easily removed.

The last point may not be so obvious but it is the most difficult to achieve. Many syntheses fall down right at the end because a protecting group cannot be removed without destroying the molecule. The next section looks at ways to make removal of protecting groups easier.

**Ethers and Amides as Protecting Groups**

Protection of alcohols and amines might look simple. Methyl ethers and simple amides are easy to make and are very resistant to a wide variety of reagents. So there is no problem in carrying out the required reaction elsewhere in the molecule i.e. turning R$^1$ in 13 and 17 into R$^2$ in 16 and 20. But sadly they are almost useless as protecting groups because such violent conditions are needed to remove them: cleavage of methyl ethers requires good nucleophiles under acidic conditions and the hydrolysis of amides needs refluxing 10% NaOH or concentrated HCl in a sealed tube at 100°C overnight.

![Chemical Diagram]

These protecting groups are used when the molecule is robust enough to take the de-protection conditions. If aniline 21 is brominated the 2,4,6-tribromo derivative 22 is formed. The yield is quantitative but we are more likely to want mono-bromination. Protection is needed against over-reaction. The amide 23 is easily made, bromination goes only in the para position (the N-acetyl group is larger than NH$_2$) and the hydrolysis does not destroy the benzene ring.$^3$
The Achilles Heel Strategy

A way round these difficulties is to use an ether or an amide that has a built-in weakness so that the over-vigorous conditions are not needed. This ‘Achilles heel’ for an ether is commonly the THP group that makes the ether into an acetal. Dihydropyran, DHP 26, is protonated on carbon 27 to give the cation 28 that captures the alcohol to give the mixed acetal 29, usually referred to as ‘the THP derivative’. After the reaction the hydrolysis needs only the weak aqueous acid used for acetals. The secret is that the weak acetal bond (b in 30) is cleaved\(^4\) rather than the strong ether bond (a in 30).

Another way to make an ether easier to remove is to make it benzylic 31 as \(\sigma\)-conjugation of the C–O bond with the benzene ring weakens it enough for it to be cleaved by catalytic hydrogenation using various transition metals.\(^5\)

This is also the key to the weakening of amides as protecting groups for amines. The amine is acylated with benzyl chloroformate 33 (as described in chapter 5) to give urethane 34. This is still an amide on the left but a benzyl ester on the right. Then the reaction is carried out. Hydrogenation cleaves the weak benzyl-O bond to give unstable carboxylic acids 36 that decarboxylate 37 spontaneously to give the altered amine \(R^2\text{NH}_2\). Though the C–N bond is cleaved, no nucleophilic attack on the carbonyl group is needed. This protecting group is so popular it has its own abbreviation Cbz (Carbobenzyloxy-) or even just Z.
Both benzyl and Cbz groups are used in a synthesis of aspartame 38, the dipeptide that is 150 times sweeter than sugar and used in many soft drinks under the name Nutrasweet™. Only one disconnection is reasonable: the amide bond in the middle of the molecule suggesting derivatives of available aspartic acid 39 and phenylalanine 40 as starting materials.

Since we need the methyl ester of phenylalanine, no further protection of that starting material is needed but the amino and one carboxylic acid group of aspartic acid need to be protected and the remaining acid activated. The Cbz group is perfect for the amino group and both acids in 41 can be esterified with benzyl alcohol.

Now one ester must be cleaved and not the other. This looks difficult and cannot easily be done by hydrolysis but peptide chemists knew that the right one was hydrolysed in base to give the required intermediate 43. Evidently the amide makes that ester more electrophilic but this was discovered by experience. Now the free acid must be activated towards nucleophilic attack: the trichlorophenyl ester 44 is ideal.

The coupling requires only a weak base and the benzyl esters are removed by hydrogenation. The benzyl esters are there for protection but the trichlorophenyl ester is there for activation, making that ester more electrophilic than the benzyl ester in 44 or the methyl ester in 40.

A close relative to Cbz is Boc (t-butyloxy carbonyl) that uses a different method to make esters easy to hydrolyse. It is added to an amine or an alcohol by the chloroformate 46 and, after the reaction, 'hydrolysed' with acid—no water being needed. The ester is protonated and the t-butyloxycarbonyl cation drops out in an S_N1 reaction 49 to give the same intermediate 36 as in the removal of the Cbz group.
Protection of Alcohols

We have already mentioned the THP group but by far the most popular protecting groups for alcohols are the various silyl groups. You will already be familiar with the Me₃Si- or TMS (TriMethylSilyl) group but this is little used for protections as it falls off so easily, often just during chromatography. More hindered is the triethylsilyl (TES) or tri-iso-propylsilyl (TIPS) groups and t-butyldimethyl silyl (TBDMS or, misleadingly TBS) and, most hindered of them all, t-butyldiphenyl silyl (t-BuPh₂Si). They are usually put on with the silyl chloride and a weak base, often imidazole in DMF, and they can be removed with oxygen nucleophiles, often in acid solution, and especially fluoride ion, often as TBAF (TetraButylAmmonium Fluoride Bu₄NF). This is particularly useful as fluoride is virtually unreactive towards most carbon atoms.

In Martin and Mulzer’s synthesis of epothilone B the starting material 50 already has a p-methoxybenzyl group on one alcohol. Protection of the other with a TBDMS group is orthogonal meaning that each group is removed under conditions that do not affect the other. Addition of isopropenyl Grignard to the aldehyde 52 creates a third alcohol 53 and now the TBAF group is removed so that an acetal 55 can be formed from the diol 54. The yields are all good and eventually the PMB group will be removed by oxidation with a quinone.

An intermediate in the synthesis of laulimalide by Davidson illustrates the differential protection of alcohols. The starting materials 56 and 57 already have an alcohol protected as a TBDMS silyl ether and a diol protected as an acetal. The alcohol in 58 is protected as a p-methoxybenzyl ether and the acetal ‘hydrolysed’ by acetal exchange to give the free diol 60. Selective protection of the primary alcohol by a bulky acyl group (pivaloyl, t-BuCO-) 61 allows silylation of the secondary alcohol with a TIPS group 62. Finally the pivaloyl group is selectively removed by DIBAL reduction to release just one free alcohol 63.
Later on, all the protecting groups will be removed: the silyl groups with fluoride and the $p$-methoxybenzyl ether by oxidation with Ce(IV). In Ley’s recently completed synthesis$^9$ of azadirachtin 64 after 22 years of hard labour the key intermediate was 65. You will notice benzyl ethers, acetals and a silyl ether. This is a more modern, one might almost say minimalist, use of protection. In an ideal world no protecting groups would be necessary but in a real synthesis they will almost certainly be required as we shall see in the rest of the book. But our aim should be to keep them to a minimum.

The Literature on Protecting Groups

‘Protecting groups’ is a very large subject. There are hundreds of different protecting groups using scores of different ideas for every important functional group. It is particularly important that you refer to the literature before you choose which protecting group to use in a synthesis. It is a reasonable assumption that this rather dull subject would spawn some rather dull catalogue-like textbooks, and it has, but fortunately there is a glorious exception. Phil Kocienski’s textbook$^{10}$
Protecting Groups is comprehensive and entertaining. If you doubt this, have a look at page 644 (yes, it’s also a long book). The extent of the subject is revealed by his chapter on protecting groups for alcohols with hundreds of protecting groups in the 176 pages and 686 references. This chapter is particularly good at selective protection and deprotection of, say, primary, secondary and tertiary alcohols. One example is the selective deprotection of either a phenol or an alcohol from the bis-silyl ether 67 using different reagents.\(^\text{11}\)

![Chem4all Image](http://www.chem4all.vn)

### Protecting Group Summary

We cannot compete with large textbooks but here is a brief selection of simple protecting groups.

<table>
<thead>
<tr>
<th>Protecting Group</th>
<th>To Add</th>
<th>To Remove</th>
<th>PG resists</th>
<th>PG reacts with</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protecting Aldehydes RCHO and Ketones R₂CO</strong></td>
<td>ROH or diol, H⁺</td>
<td>H⁺, H₂O</td>
<td>nucleophiles, bases, reducing agents</td>
<td>electrophiles, oxidising agents</td>
</tr>
<tr>
<td>Acetal (Ketal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protecting Carboxylic Acids RCO₂H</td>
<td>CH₂N₂</td>
<td>NaOH, H₂O</td>
<td>bases, electrophiles</td>
<td>strong bases</td>
</tr>
<tr>
<td>Ester: RCO₂Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ester: RCO₂Et</td>
<td>EtOH, H⁺</td>
<td>NaOH, H₂O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ester: RCO₂Bn</td>
<td>BuOH, H⁺</td>
<td>H₂, cat or HBr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ester: RCO₂t-Bu</td>
<td>t-BuOH, H⁺</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anion: RCO₂⁻</td>
<td>base</td>
<td>H⁺</td>
<td>nucleophiles</td>
<td>electrophiles</td>
</tr>
<tr>
<td>Protecting Alcohols ROH</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ether: ROBn</td>
<td>PhCH₂Br, base</td>
<td>H₂, cat or HBr</td>
<td>see text</td>
<td>nucleophiles</td>
</tr>
<tr>
<td>Silyl ether</td>
<td>R₃SiCl, base</td>
<td>F⁻ or H⁺, H₂O</td>
<td>see text</td>
<td>nucleophiles</td>
</tr>
<tr>
<td>Acetal: THP</td>
<td>DHP, H⁺</td>
<td>H⁺, H₂O</td>
<td>bases</td>
<td></td>
</tr>
<tr>
<td>Ester: ROCOR’</td>
<td>R’COCl, pyr</td>
<td>NH₃, MeOH</td>
<td>electrophiles</td>
<td>nucleophiles</td>
</tr>
<tr>
<td>Protecting Phenols ArOH</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ether: ArOMe</td>
<td>Me₂CO₃, K₂CO₃</td>
<td>H₂O, BBr₃</td>
<td>bases</td>
<td>electrophiles</td>
</tr>
<tr>
<td>ArOCH₂OMe</td>
<td>MeOCH₂Cl, base</td>
<td>HOAc, H₂O</td>
<td>bases</td>
<td>electrophiles</td>
</tr>
<tr>
<td>Protecting Amines RNH₂</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Amides</td>
<td>RCOCl</td>
<td>NaOH or HCl in water</td>
<td>electrophiles</td>
<td>bases and nucleophiles</td>
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<tr>
<td>RNHCOR’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethanes</td>
<td>RCOCl</td>
<td>see text</td>
<td>electrophiles</td>
<td>bases and nucleophiles</td>
</tr>
<tr>
<td>RNHCO₂R’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protecting Thiols RSH</td>
<td>AcCl, base</td>
<td>NaOH, H₂O</td>
<td>electrophiles</td>
<td>oxidation</td>
</tr>
</tbody>
</table>
References

4. *Vogel* page 552.
One Group C–C Disconnections I: Alcohols

**Background Needed for this Chapter** Reference to Clayden, *Organic Chemistry*: Chapter 9: Using Organometallic Reagents to Make C–C Bonds.

We now leave disconnections of bonds between carbon and other atoms (C–X disconnections) and turn to the more challenging C–C disconnections. These are more challenging because organic compounds contain many C–C bonds and it is not clear at first which ones should be disconnected. There is some very good news: the synthons that we met in chapter 6 for two-group C–X disconnections are the ones we shall use for one-group C–C disconnections. We start with an introduction to the three main types. In each case we shall replace one of the heteroatoms by a carbon unit "R".

For compounds with two heteroatoms joined to the same carbon, we used a 1,1-diX disconnection 1 removing one heteroatom to reveal a carbonyl compound, here an aldehyde, and a heteroatom nucleophile 2. Replacing the heteroatom by R², we disconnect in the same way to reveal the same aldehyde and some nucleophilic carbon reagent 4, probably R²Li or R²MgBr.

![1,1-diX Disconnections:](image)

![The Corresponding C–C Disconnection:](image)

For compounds with a 1,2-relationship 5 we used an epoxide 6 at the alcohol oxidation level in combination with a heteroatom nucleophile. Disconnecting the corresponding C–C bond 7, we use the same epoxide and a carbon nucleophile such as RLi or RMgBr.

![1,2-diX Disconnections:](image)

![The Corresponding C–C Disconnection:](image)

The same 1,2-diX relationship at the carbonyl level was disconected 8 to give carbon electrophilic 9, probably an α-bromoketone, and a heteroatom nucleophile. Now we come to some more good news. We generally preferred nucleophilic heteroatoms but we can use nucleophilic or electrophilic carbon atoms whichever is better. Here we should much rather use the nucleophilic carbon synthon 11 as it is an enolate.

Stuart Warren and Paul Wyatt  
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The 1,3-diX relationship 12 was quickly recognised as conjugate addition to the enone 13 in chapter 6. The corresponding C–C disconnection 14 uses the same enone 13 but the nucleophilic carbon species should be a copper derivative: RCu, R₂CuLi or RMgBr with Cu(I)Br.

Reagents for Nucleophilic Carbon

The simplest unfunctionalised carbon nucleophiles (15 and 17) are made from alkyl halides with various metals such as Li(0) or Mg(0) or by exchange with available organometallic reagents such as butyl-lithium (BuLi) in anhydrous coordinating solvents like ether (Et₂O) or THF (tetrahydrofuran 16). Enolates 11 are very important and will be discussed at length in later chapters.

‘1,1 C–C’ Disconnections: The Synthesis of Alcohols

Disconnection 3 shows that any alcohol may be disconnected at a bond next to the OH group. Isomeric alcohols 18 and 20 can both be made from acetone using perhaps a Grignard reagent 19 in the first case and available BuLi in the second.

The synthesis of 18 exemplifies the Grignard method. The reagent is made from the alkyl halide with magnesium metal in dry ether and combined, without isolation, with the electrophile—all steps being carried out under strictly anhydrous conditions.

It may be necessary to disconnect structural C–X bonds before doing the C–C disconnection as with the amineester wanted for evaluation as an analgesic.
the tertiary alcohol $23$ and removal of the phenyl group shows a hidden 1,3-diX relationship between ketone and amino groups $24$.

The synthesis is straightforward with available PhLi being used instead of a Grignard. The acylation of the tertiary benzylic alcohol $23$ needs mild conditions to avoid dehydration.

In general there is a choice of which C–C bond should be disconnected and available starting materials may give a clue. We do not wish to disconnect the aromatic ring of the heterocyclic alcohol $28$ so we can choose between bonds a and b.

It turns out that both the aldehyde $29$ and the easily made bromo-acetal $32$ are commercially available and so route b was chosen with the protected Grignard reagent $33$ as the carbon nucleophile (compare compound $10$ in chapter 9).

**Aldehydes and Ketones**

The simplest route to aldehydes and ketones using the same strategy is oxidation of an alcohol. So the analysis involves FGI back to the alcohol and then a C–C disconnection of one of the bonds next to the OH group. Lythgoe$^4$ wanted to make a series of ketones $34$ with various R groups to demonstrate a new alkyne synthesis. Disconnection of the C–R bond of the alcohol $35$ meant that they could all be made from aldehyde $36$ which can be made by the same strategy.
The oxidation of 35 presents no problems as over-oxidation cannot occur. But aldehyde 36 could be oxidised to the corresponding carboxylic acid so care was needed. In fact PCC (pyridinium chlorochromate: CrO₃ and HCl dissolved in pyridine) could be used for both.⁵

```
   Br  1. Mg, Et₂O  CHO
     2. CH₂O →  3. PDC  1. n-HexMgBr → 34; 68% yield
     36
```

Direct addition of RMgBr or RLi to esters does not give ketones (see below) but addition to nitriles does⁶ (chapter 13).

**Oxidising Agents for the Conversion of Alcohols to Aldehydes**

The difficulty is over-oxidation. One simple solution is to oxidise all the way to the carboxylic acid and reduce selectively with, say DIBAL (i-Bu₂AlH). But the reagents in the table give reasonable results and can also be used for the oxidation of secondary alcohols to ketones.⁷ Full descriptions are in Fieser⁸ or the volume of *Comprehensive Organic Synthesis* devoted to oxidation.⁹

<table>
<thead>
<tr>
<th>Name</th>
<th>Reagents</th>
<th>For RCH₂OH to RCHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>Na₂Cr₂O₇, H⁺</td>
<td>distil out RCHO as formed</td>
</tr>
<tr>
<td>Jones</td>
<td>CrO₃, H₂SO₄, acetone</td>
<td>distil out RCHO as formed</td>
</tr>
<tr>
<td>Collins</td>
<td>CrO₃, pyridine</td>
<td>use in CH₂Cl₂ solution</td>
</tr>
<tr>
<td>PCC</td>
<td>CrO₃, pyridine.HCl</td>
<td>no modification needed</td>
</tr>
<tr>
<td>PDC</td>
<td>(pyridine.H⁺)₂ Cr₂O₇</td>
<td>use in CH₂Cl₂ solution</td>
</tr>
<tr>
<td>Swern</td>
<td>1. (COCl)₂, DMSO, 2. Et₃N</td>
<td>no modification needed</td>
</tr>
</tbody>
</table>

References for table: Na₂Cr₂O₇, H⁺: *Vogel*, p. 588, Collins,¹⁰ PCC,¹¹ PDC,¹¹ Swern.¹²

**Carboxylic Acids**

The same disconnection 41 can be used for carboxylic acids with CO₂ as the electrophile for a Grignard reagent 40. Dry ice (solid CO₂) is particularly convenient for these reactions. Switching polarity by FGI to the nitrile 42, the same disconnection now uses cyanide ion as the nucleophile but the same alkyl halide 39 that was used to make the Grignard reagent. Mechanistic considerations should decide between these alternatives.

```
R     FGI    R     C-C    FGI    C-C    R + °CN
Br     39    →Br     40    →CO₂H    41    →CN    42    →Br + 39
```

If the carboxyl group is attached to a tertiary, or even a secondary carbon atom, the S₉2 reaction with cyanide will not be so good and the carboxylation of a Grignard reagent is probably better. Pivalic acid 44 is available but can be made from i-BuCl in good yield.¹³ A detailed
procedure\textsuperscript{14} for the acid 46 describes how the acid is extracted from the ether with aqueous NaOH, separated from the water by neutralisation with HCl, and distilled.

\[
\begin{align*}
\text{Cl} & \xrightarrow{1. \text{Mg, Et}_2\text{O}} \text{CO}_2\text{H} & 43 & \rightarrow \text{CO}_2\text{H} & 44; 70\% \text{ yield} \\
\text{CO}_2(\text{s}) & \xrightarrow{2. \text{CO}_2(\text{s})} \\
\end{align*}
\]

If on the other hand the S\textsubscript{N}2 reaction with cyanide is favoured, as with allylic 47 or benzylic 50 halides, that method is better.\textsuperscript{15} Hydrolysis of the nitrile 48 gives the acid 49 but treatment with an alcohol in acidic solution gives the ester 52 directly.\textsuperscript{16}

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{CuCN}} \text{CN} & 47 & \rightarrow \text{CN} & 48; 84\% \text{ yield} \\
\text{CN} & \xrightarrow{\text{conc. HCl}} \text{CO}_2\text{H} & 49; 82\% \text{ yield} \\
\text{Ph} & \xrightarrow{\text{NaCN}} \text{CN} & 50 & \rightarrow \text{CN} & 51; 90\% \text{ yield} \\
\text{EtOH} & \xrightarrow{\text{H}^+} \text{CO}_2\text{Et} & 52; 87\% \text{ yield} \\
\end{align*}
\]

Acids can also be made by the oxidation of alcohols and acid derivatives are available from the acids via the acid chloride. Since acids can also be reduced to alcohols, there is a great deal of interdependence in all these methods. The synthesis of carbonyl compounds by one-group C–C disconnections is discussed more fully in chapter 13.

‘1,2 C–C’ Disconnections: The Synthesis of Alcohols

The analogy between this type of C–C disconnection and 1,2-diX disconnections was explained at the start of this chapter with compounds 5, 6 and 7. The epoxide route works particularly well if the epoxide is mono-substituted as the reaction with nucleophilic carbon should then be regioselective. Alcohol 53 is used in perfumery and can be disconnected 53a at the next-but-one bond to the alcohol group with the idea of using the epoxide 54 made from the but-1-ene.

\[
\begin{align*}
\text{Ph} & \xrightarrow{2} \text{OH} & 53 & \xrightarrow{1.2 \text{C–C}} \text{PhMgX} + \text{CO}_2\text{H} & 54 \\
\text{Ph} & \xrightarrow{3} \text{OH} & 53a & \xrightarrow{2 \times \text{C–O}} \text{but-1-ene} \\
\end{align*}
\]

A Grignard or organo-lithium reagent would attack at the less hindered end of the epoxide and the Grignard route gives the alcohol 53. In chapter 12 we shall see that this reaction is stereospecific.

\[
\begin{align*}
\text{but-1-ene} & \xrightarrow{\text{RCO}_2\text{H}} \text{O} & 54 & \xrightarrow{\text{PhMgBr}} \text{Ph} & 53 \\
\end{align*}
\]

We shall not extend the discussion on the 1,2-style of C–C disconnection as it is treated extensively, particularly at the carbonyl oxidation level, later in the book. We simply offer a table of the large number of derivatives that can be made from the alcohols we have been discussing in this and previous chapters. In all these cases, the first step would be FGI to the alcohol and then a C–C disconnection could be chosen.
TABLE 10.2 Compounds made from alcohols

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Product</th>
<th>Chap</th>
<th>Further Products</th>
<th>Chap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>aldehydes ketones acids</td>
<td>10</td>
<td>amines by reductive amination or reduction of amides</td>
<td>8</td>
</tr>
<tr>
<td>Esterification</td>
<td>esters</td>
<td>4</td>
<td>amines by reduction of amides</td>
<td>8</td>
</tr>
<tr>
<td>Tosylation</td>
<td>ROTs</td>
<td>4</td>
<td>other substitutions (see below)</td>
<td>4</td>
</tr>
<tr>
<td>HBr or PBr₃</td>
<td>bromides</td>
<td>4</td>
<td>ethers, sulfides</td>
<td>4</td>
</tr>
<tr>
<td>SOCl₂</td>
<td>chlorides</td>
<td>4</td>
<td>thiols</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nitriles</td>
<td>10</td>
</tr>
</tbody>
</table>

Example of the Synthesis of Alcohols and Related Compounds

The alcohol 55 was needed for the synthesis of a bicyclic amine. Disconnection either side of the alcohol gives the aldehyde 57 and the Grignard 56 as starting materials.¹⁷ But could we not also disconnect the other side as well?

Symmetrical alcohols can in fact be made in one step from Grignard reagents and esters, as the reaction first produces the aldehyde 57 which is more electrophilic than the ester and so reacts again. There is a warning here! Aldehydes cannot be made by acylation of Grignard reagents with esters. But if two reactions are wanted, this is a good method.

The tertiary chloride 58 was needed for a study of the effects of electron-withdrawing groups on the S₉1 reaction. FG1 to the alcohol 59 suggests a C–C disconnection to a Grignard reagent 60 and acetone.

The nitro group must be introduced at some stage and the other substituent is always large and ortho, para-directing so it doesn't seem to matter when. As they wanted to make a series of compounds with electron-withdrawing groups on the benzene ring, they chose to make 62 as a common intermediate and nitrate last.¹⁸
Darifenacin 63 is Pfizer’s treatment for urinary urge incontinence. Disconnection at the C–N bond with some amine synthesis in mind (chapter 8) gives a much smaller heterocycle 64 that can again be disconnected in the middle with the idea of alkylating some enolate such as 65 with the derivative of an alcohol 66. This is attractive because 66 is available as a single enantiomer cheaply from the amino acid hydroxyproline.19

There are two problems. Enolates of primary amides are not very practical as the NH protons are more acidic than the CH protons. The solution is to use the nitrile and hydrolyse it later to the amide. A more serious problem is that the SN2 reaction we want to use to couple the two together will go with inversion and that will give the biologically inactive enantiomer of darifenacin. The solution is a double inversion. Protection of the amine by tosylation 67 is followed by tosylation of the alcohol with inversion using a Mitsunobu-style reaction. This unusual esterification goes reliably with inversion.20

The nitrile 70 gives a stabilised anion with NaH that reacts with the tosylate with inversion as expected. The rather unusual sulfonamide deprotection with HBr in phenol gave the amine 72 that was coupled to the rest of the molecule as an amide. Reduction of the amide to the amine and, finally, hydrolysis of the nitrile to the amide gave darifenacin 63.

**Other One-Group C–C Disconnections**

There are many other reactions that make C–C bonds using only one functional group. Among the most important involve alkynes by alkylation 73 (chapter 16), alkenes by the Wittig reaction 74 (chapter 15) and nitro compounds by alkylation 75 (chapter 22). Disconnections of alkenes outside the double bond 76 and especially disconnections of dienes between the double bonds 77 use palladium chemistry and are discussed extensively in *Strategy and Control*.
Carbon–Carbon Disconnections to Avoid

All the disconnections we have mentioned use functional groups to guide us. Nowhere will you find the disconnection of one alkyl group from another 78 without any functionality. It might seem that the reaction of a Grignard reagent 79 with an alkyl halide 80 would make 78, and so it might. But these species will be in equilibrium with 81 and 82. So, even if the coupling does work, we would get a mixture of 78 and both dimers. It is very much better to let functional groups guide your disconnections.

\[
\begin{align*}
R^1 & \begin{array}{c} \longrightarrow \\ 78 \end{array} & R^1 & \longrightarrow & MgBr & + & Br & \begin{array}{c} \longrightarrow \\ 80 \end{array} & R^2 & \begin{array}{c} \leftrightarrow \\ 81 \end{array} & R^1 & \longrightarrow & Br & + & BrMg & \begin{array}{c} \longrightarrow \\ 82 \end{array} & R^2
\end{align*}
\]

References

General Strategy A: Choosing a Disconnection

This is the first of four General Strategy chapters in which we discuss important points that apply to the whole of synthetic design rather than one particular area. This chapter concerns general principles to help you choose one C–C disconnection rather than another. Even a simple molecule like the alcohol 1, introduced in chapter 1 as a component of the elm bark beetle pheromone, can be disconnected at any of the five marked bonds.

1: component of the elm bark beetle pheromone

Greatest Simplification

Only one of the five bonds 1a is a good choice and for two reasons. We aim to achieve the greatest simplification in our disconnections so that we get back quickly to simple starting materials. This makes the synthesis as short as possible. So we disconnect bonds that are:

(a) Towards the middle of the molecule. This breaks the molecule into two reasonably equal parts and is much better than simply lopping one atom off the end.

(b) At a branchpoint in the molecule: this is more likely to give simple straight chain starting materials. Here we get the aldehyde 2 and the Grignard reagent 3 coming from the straight chain halide 4. Both 2 and 4 are commercially available.

The synthesis is a one-step process derived from the chemistry we were discussing in the last chapter.¹

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We can extend these guidelines when we realise that a junction between a ring and a chain and, even more, a junction between two rings, is always at a branchpoint. The series of drugs based on bicyclic structure 5 has an excellent disconnection between the two rings.

The Grignard reagent 7 is made from the halide that comes eventually from phenol by chlorination and methylation. We shall discuss the synthesis of ketones like 6 in chapter 19.

**Symmetry**

We saw symmetry put to good use at the end of the last chapter and it may well help if we can do two identical disconnections at once. The symmetrical tertiary alcohol 10 can be made from two molecules of a Grignard reagent 11 and one of ethyl acetate. Then back to the alcohol 12 by FGI and a disconnection at the branchpoint gives the starting materials.

This synthesis was carried out by Grignard himself. The bromide 16 was made from the alcohol 12 with PBr₃—a good reagent when an S_{N}2 displacement is needed.

**Recognisable Starting Materials**

A very practical guideline is to look for starting materials you can buy. It is obviously impossible to give a list of such compounds (though we’ve done our best with some simple compounds) or for any individual chemist to know what’s available. In addition, what’s available varies from year to year and sometimes from week to week. Then the requirements of research chemists, who often need only a gram of something, development chemists, who need kilograms, and production chemists who need tonnes are very different indeed, especially in the price they are prepared to pay. The solution is to use suppliers’ catalogues. They are free on request from the main suppliers such as Aldrich or Fluka.
Still using symmetry, the tertiary alcohol 17 needs a butyl nucleophile and a methacrylate ester. You can buy a railway tanker full of BuLi if you want and methacrylate esters are used in enormous quantities to make polymers. You won’t always be as lucky as this.

In less favourable circumstances, look for starting materials that can easily be made. The hydroxyaldehyde 20 was an intermediate in Büchi’s synthesis of the natural product nuciferal 21.

The tertiary alcohol is an obvious place to disconnect. Rejecting the poor disconnection of one carbon atom 20a, we have a choice between 20b and 20c giving one of two ketones 23 or 24 and Grignard reagents made from one of two halides 22 or 25. We can easily make 22 and 24 by halogenation or Friedel-Crafts acylation of toluene. But what about 23 and 25?

We have not met methods to make 23 and, though it could be made, there is a serious chemoselectivity problem in getting the Grignard reagent to attack the less reactive ketone in the presence of the aldehyde. Büchi preferred route c as he knew how to make the protected version 27 of 25 that will be needed for the Grignard reagent. We know this too as it was compound 32 in chapter 10. The Grignard reagent from 27 was combined with the ketone 24 to give a protected version of the intermediate 20. Büchi preferred to keep the acetal in the remaining steps of the synthesis.

Returning to a series of compounds from the last chapter, Bunnett and Sridharan made one of them 29 by a different route. They went back to the alcohol as before but then disconnected the two methyl groups 30. One reason was that it is difficult to add a MeO group to a benzene ring, but the main reason was that the methyl ester 31 is readily available.
The synthesis is straightforward but no yields are given in the paper.\(^6\)

Available Compounds

A small selection of commonly used compounds but the Aldrich catalogue has over 34,000 entries.

*Straight Chain Compounds:* \(C_1\) to about \(C_{10}\) and more in many cases
  Alcohol, alkyl halides, acids, aldehydes, amines, nitriles, ketones.

*Branch Chain Compounds:* as above based on these skeletons (and others):

\[
\begin{align*}
\text{i-propyl} & \quad \text{t-butyl} & \quad \text{i-butyl} & \quad \text{t-amyl} & \quad 1-\text{X-3-Me-butane} & \quad 2-\text{ethylhexyl}
\end{align*}
\]

*Cyclic Compounds:* \(C_4\) to \(C_{10}\) and others:
  Ketones, alcohols, alkenes, halides, amines.

*Aromatic Compounds:* Very considerable variety—see catalogues.

*Heterocyclic Compounds:* Saturated and unsaturated in great variety.

*Monomers for Polymers:* Butadiene, isoprene, styrene
  Acrylates, methacrylates, unsaturated nitriles, chlorides and aldehydes.

Summary of Guidelines for Good Disconnections

1. Make the synthesis as short as possible.
2. Use only disconnections corresponding to known reliable reactions.
3. Disconnect structural C–X bonds first and try to use two-group disconnections.
4. Disconnect C–C bonds using the FGs in the molecule.
   (a) Aim for the greatest simplification. If possible
       – disconnect near the middle of the molecule
       – disconnect at a branch point
       – disconnect rings from chains
   (b) Use symmetry (if any).
5. Use FGI to make disconnections easier.
6. Disconnect back to available starting materials or ones that can easily be made.

Only some of these guidelines may apply to any given target molecule and they may well contradict each other. Developing judgement in choosing good disconnections can come only with practice. There are many different approaches to any reasonably complicated target and no ‘right’ answer.
References

Strategy V: Stereoselectivity A

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 16: Stereochemistry.

The biological properties of organic molecules depend on their stereochemistry. This is true for drugs, insecticides and insect pheromones, plant growth regulators, perfumery and flavouring compounds, as indeed for all compounds having biological activity. The cis-hydroxyaldehyde 1 has a strong and pleasant smell and is used in lily of the valley perfumes, whereas the trans isomer 2 is virtually odourless. Notice that these are diastereoisomers: the compounds are achiral. Any useful synthesis must give pure 1, not a mixture of 1 with the more stable diequatorial 2—at equilibrium there is 92% of 2 and only 8% of 1.

The elm bark beetle pheromone multistriatin 3 is a more complicated example. You may recall from chapter 1 that a single isomer alone attracts the beetle. Making the right diastereoisomer by stereoselective synthesis is not enough. The compound must be a single enantiomer too. In this chapter we consider making the right diastereoisomer of compounds with several chiral centres and first address the question of making single enantiomers. This is only a brief discussion. You are referred to Strategy and Control¹ for a much more detailed analysis and to Clayden Organic Chemistry for the background.²

Enantiomerically Pure Compounds

We shall discuss two strategies in the making of single enantiomers. Either we can resolve a racemic compound somewhere in the course of the synthesis or we can use a single enantiomer as starting material. Other strategies are discussed in detail in Strategy and Control.

Resolution

Enantiomers cannot be separated by the normal processes of purification: crystallisation, distillation or chromatography. But diastereoisomers can. Resolution involves using an enantiomerically
pure ‘resolving agent’ to convert our racemic compound into a mixture of diastereoisomers that can be separated by these processes. When Cram wanted to study the stereochemistry of elimination reactions he needed a strong enantiomerically pure base that would not substitute. In other words an asymmetric version of LDA. He chose 4, obviously obtained from 5 and BuLi. The usual FGI and C–N cleavage 6 led back to the acid chloride 7 of available pivalic acid (t-BuCO₂H) and the amine 8.

He prepared amine 8 by a kind of reductive amination of the ketone 9 via the N-formyl amine 10 and made it enantiomerically pure by resolution with malic acid 11—a cheap enantiomerically pure compound.⁵

This would not be necessary nowadays as the preparation and resolution of 8 is an undergraduate experiment.⁵ A more normal reductive amination gives racemic 8 and crystallisation of the tartrate salt 12 from methanol gives enantiomerically pure (+)-(R)-8 after neutralisation. In fact this nearly perfect resolution gives both enantiomers of 8. One tartrate salt crystallises out from MeOH and the other remains in solution. The salts are diastereoisomers and have different physical properties. Since no covalent bond is formed in making the salt 12, simple neutralisation with NaOH gives pure amine 8 and the tartaric acid remains in solution as its sodium salt.

Cram finished his synthesis by making and reducing the amide 6. Both steps go in excellent yield and, more importantly, without any racemisation as the chiral centre is not involved in either step. These principles are involved in all classical resolutions.

Enantiomerically Pure Starting Materials

There are very many enantiomerically pure starting materials available cheaply from nature. The amino acids are varied in structure and the hydroxyacids such as malic acid 11 and lactic acid 13 provide another resource. We shall give just one example of this kind of synthesis. Ethyl lactate 14 can be converted into the mesylate (a leaving group like tosylate) 15 and then reduced to the
primary alcohol 16 with alane made from LiAlH₄ and concentrated H₂SO₄. This is not isolated but gives the epoxide 17 on treatment with base. The chiral centre is specifically inverted in the intramolecular S_N2 reaction.⁶

**Stereospecific and Stereoselective Reactions**

**Stereospecific Reactions**

Whether you are dealing with enantiomerically pure or racemic compounds, once the first chiral centre (or centres) is in place, new chiral centres must be introduced. Stereospecific reactions give specific and predictable stereochemical outcomes because the mechanism of the reaction demands this. The formation of 17 from 16 had to give that enantiomer as the nucleophilic oxyanion had to approach the chiral centre from the back (inversion) as all S_N2 reactions must go with inversion. Starting with enantiomerically pure materials, each enantiomer of the tosylate 18 must react in an S_N2 reaction to give an inverted acetate. One enantiomer of 18 gives one enantiomer of 19 and the other enantiomer of 18 gives the other enantiomer of 19 by stereospecific inversion.

If we are dealing with diastereoisomers the same thing applies. Compound 20 is not chiral so the question of enantiomers doesn’t arise but each diastereomer of 20, syn or anti gives a different diastereomer of 21 with inversion.

Dihydroxylation of an alkene with OsO₄ is a specifically cis reaction: the two OH groups add to the same side of the alkene. So E-22 gives one diastereomer (syn as drawn) of the diol 23 while Z-22 gives, by syn addition, a diol that can be re-drawn after rotation of a bond, as anti-23.

However, should you wish to make both syn and anti-diols from an alkene when only one isomer (E- or Z-) can be made, such as cyclopentene 25, you need another method. Epoxidation
is also a syn-specific method but opening the epoxide ring by an $S_N2$ reaction inverts one of the centres to set up an anti relationship. Strongly basic reagents are best avoided so acetate can be used as the nucleophile and the ester 27 can be cleaved with ammonia in methanol with attack only at the carbonyl group.

The table gives a list of a few stereospecific reactions but a knowledge of the mechanism of any reaction you contemplate in a synthesis is the one essential way to be sure of the stereochemical outcome.

### Stereospecific Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Chemistry</th>
<th>Result</th>
</tr>
</thead>
</table>
| Substitution $S_N2$ | \[
    \begin{align*}
    &R^1 \quad \text{Nu} \\
    &R^2 \quad \text{Nu}
    \end{align*}
\] | inversion |
| Elimination E2 | \[
    \begin{align*}
    &R \quad \text{base} \\
    &R \quad \text{base}
    \end{align*}
\] | anti-peri-planar H and X |
| Electrophilic addition to alkenes | \[
    \begin{align*}
    &R \quad \text{RCO}_2\text{H} \\
    &R \quad \text{OsO}_4
    \end{align*}
\] | cis addition |
| Electrophilic addition to alkenes | \[
    \begin{align*}
    &R \quad \text{Br}_2 \\
    &R \quad \text{PhSCl}
    \end{align*}
\] | trans addition |
| Hydrogenation of alkynes and alkenes | \[
    \begin{align*}
    &R \quad \text{H}_2, \text{Pd/C} \\
    &R \quad \text{H}_2, \text{Pd/C}
    \end{align*}
\] | cis addition |
| Rearrangements | \[
    \begin{align*}
    &\text{R}^* \quad \text{or} \\
    &\text{R}^*
    \end{align*}
\] | retention at R* inversion at migration terminus |
| Reactions not involving chiral centre(s) | anything | retention |
The entry ‘rearrangement’ may surprise you but it can be very valuable as in an alternative synthesis\(^7\) of the amine 8. Enantiomerically pure acid 28 is converted into the azide 29 that loses nitrogen to give a nitrene. This nitrogen atom has only six electrons and an empty orbital into which the whole side chain can migrate 30. It does so with at least 99.6% retention of configuration to give the isocyanate 31 that picks up water to give the unstable carbamic acid 32 which loses CO\(_2\) spontaneously to give the amine 8. The acid 28 is not now available in enantiomerically pure form so the resolution with tartaric acid is now preferred. In any case, both enantiomers of the amine 8 are available and we would now probably use it to resolve the acid 28.

![Chemical structure](http://www.chem4all.vn)

### Diastereoselective Synthesis of Multistriatin

We promised in chapter 1 that a synthesis of the elm bark beetle would appear here is its. It has four chiral centres but one of them (marked as a hidden carbonyl group) is unimportant. Disconnecting the acetal reveals keto-diol 33. If we make 33 it must cyclise to 3—not other stereochemistry is possible. Further C–C disconnection with alkylation of an enolate in mind reveals symmetrical ketone 34 and a diol 35 with a leaving group (X) at one end and the two chiral centres (marked with circles) adjacent.

![Chemical structure](http://www.chem4all.vn)

The leaving group will come from an alcohol so the basic skeleton is a 1,2,3-triol 36 that is nearly symmetrical and becomes symmetrical with a C–C disconnection to the symmetrical epoxide 37. Both starting materials 34 and 37 are available and are symmetrical: we just have to make 37. The epoxide comes from the Z-alkene 38 and that can be made by Lindlar reduction of the alkyne 39.

![Chemical structure](http://www.chem4all.vn)

The alkyne is actually available as it is easily made from acetylene and formaldehyde. Two decisions remain: how do we distinguish the three alcohols in 36 and what reagent do we use for Me\(^+\) in the reaction on the epoxide? Protection as the cyclic acetal 40 makes epoxidation straightforward and Me\(_2\)CuLi turned out to be the best reagent for opening the epoxide. We now have two of the OHs protected 42 but they are the wrong two!
Acetal formation is thermodynamically controlled and five-membered rings are more stable than seven-membered. So the ingenious solution was to submit 42 to acid when it rearranged by acetal exchange to 43. Now the right OH group is unprotected and it can be transformed into the iodide 44 ready for alkylation of the lithium enolate of 34. Treatment with acid again isomerises the acetal 45 into multistriatin 3 with loss of acetone. No attempt was made to control the centre next to the carbonyl group in 45: cyclisation gave 85% of 3 with an equatorial methyl group and only 15% of the other diastereoisomer resulting from the uncontrolled centre in 45.

But it is important that multistriatin be made in enantiomerically pure form as well as one diastereomer. Looking back over the synthesis, the first chiral intermediate is 42 and, after some failures, reaction with the isocyanate (+)-(R)-46 gave a mixture of the urethanes 47 that could be separated by crystallisation. Removal of the urethane by reduction with LiAlH₄ gave enantiomerically pure alcohol 42 from which enantiomerically pure (>99%) multistriatin 3 could be made by the methods above.

**Stereoselective Reactions**

We shall use stereoselective to describe reactions that have two mechanistically acceptable but stereochemically different pathways so that the molecule may select the more favourable—i.e. faster—pathway (kinetic control) or the more stable product (thermodynamic control). These reactions commonly involve setting up one or more new chiral centres in the presence of others.

The ketone 48 could be reduced to either alcohol 49 or 50. The equatorial alcohol 49 is more stable and so equilibraining reducing agents like i-PrOH with (i-PrO)₂Al give⁹ mainly 49. But the equatorial approach 51 is kinetically favoured as the two marked axial Hs hinder approach from the other side. Large reducing agents like LiAlH(Or-Bu)₃ give¹⁰ mostly the axial alcohol 50.
Sometimes both diastereomers of a compound are needed and then poorly diastereoselective reactions are a boon. Both syn and anti tosylates 55 were needed to study the stereochemistry of reactions. Reduction of the ketoester (see preparation in chapters 19 and 21) in two stages gave a mixture of syn and anti diols 54, separable by column chromatography.

Each diol was selectively tosylated on the primary alcohol to give syn and anti tosylates 55 which were each treated with base [the anion of DMSO: MeS(O)CH₂⁻]—syn-55 cyclised to give the bicyclic ether 56 in good yield while anti-55 fragmented to give volatile hexenal 57.

Conformational Control in Six-Membered Rings

If a new chiral centre is formed on a saturated six-membered ring, conformational control is a possibility. We have already seen conformational effects in the reduction of ketone 48 and the same kind of arguments apply to attack on ketones by carbon nucleophiles. The alcohol 59, needed to make an analgesic 58, can obviously be made from the ketone 60 and that is the result of conjugate addition to cyclohexenone.

Addition of Me₂NH to cyclohexenone followed by reaction with PhLi, without isolation of 60, gives 59 in 60% overall yield. As you would expect, a large nucleophile such as PhLi prefers to add from the equatorial side. Notice that it adds to 60 on the same side as the Me₂N group—obviously nothing to do with steric hindrance. The Me₂N group merely fixes the conformation and the PhLi then adds equatorially. Acylation with the anhydride gives the drug 58.

Axial Attack to Make a Chair

When the starting material is not a chair but a flattened chair, the first priority is to make a proper chair for the product. Strangely this means axial attack by nucleophiles on such electrophiles as
cyclohexenone 62, epoxides 65, and bromonium ions 68. Though the products rapidly equilibrate to all equatorial conformations 64e, 67e and 69e, they are formed initially in axial 64a or trans-di-axial conformations 67a and 69a.

Stereochemical Control in Folded Molecules

If two small rings (3-, 4- or 5-membered) are fused together (that is with two adjacent atoms common to both) they must have cis stereochemistry at the ring junction and a folded conformation like a half-opened book. We saw earlier that 70 had to have a cis ring junction: the compound anti-55 that might have cyclised to the trans ring junction fragmented instead. This compound has a folded conformation 70a. We shall deal with folded conformations in chapter 38 but meanwhile, notice that 70a and 72a show an ‘outside’ (the cover of the book) and an ‘inside’ (the pages of the book). Epoxidation of 71 goes on the outside of the folded molecule to give 72.

Control in epoxidation of small rings by another substituent is easy to understand as the rings are virtually flat and we do not have to worry about axial and equatorial substituents. So the simple (achiral) cyclopentene 73, with a large substituent (R = t-BuMe₂Si) on the ring, gives the anti-epoxide 74 because of steric hindrance. However, the free alcohol 75 epoxidises on the same face as the OH group to give 76. The only reasonable explanation is that the OH group hydrogen bonds to the reagent and delivers it to the same face.¹³
References

2. Clayden *Organic Chemistry* chapters 16, 18, 32, 33 and 34.
One Group C–C Disconnections II: Carbonyl Compounds

**Background Needed for this Chapter** Reference to Clayden, *Organic Chemistry*: Chapter 9: Using Organometallic Reagents to Make C–C Bonds. Chapter 26: Alkylation of Enolates

In chapter 10 we compared C–C disconnections with related two-group C–X disconnections, mainly at the alcohol oxidation level. In this chapter we deal more fully with carbonyl compounds, chiefly aldehydes and ketones, by two related disconnections. We start by comparing the acylation of heteroatom by acid derivatives such as esters (a 1,1-diX disconnection 1 that can also be described as a one-group C–X disconnection) with the acylation of carbon nucleophiles and move on to compare the 1,2-diX disconnection 3 with the alkylation of enolates 6. Here we have reversed the polarity. We mention regioselectivity—a theme we shall develop in chapter 14.

1,1-diX Disconnections:

\[
\begin{align*}
&\overset{1,1-\text{diX}}{R^1} \xrightarrow{C-X} \overset{1,1-\text{diX}}{R^2} \xrightarrow{C^2} \overset{1,1-\text{diX}}{R^1} \\
&\quad \text{The Corresponding C–C Disconnection:} \\
&\quad \overset{1,1-\text{diX}}{R^1} \xrightarrow{C^2} \overset{1,1-\text{diX}}{R^2} \\
\end{align*}
\]

1,2-diX Disconnections:

\[
\begin{align*}
\overset{1,2-\text{diX}}{R^1} \xrightarrow{C-X} \overset{1,2-\text{diX}}{R^2} \xrightarrow{C^2} \overset{1,2-\text{diX}}{R^2} \\
\quad \text{The Corresponding C–C Disconnection:} \\
\quad \overset{1,2-\text{diX}}{R^1} \xrightarrow{C^2} \overset{1,2-\text{diX}}{R^2} \\
\end{align*}
\]

**Synthesis of Aldehydes and Ketones by Acylation at Carbon**

The disconnection 2a is not useful because, as MeO⁻ is the best leaving group from the tetrahedral intermediate 7, the ketone 2 is formed during the reaction. The ketone is more electrophilic than the ester so it reacts again and the product is the tertiary alcohol 8.

---

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One solution is to use an acid chloride as an acylating agent since that is more electrophilic than the ketone. The problem with this approach is that we wish to combine two extremely reactive compounds and an uncontrollable reaction ensues. Successful acylation of the much less reactive, and therefore more selective, organo-copper reagents is known. Treatment of organo-lithium reagents with Cul in dry THF at $-78^\circ$C gives dialkyl copperolithiums or cuprates$^4$ R$_2$CuLi. These react cleanly with acid chlorides, again at low temperature, to give ketones.$^2$

\[
\text{Cu(II)} \xrightarrow{RLi} \text{RCu} \xrightarrow{RLi} \text{R}_2\text{CuLi}
\]

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{Cl} \\
\text{R}_2\text{CuLi}
\end{array} \xrightarrow{\text{R}_2\text{CuLi}} \begin{array}{c}
\text{O} \\
\text{R}^1 \\
\text{R}^2
\end{array}
\]

A simple example that also shows some chemoselectivity is the preparation of the ketones 12; R = Et or Pr by reaction of the bromoacid chloride 11 with the appropriate dialkyl copper lithium. The bromoacid 10 is available and can be converted into a range of bromoketones by this method.$^3$

\[
\begin{array}{c}
\text{Br} \\
\text{HO} \\
\text{Br}
\end{array} \xrightarrow{\text{R}_2\text{CuLi}} \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{R}
\end{array}
\]

Only one alkyl group is transferred from R$_2$CuLi and to avoid wasting the other R group, complexing agents can be added. Posner$^4$ uses a PhS group to stabilise the organo-copper reagent 14 with one $t$-Bu group that is cleanly transferred to the acid chloride. Friedel-Crafts reactions of $t$-BuCOCl are plagued with loss of CO so this is a better method.

\[
\begin{array}{c}
\text{PhSH} \\
\text{1. BuLi} \\
\text{2. Cu(II)} \\
\text{THF, 25}^\circ\text{C}
\end{array} \xrightarrow{\text{PhSCu}} \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\]

In his synthesis of the [4,4,4] propellane, Paquette made the diester 16 easily but wanted the mono methyl ketone 18. Rather than add MeLi directly, he first hydrolysed one ester to the free acid 17 and then made the acid chloride with oxalyl chloride. Reaction with Me$_2$CuLi gave the ketone in excellent yield.$^5$

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array} \xrightarrow{\text{NaOH}, \text{H}_2\text{O}, \text{MeOH}} \begin{array}{c}
\text{CO}_2\text{H} \\
\text{CO}_2\text{Me}
\end{array} \xrightarrow{\text{1. (COCl)}_2, \text{2. Me}_2\text{CuLi}} \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\]

Direct Formylation of Organo-Lithiums with DMF

Another method is to use a much less electrophilic acylating agent than an ester. This sounds crazy but DMF 20 reacts directly with organo-lithium compounds to give good yields of aldehydes
Now the tetrahedral intermediate 21 is stable under the reaction conditions as Me₂N⁻ is such a bad leaving group. The aldehyde 23 is formed only during work-up in aqueous acid 22.

The orgaao-lithium reagent can be made by exchange of Li for a halide or by deprotonation. With di-iodide 24, one iodine may be exchanged with one equivalent of BuLi and the aldehyde 25 is the product. The aromatic heterocycle isothiazole 26 has its most acidic hydrogen (marked) next to sulfur and it gives one aldehyde 27 in good yield.

A more reactive equivalent for ketone synthesis is a nitrile 28. Addition of a Grignard reagent gives an intermediate 29, stable under the reaction conditions, rather like 21. Hydrolysis in acid solution releases the ketone 2. The exactly analogous reagent to DMF would be a tertiary amide but these are often so unreactive as to be useless.

Grignard reagents are usually better than organo-lithiums in these reactions and may be even better with a catalytic amount of copper (I). A good example is the coupling of the Grignard reagent derived from 30 with the protected nitrile 31 giving an excellent yield of the ketone 32. As a bonus, the protecting group drops off in the work-up.

These reactions may be intramolecular giving five- or six-membered cyclic ketones such as the spiro (two rings with one common atom) compound 34 and the hindered cyclohexanone 36.
Please note that this whole section—indeed all of the chapter so far—relates to the C–C disconnection between the carbonyl group and whatever is joined to it. The nucleophilic reagent is an organometallic derivative of Li, Cu or Mg and the electrophile is an acid chloride, a tertiary amide or a nitrile. In the next section we disconnect the C–C bond one further from the carbonyl.

 Carbonyl Compounds by Alkylation of Enols

Disconnection 37 again uses the natural polarity of the carbonyl group but at the next bond 37 since we hope to use some enolate derivative 38 in an alkylation reaction. But—and it is a big but—do not think for a moment that you can make 37 just by mixing the ketone 39 with an alkyl halide and some base. The problem is that the ketone is itself electrophilic and the self-condensation by the aldol reaction (chapter 19) is generally preferred to alkylation.

Analysis

We need first of all to convert the ketone 39 completely into some enolate derivative so that there is no ketone left for self-condensation. In this chapter we shall restrict ourselves to lithium enolates 40 and anions 42 of 1,3-dicarbonyl compounds 41. Each of these reagents acts as the enolate anion of acetone 38; R² = Me.

Lithium Enolates of Simple Carbonyl Compounds

Lithium enolates 40 are usually made with LDA (Lithium Di-isopropylAmide). We need a strong base—one strong enough to convert the ketone immediately into the lithium enolate. Butyl lithium would be strong enough but it attacks the carbonyl group as a nucleophile instead. We therefore use the BuLi to make LDA—a strong but very hindered base that usually does not attack the carbonyl group. The reagent LDA is prepared in dry THF at low temperature and the ketone added by syringe also at low temperature. The lithium atom bonds to the oxygen and the amide is then in perfect position to remove the proton 43.
If the ketone is symmetrical, as here, or can form an enolate on one side only, or if we are dealing with an ester, enolate formation and hence alkylation is unambiguous. In Corey’s synthesis of cafestol, an anti-inflammatory agent from coffee beans, he first alkylated ketone 44 on the only possible side and converted the product 45 into the new alkylation agent 46.

Next he made the lithium enolate 48 from the unsaturated ester 47 — only the marked hydrogen can be removed — and alkylated this with 46. Almost all of the skeleton of cafestol is assembled in this important step.

Enolates of 1,3-Dicarbonyl Compounds

You should appreciate that syringe techniques in scrupulously dry apparatus and solvents at \(-78^\circ C\) are not the easiest. An alternative to using a very strong base is to modify the ketone so that the enolate is formed much more easily. This is done by adding an ester group 41 that has the sole function of making the enolate 42 conjugated — the negative charge is shared by both oxygen atoms. Only a relatively weak base is needed to make the enolate 42 and the usual choice is the alkoxide of the ester. Alkylation occurs on the middle carbon and the product 50 can be decarboxylated by ester hydrolysis and heating the free acid.

The hydrolysis gives the anion 52 that is protonated to give the keto-acid 53. Often spontaneously, but always on heating, decarboxylation by a cyclic mechanism 54 gives the enol 55 of the alkylated ketone 51.
The extra ester group is not normally added to the preformed ketone as ethyl acetoacetate 41 is available and the diester is available diethyl malonate 59. If it is necessary to make the 1,3-dicarbonyl compound, this can be done by methods described in chapters 19 and 20. The carboxylic acid 56 can be disconnected at the branchpoint to an alkyl halide and the synthons 58 that could be realised as the anion of diethyl malonate 59 or the lithium enolate of ethyl acetate.

One published synthesis uses the malonate route. Ethoxide is used as the base so that it doesn’t matter if it attacks the esters as a nucleophile.

A good example of a ketone made by this strategy is used in the synthesis of terpenes. After the usual ‘1,2’ C–C disconnection, adding the ester group to the enolate 64 gives ethyl acetoacetate 41.

The alkylation goes well as 63 is the reactive alkylic halide ‘prenyl bromide’ and hydrolysis and decarboxylation occur as usual.

**Carbonyl Compounds by Conjugate Addition**

The remaining style of C–C disconnection takes us straight to conjugate addition and we are still using the natural polarity of the carbonyl group. Conjugate addition of a heteroatom to the enone 66 gives the 1,3-relationship in 65 and the same process with a carbon nucleophile gives 67.

**1,3-diX Disconnections:**

We can use either organo-lithiums or Grignard reagents as the carbon nucleophiles but we need copper (I) to ensure conjugate addition. Without Cu(I) both nucleophiles are inclined to add.
directly to the carbonyl group. We can use the same reagents that we used to make ketones in this chapter.

\[
\text{R}^1\text{MgBr} + \text{Cu(I) catalyst} \quad \text{or } \text{R}^1\text{Cu} \text{ or } \text{R}^1\text{CuLi} \\
\text{R}^1 \quad \text{R}^2
\]

In Corey’s synthesis\(^{16}\) of a marine allomone, he wanted the cyclic ketone 68. The Friedel-Crafts disconnection gives some derivative of the carboxylic acid 69 and disconnection between the branchpoints gives the unsaturated acid 70 (it doesn’t matter whether this is the \(E\) - or \(Z\) - isomer as the alkene disappears).

\[
\text{C-C} \quad \text{C-C} \quad + \text{i-PrX}
\]

In practice he used the \(E\)-unsaturated ester 71, as that was easier to make, and added isopropyl Grignard with a CuSPh catalyst (see compound 13 above) to avoid wasting one equivalent of the Grignard. The ester product 72 cyclised to the target with polyphosphoric acid without a specific ester hydrolysis step. No doubt this works so well because it is an intramolecular reaction giving a five-membered ring.

\[
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \quad \text{MeO}_2\text{C}
\]

Aromatic compounds are good enough nucleophiles to add in conjugate fashion under Friedel-Crafts conditions so that no organo-metallic reagent is needed. Benzene adds to cinnamic acid 74 with AlCl\(_3\) as catalyst to give 73 in one step.\(^{17}\)

\[
\text{Ph} \quad \text{Ph} \quad \text{Ph}
\]

In the synthesis of the diol 75 stereochemistry is important. The diol could be made from the keto-ester by stereoselective reduction using a suitable reducing agent (chapter 12) as the alcohol on the six-membered ring is axial.\(^{18}\)
Disconnection of the ketone 76 with conjugate addition in mind could remove the vinyl group 76a or the methyl group 76b. There are two reasons why we prefer a. The addition is likely to occur from the opposite face of the molecule to the CO₂Et group and that is where we want the vinyl group. Conjugate addition to 78 might occur at the β-position but it could equally well occur at the very exposed δ-position. The starting material 77 is also the available Hagemann’s ester 77.

![Chemical Structures](http://www.chem4all.vn)

The vinyl Grignard reagent was used with Cu(I) catalysis and the reduction of both ester and ketone was achieved with LiAlH₄. The stereoselectivity was excellent and 75 could easily be separated from the minor equatorial alcohol. In the next chapter we shall revisit both the use of copper in getting regioselectivity and the stereoselectivity of such reactions.

![Chemical Structures](http://www.chem4all.vn)

References

2. Vogel, page 616.
Strategy VI: Regioselectivity

Background Needed for this Chapter References to Clayden, Organic Chemistry:
Chapter 10: Conjugate Addition, Chapter 26: The Alkylation of Enolates

Chapter 5 dealt with chemoselectivity: how to react one functional group rather than another. Now we must face a more subtle and demanding problem: how to react one specific part of a single functional group and no other. This is regioselectivity. We have already seen that anions of phenols 2 are alkylated at oxygen to give ethers 3 while enolate anions 5 are alkylated at carbon to form a new C-C bond 6.

By and large in those two cases what you get is what you want. We shall look at two important aspects of regioselectivity where we may want either result. We should like to be able to alkylate unsymmetrical ketones 8 on one side or the other to give 7 or 9. We should like to add nucleophiles to enones 11 either directly at the carbonyl group to give 12 or in conjugate fashion, as we have been discussing in the last chapter, to give 10.

The Regioselective Alkylation of Ketones

In the last chapter we used two specific enol equivalents for alkylation reactions: lithium enolates and 1,3-dicarbonyl compounds. Both will help us to solve the regioselectivity problem in the
alkylation of unsymmetrical ketones. Suppose we want to make 13. At first sight it appears that we must alkylate an unsymmetrical ketone on the more substituted side. But, if we remove the benzyl group and add our activating CO₂Et group to give 14 it is clear that we can make this by another alkylation and the activating group will promote both.

Benzyl is the more reactive bromide so it makes sense to add it last since making the quaternary carbon will be difficult. This was the order followed in the published synthesis.¹

If we had wanted the isomeric ketone 19 with the benzyl group on the other side of the carbonyl, we could use a property of lithium enolates we have kept secret until now. Enolate formation with LDA goes on the less hindered alkyl side chain, particularly if it is a methyl group. We could start with acetone 16, alkylate on one side with PrBr to give 17 and then treat again with LDA. Now kinetic selectivity gives the lithium enolate 18 (not isolated) and benzylation must give 19. This regioselectivity might be clear if you look at the intramolecular mechanism for proton removal in chapter 13, diagram 43. An alkyl group on the carbon atom being deprotonated would be sterically hindering.

This looks very clean but a careful study² of the closely related ketone 20 shows that the ratio of less substituted 21 to more substituted enolate 23 is 87:13 so the product 22 is inevitably contaminated with 24.
Regioselectivity is better when the contrast is between secondary and tertiary centres as with cyclic ketone 25. The less substituted lithium enolate 26 is formed almost exclusively (99:1) in dimethoxyethane.\textsuperscript{3}

\[
\begin{align*}
\text{O} & \quad \text{1. LDA, -40 °C} \quad \text{MeO} \\
\text{25} & \quad \text{O} \\
& \quad \text{OMe} \\
& \quad \text{26} \\
& \quad \text{2. BnBr} \\
& \quad \text{27}
\end{align*}
\]

It is however possible to make such compounds in good yield from 1,3-dicarbonyl starting materials. Another isomer of 13 and 19 is the branched ketone 28. Disconnecting by a method from chapter 13, we can use the acid derivative 29 which could be made from malonate 31 by two alkylations via 30.

\[
\begin{align*}
\text{Ph} & \quad \text{C–C} \quad \text{Ph} \\
\text{28} & \quad \text{Cl} \\
& \quad \text{FGL} \\
& \quad \text{Ph} \\
& \quad \text{CO}_2\text{Et} \\
\text{29} & \quad \text{C–C} \\
& \quad \text{CO}_2\text{Et} \\
& \quad \text{30} \\
& \quad \text{CO}_2\text{Et} \\
& \quad \text{31}
\end{align*}
\]

The published synthesis uses a cadmium reagent but we should rather use copper nowadays.\textsuperscript{4} Double alkylation of malonate, again adding the benzyl group last, gives 33. Hydrolysis and decarboxylation releases the free acid 34 which is easily converted into its acid chloride and then with Pr\textsubscript{3}Cd, or perhaps better Pr\textsubscript{3}CuLi, into the target molecule 28.

\[
\begin{align*}
\text{NaOEt} & \quad \text{Me} \\
\text{31} & \quad \text{Me} \\
& \quad \text{CO}_2\text{Et} \\
& \quad \text{1. NaOEt} \\
& \quad \text{2. BnBr} \\
& \quad \text{32} \\
& \quad \text{Ph} \\
& \quad \text{CO}_2\text{Et} \\
1. \text{NaOH} & \quad \text{H}_2\text{O} \\
\text{33} & \quad \text{Ph} \\
& \quad \text{H}^{\ominus} \text{heat} \\
& \quad \text{CO}_2\text{H} \\
1. \text{SOCl}_2 & \quad \text{28} \\
& \quad \text{2. Pr}_3\text{Cd}
\end{align*}
\]

### Regioselectivity in Nucleophilic Addition to Enones

The problem of getting direct (1,2-) or conjugate (1,4- or Michael) addition to α,β-unsaturated compounds such as enones 11 can be solved without finding abstruse strategies by choice of reagents.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{10} \quad \text{1,4- or Michael or conjugate addition} & \quad \text{Nu}^{\ominus} \\
& \quad \text{Nu}^{\ominus} \\
\text{11} \quad \text{1,2- or direct addition} & \quad \text{R}^1 \quad \text{R}^2 \\
& \quad \text{Nu}^{\ominus} \\
\text{12} \quad \text{Nu}^{\ominus} \quad \text{OH}
\end{align*}
\]

The general principles are:

1. The conjugate addition product 10 is thermodynamically favoured as the weak C=C bond has been lost but the strong C=C bond retained. The direct addition product 12 is kinetically favoured.
2. Direct addition is more easily reversed than conjugate addition. So the more stable the nucleophile, the more reversible 1,2-addition becomes and the more 1,4-addition predominates.
3. The C=O site is the ‘harder’ and the site of conjugate addition the ‘softer’ electrophilic site; so more basic nucleophiles tend to do 1,2-addition and less basic nucleophiles tend to prefer 1,4-addition.

We saw in chapter 6 that the more electrophilic the α,β-unsaturated compound, the more likely it is to do direct addition with heteroatoms and the same is true for carbon nucleophiles. Grignard reagents normally add direct to α,β-unsaturated aldehydes\(^5\) such as 35 but may add in conjugate fashion to α,β-unsaturated esters,\(^6\) particularly if they have a large esterifying group, such as the sec-butyl group in 37.

\[\text{CHO} \xrightarrow{\text{R} \text{MgBr}} \text{OH} \quad 36; \text{85-90\% yield}\]
\[\text{O} \xrightarrow{n-\text{BuMgBr}} \text{O}_{\text{Os-Bu}} \quad 37; \text{60\% yield}\]

Among nucleophiles we saw again in chapter 6 that the softer, less basic nucleophiles such as sulfur are good at conjugate addition, hydride reducing agents and \(\text{RO}^-\) are better at direct addition, while amines are somewhere in the middle. This means\(^7\) that α,β-unsaturated aldehydes, ketones and esters may all be reduced at the carbonyl group with \(\text{NaBH}_4\) (for aldehydes and ketones) or \(\text{LiAlH}_4\) for esters such as 40. Catalytic hydrogenation however is not an ionic reaction and simply reduces weak bonds\(^8\) such as C=C and not C=O.

\[\text{LiAlH}_4 \quad \text{OH} \quad \text{O} \xrightarrow{\text{Pd/C}} \text{Et} \quad \text{Et}\]

An example is the preparation of the unsaturated alcohol 42 whose benzyl ether was needed for a Diels-Alder reaction. Reduction of the diene ester 43 with \(\text{LiAlH}_4\) gave 85% of the alcohol. The starting material 43 is easily made\(^9\) by methods discussed in chapters 15 and 19.

\[\text{FGI reduction} \quad \text{red.} \quad \text{CO}_2\text{Et} \quad \text{LiAlH}_4 \quad \text{TM}42 \quad \text{85\% yield}\]

**Carbon Nucleophiles in Conjugate Addition**

The very basic and aggressive nucleophilic organo-lithiums tend to do direct addition to all α,β-unsaturated carbonyl compounds. The rather less basic Grignard reagents may add in either sense, as we saw for compounds 35 and 37. We saw in the last chapter how Cu(I) is the key to persuading either RLi or RMgBr to add in a conjugate fashion.\(^10\) If we react 11 with a Grignard reagent with Cu(I) catalysis we get 44 as the product. With \(\text{R}_2\text{CuLi}\) the initial product is actually the lithium enolate 45 giving us the opportunity to add an electrophile to make 46. Of course, if the electrophile is a proton, the product is still 44.
As we saw in chapter 13, addition of a cuprate to a cyclic enone such as 47 followed by trapping with an electrophile gives anti stereochemistry 48.

So when chemists at Dortmund wished to make the syn compound 49, they chose to add diallyl copper lithium to the enone 50 with one side chain already in place.\(^\text{11}\) This gave the lithium enolate 51 and protonation gave the syn compound 49. The choice of acid was important: phenols were good and 52 was the best.

Thermodynamic control dominates when a cis ring junction is preferred, as between the flat five-membered and the six-membered ring in 55. Reversible protonation of the lithium enolate 54 occurs on the same face as the methyl group on the exo face (chapter 12). The molecule prefers a folded conformation.

Stereochemistry may be created during the addition step as in the formation of 57 and 59. Cuprate addition to 56 gives\(^\text{12}\) a 98:2 ratio of anti:syn products 57. The addition of PhLi and Cu\(_2\)I\(_2\) (and perhaps Ph\(_2\)CuLi) to 58 gives\(^\text{13}\) a 96:4 anti:syn ratio of 59. In both cases the cuprate has added from the opposite face to the substituent but the stereochemistry of 57 is probably dominated by axial attack giving a chair product (chapter 12) while 59 has both substituents equatorial.

But most of the time we are chiefly concerned with getting the carbon nucleophile to add 1,4. The synthesis of the unsaturated ketoce 62 makes two more points. While we cannot do S\(_N\)2 reactions on vinyl halides, they make good organo-lithium and copper reagents and, in the
addition to cyclohexenone, propenyl bromide both forms the cuprate and adds with retention at the alkene.\textsuperscript{14} This leads us on to the next chapter.

\[ \text{propenyl bromide} \rightarrow \text{cuprate addition} \]

References

Alkene Synthesis

Background Needed for this Chapter: Reference to Clayden, Organic Chemistry: Chapter 19: Elimination Reactions; Chapter 31: Controlling the Geometry of Alkenes

Synthesis of Alkenes by Elimination Reactions

Alkenes can be made by the dehydration of alcohols 2, usually under acidic conditions, the alcohol being assembled by the usual methods. This route is particularly good for cyclic alkenes 3 and those made from tertiary and/or benzyl alcohols as the E1 mechanism works well then. The same alkene is formed from 2 regardless of which side eliminates but 4 gives a 76% yield of an 80:20 mixture of 5 and 6.

Acids must be fairly strong for this job and must have a non-nucleophilic counterion to avoid substitution. Popular ones are KHSO₄ and TsOH (crystalline and easier to handle than H₂SO₄ or H₃PO₄) and the less acidic POCl₃ in pyridine. Little control is found over the position or geometry of the alkene though in many simple cases, such as 2, this doesn’t matter. Notice however that if R = Alkyl, very little exocyclic alkene, if any, is among the product.

When Zimmermann and Keck wished to study the photochemistry of a series of alkenes of the general structure 7 they could have put the OH group at either end of the double bond but they chose the branchpoint 8 because dehydration of the tertiary benzylic alcohol should be very easy and there is no ambiguity in the position of the alkene whatever R may be. They used the Grignard method and dehydrated 8 with POCl₃ in pyridine.

Eliminations on alkyl halides follow essentially the same strategy except that the reaction is now done by the E2 mechanism with a strong hindered base to avoid SN₂ reactions. This


Stuart Warren and Paul Wyatt
approach is good for terminal alkenes 10 as the elimination is successful on primary halides. The alcohol 12 can be made by any method (chapter 10).

\[
\begin{align*}
\text{R}^- & \xrightarrow{\text{FGI}} \text{R}^- \text{Br}^- & \xrightarrow{\text{FGI}} \text{R}^- \text{OH}^- & \xrightarrow{\text{Li or RMgBr}} \text{R}^- \text{O}^- \\
\end{align*}
\]

So a typical synthesis might involve treating the alcohol 10 with PBr₃ to make the bromide and eliminating with t-BuOK. There is again no ambiguity in the position of the alkene.

\[
\begin{align*}
\text{R}^- & \xrightarrow{\text{PBr}_3} \text{R}^- \text{Br}^- & \xrightarrow{t-\text{BuOK}} \text{R}^- 10 \\
\end{align*}
\]

Dienes can be made by this elimination strategy if vinyl Grignards are used as the vinyl group blocks dehydration in that direction and makes the cation intermediate in the E₁ reaction allylic. An interesting example³ is the four-membered ring compound 13, disconnected via the allylic alcohol 14 to cyclobutanone 15.

\[
\begin{align*}
\text{R}^- & \xrightarrow{\text{FGI}} \text{R}^- \text{OH}^- & \xrightarrow{\text{OH}} \text{R}^- \text{O}^- & \xrightarrow{\text{BrMg}} \text{R}^- 15 \\
\end{align*}
\]

Cyclobutanone 15 is available, and also very electrophilic, so addition of the vinyl Grignard and dehydration with the rather unusual reagent iodine gave the diene 13. This diene will be used in a Diels-Alder reaction in chapter 17.

\[
\begin{align*}
\text{Br}^- & \xrightarrow{1. \text{MgEt}_2\text{O}} \text{Br}^- & \xrightarrow{2. 15} \text{I}_2 & \xrightarrow{\text{heat}} \text{R}^- 13; 72\% \text{ yield} \\
\end{align*}
\]

**Alkene Synthesis by the Wittig Reaction**

The most important method of alkene synthesis is now the Wittig reaction⁴ which gives full control over the position of the double bond and some control over its geometry. A phosphine, usually triphenyl phosphine Ph₃P, reacts with an alkyl halide in an S₂K₂ reaction to give a phosphonium salt 18. Treatment with base, often BuLi, gives the phosphonium ylid 19. An ylid is a species with positive and negative charges on adjacent atoms. Reaction with an aldehyde gives the alkene, usually the Z-alkene 20 if R¹ is an alkyl group, and triphenylphosphine oxide 21.

\[
\begin{align*}
\text{Br}^- & \xrightarrow{17} \text{R}^- \xrightarrow{} \text{Ph₃P}^+ \xrightarrow{\text{base}} \text{Ph₃P}^+ \xrightarrow{} \text{R}^1 \xrightarrow{\text{R^2CHO}} \text{Z-alkene} & \xrightarrow{\text{Ph₃P=O}} 21; \text{phosphine oxide} \\
\end{align*}
\]

The mechanism for the formation of the alkene is open to discussion especially as there is no agreement on the source of the stereoselectivity.⁵ We suggest that the carbon end of the ylid
adds to the aldehyde 22 and the ‘betaine’ then cyclises 23 to the four-membered ring which fragments to give the products 24. There is no doubt about intermediate 24 nor that its decomposition must be stereospecific. So the Z-alkene 20 is formed from the cis oxaphosphetane 24.

As the Wittig reaction forms both π and σ-bonds, the disconnection is right across the middle of the alkene giving a choice of starting materials. So with the exo-cyclic alkene 26, very difficult to make by elimination methods, we could use formaldheyde or cyclohexanone as the carbonyl component with either phosphonium salt 25 or 28. It is a matter of personal choice whether you draw the ylid, the phosphonium salt or the alkyl halide at this stage.

Wittig did this synthesis with the iodide 29, which he made himself, to give 26 in low yield (46%) but higher yields are routinely obtained nowadays: Vogel reports 64% from the commercially available bromide 30 using the sodium salt of DMSO as base.

Trisubstituted alkenes 32 are no trouble as either a secondary halide 35 or a ketone can be used. As both 33 and 35 are available we choose them.

The synthesis is straightforward but does produce a mixture of geometrical isomers. This is another case where dehydration, even of the tertiary alcohol 36, would probably give a mixture of positional (and geometrical) isomers.
Wittig Reactions with Stabilised Ylids

The unstable aspect of the ylid is the carbanion: phosphonium salts are stable compounds so any substituent that stabilises the anion also stabilises the ylid and this reverses the stereoselectivity to favour the $E$-alkene. Even benzylic ylids give $E$-alkenes as in the reaction\(^9\) with the anthracene 37 that gives a good yield of crystalline 38 having a coupling constant between the two marked Hs of 17 Hz. One possible explanation is that the formation of the betaine or oxaphosphetane is reversible if the ylid is stabilised and only the faster of the two eliminations occurs to give the $E$-alkene.

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{\text{Ph}_2\text{P} \quad \text{Ph} \quad \text{Cl}^\ominus} \quad \text{H} \\
\text{37} & \quad \xrightarrow{50\% \text{NaOH in H}_2\text{O} \quad \text{CH}_2\text{Cl}_2} \quad \text{H} \\
& \quad \text{E-38; 74\% yield}
\end{align*}
\]

Applications of the Wittig Reaction

An excellent application of the distinction between stabilised and unstabilised ylids is in the synthesis of leukotriene antagonists.\(^10\) The intermediate 39 (R is a saturated alkyl group of 6, 11 or 16 carbon atoms) was needed and disconnection of the Z-alkene with a normal Wittig reaction in mind followed by removal of the epoxide exposed a second alkene with the $E$ configuration that could be made from the aldehyde 43 and the stabilised ylid 42.

\[
\begin{align*}
\text{R} & \quad \xrightarrow{\text{C-C}} \quad \text{Wittig} \quad \text{O} \\
\text{39} & \quad \xrightarrow{\text{OH} \quad \text{CO}_2\text{Me}} \quad \text{O} \\
\text{40} & \quad \xrightarrow{\text{FGI}} \quad \text{C-C} \\
\text{41} & \quad \xrightarrow{\text{C-C}} \quad \text{Wittig} \\
\text{42} & \quad \xrightarrow{\text{OH} \quad \text{CO}_2\text{Me}} \quad \text{O} \\
\text{43} & \quad \xrightarrow{\text{OH} \quad \text{CO}_2\text{Me}} \quad \text{O}
\end{align*}
\]

This ylid is so stable that it is commercially available and reacts cleanly with 43 to give only $E$-41. Epoxidation under alkaline conditions gives the trans epoxide 40 and a normal Wittig on an unstabilised ylid gives 39: the yield depends on R.

\[
\begin{align*}
\text{42} & \quad \xrightarrow{\text{OH} \quad \text{CO}_2\text{Me}} \quad \text{O} \\
\text{41; 47\% yield, E only} & \quad \xrightarrow{\text{H}_2\text{O}_2 \quad \text{pH 9.5}} \quad \text{OH} \quad \text{CO}_2\text{Me} \\
\text{40; 60\% yield} & \quad \xrightarrow{\text{RCH}_2\text{PPh}_3} \quad \text{BuLi} \quad \text{39}
\end{align*}
\]

When the substituent becomes very anion-stabilising, as in 42, the ylid may not react with ketones and anions of phosphonate esters are usually preferred in the Horner-Wadsworth-Emmons (HWE) variant.\(^11\) The reagent triethyl phosphonoacetate 46 is made by combining a phosphite $(\text{EtO})_2\text{P}$ instead of a phosphine, with ethyl bromoacetate. Displacement of bromide 44 gives a phosphonium ion that is dealkylated by bromide 45.
Barrett used the reaction at the start of his synthesis of an antibiotic.$^{12}$ The HWE reaction with the enal 47 gives the diene ester 48 and by reduction with DIBAL, the dienol 49.

The ‘optical brightener’ Palanil 50—it makes your clothes look ‘whiter than white’ and your T-shirts fluoresce in UV light—can be disconnected by the Wittig strategy to two molecules of the phosphonium ylid 51 and one of the dialdehyde 52. The availability of the dialdehyde, used in the manufacture of terephlene, makes this route preferable to the alternative.

As the ylid 51 is stabilised by the nitrile as well as the benzene ring, the phosphonate ester 54 is preferred in the manufacture and the reaction is strongly trans selective.$^{13}$ The by-product is the anion of dimethyl phosphate 55 which is water-soluble and very easy to separate from the product 50. By contrast, triphenylphosphine oxide is insoluble in water and can be difficult to separate from the alkene.

Many insect pheromones are derivatives of simple alkenes. Disparlure 56, an attractant for the gypsy moth, is an epoxide derived by stereospecific epoxidation from the Z-alkene 57. As neither substituent is anion-stabilising, a simple Wittig should give the right geometry.
The synthesis was carried out this way,\textsuperscript{14} though no doubt the alternative combination would also work well. The synthetic material is as attractive to the moth as the natural pheromone.

\begin{equation}
\begin{array}{c}
\text{Br} \quad 59 \\
\text{Ph}_3\text{P} \quad 58 \\
\quad \text{86\% yield} \\
\text{1. BuLi} \quad 57 \\
\quad \text{91\% yield} \\
\quad \text{2. C}_{10}\text{H}_{12}\text{CHO} \quad \text{mCPBA} \quad 56 \\
\quad \text{83\% yield}
\end{array}
\end{equation}

\textbf{Dienes by the Wittig Reaction}

Conjugated dienes are needed for the Diels-Alder reaction (chapter 17) and Wittig disconnection 61 reveals that the choices here are more important. The easily prepared enals 62 would react with an unstabilised ylid 63 to give a Z-alkene but the conjugated allylic ylid 60 might give the E-alkene.

\begin{equation}
\begin{array}{c}
\text{R}^1 \quad \text{PPh}_3 \quad \text{R}^2 \\
\text{Wittig} \quad a \\
\text{R}^1 \quad \text{PPh}_3 \quad \text{R}^2 \\
\text{Wittig} \quad b \\
\text{CHO} + \text{R}^2 \\
\text{R}^1 \\
\text{CHO} + \text{R}^2
\end{array}
\end{equation}

The mono-substituted butadiene 66 was needed with a \textit{trans} alkene in the middle. So disconnection 61a looks good and the allyl phosphonium salt 65 did indeed give \textit{E}-66 though in poor yield. These low molecular weight hydrocarbons are difficult to isolate as they are volatile.

\begin{equation}
\begin{array}{c}
\text{Br} \quad 64 \\
\text{Ph}_3\text{P} \quad 65 \\
\quad \text{1. BuLi} \quad \text{2. PrCHO} \\
\quad \text{E-66; 52\% yield}
\end{array}
\end{equation}

Diaryl butadienes 69 can be made by method 61b as the ylid from 68 is conjugated and will give one \textit{E}-alkene while the other comes from an aldol condensation used to make the enal.\textsuperscript{15} (chapter 19).

\begin{equation}
\begin{array}{c}
\text{1} \quad \text{Ar}^2 \quad \text{Ph}_3\text{P} \quad \text{2. base} \\
\text{67} \quad \text{68} \quad \text{Ar}^2 \quad \text{Ar}^1 \\
\quad \text{Ar}^1 \quad \text{E,E-69}
\end{array}
\end{equation}

Though the Wittig is the most important, there are many other ways to make alkenes using a variety of elements in the periodic table keeping the same disconnection.\textsuperscript{16}

\textbf{References}

Strategy VII: Use of Acetylenes (Alkynes)

Background Needed for this Chapter Reference to Clayden, Organic Chemistry. Chapter 9: Using Organometallic Reagents to Make C–C Bonds.

This strategy chapter is rather different. We shall look at one class of starting material—alkynes or acetylenes—and see what special jobs they can do in synthesis. In particular, we shall see how they can solve some problems we have already met. Acetylene itself is readily available and its first important property is that protons on triple bonds are much more acidic than most CH protons. Acetylene forms a genuine anion 4 with sodium in liquid ammonia, a lithium derivative 1 with BuLi and a Grignard reagent 2 by reaction with a simple alkyl Grignard such as EtMgX.

These derivatives react with the type of carbon electrophiles we have already met such as alkyl halides, aldehydes and ketones, and epoxides to give 5, 6 and 7 respectively.

Oblivon 8 is clearly an adduct of acetylene and a ketone 9 and the synthesis is trivial. This example and the next are from the patent literature1 so we are guessing at the details and have no yields.

These products still have an acidic hydrogen on the triple bond so they can react again with base and an electrophile. Surlynol 10 is clearly an acetylene diadduct with the same ketone 11 being used twice.2

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This time a second treatment with base will be needed to make the second anion. As the OH proton in 12 is more acidic ($pK_a \sim 16$) than the alkyne proton ($pK_a \sim 25$), two molecules of base will be needed and the most reactive ‘anion’ (alkyne) reacts first.

The Reduction of Alkynes to Alkenes

Otherwise few of these acetylene adducts are important in their own right but they are valuable intermediates because disubstituted acetylenes 15 can be reduced at will to either $E$- or $Z$-alkenes by different reducing agents. Catalytic hydrogenation using the Lindlar catalyst, to stop reduction to the alkane, adds a molecule of hydrogen to one side of the triple bond to give $Z$-14. Addition of solvated electrons, formed when sodium metal dissolves in liquid ammonia, may give the dianion 16 with the two negative charges in sp$^2$ orbitals as far from each other as possible, and certainly gives $E$-14 on protonation with a weak base such as $t$-BuOH.

We saw the cis-selective reduction when we made compound 30 in chapter 12; the starting material cis-butenediol 18 is readily available as it is made by the Reppe process. There is a fascinating story of the reluctant Reppe not divulging the details to the allies after the second world war.

An unsymmetrical example is the allylic halide 19 needed for the synthesis of cis jasmine. Obvious disconnections take us back to 21 and a simple three-component synthesis.

As the alcohol 22 was available it was simply a case of putting in the ethyl group. Of course the alternative order of events might be better. Since the reduction to the cis-alkene can be done either before or after incorporation into the cis-jasmone skeleton, 22 was also transformed into the propargylic bromide 24.
The \textit{trans} acetate 25 is the pheromone used to trap pea moths.\textsuperscript{6} Changing the \textit{E}-alkene into the acetylene allows the disconnection next to what was the double bond. The only problem is how to make a mono-bromide from the symmetrical diol 30.

\begin{align*}
\text{FGI} & \rightarrow \begin{array}{c}
\text{(CH}_2\text{)}_9\text{OH} \\
\end{array} \\
\text{PBr}_3 & \rightarrow \begin{array}{c}
\text{Br-}(\text{CH}_2\text{)}_9\text{O\text{THP}}
\end{array}
\end{align*}

Experiments showed that protecting one end of the diol 30 as the THP derivative 31 (chapter 9) gave good yields and the monobromo compound 32 was used to alkylate acetylene with the methyl group added later. Reduction and deprotection gave the \textit{E}-alcohol 26 and acetylation gave the pheromone 25.

The \textit{Synthesis of Dienes}

In chapter 15 we saw that dienes could be made by the Wittig reaction and also by the addition of vinylolithiums or Grignard reagents to ketones followed by dehydration of the allylic alcohol product. Derivatives of acetylenes can do the same job. The first disconnection is the same but a reagent for the synthon 40 replaces the vinyl metal derivative.

The published synthesis\textsuperscript{7} of 36 uses the sodium salt and the reduction goes in excellent yield. Only the dehydration with KHSO\textsubscript{4} is poor.

\begin{align*}
\text{H}_2\text{Pd/BaSO}_4 & \rightarrow \begin{array}{c}
\text{OH} \\
\end{array}
\end{align*}
Ketones by Hydration of Acetylenes

A rather different reaction of acetylenes is the addition of water, usually catalysed by Hg(II), to give ketones. Terminal acetylenes 41 reliably give methyl ketones 44 as the intermediate vinyl cation 42 is secondary. Water adds to the cation 42 to give the enol 43 which equilibrates to the ketone 44 with the loss of Hg(OAc)₂.

Symmetrical acetylenes can also be hydrated to one ketone as the two possibilities are the same. An intriguing example is the hydration of the diol 45 that presumably gives the ketone 46. This is not isolated as, under the conditions of the reaction, formation of the cyclic ether 47 is faster than the hydration.⁸

The very unsymmetrical acetylene 48, with a ketone on one side of the alkyne and a cis-alkene on the other, hydrates completely regioselectively⁹ to the diketone 49.

The involvement of the ketone in the intermediate 50 shows why water adds to one end of the alkyne and not the other. We have already seen above how the cis double bond in molecules of this sort can be made from alkyynes and so both main uses of alkyynes appear here.

In fact, the diketone 49 was not isolated but was cyclised with dilute aqueous base to give cis-jasmone 52 in excellent yield. We shall be exploring reactions of this sort in chapters 18–28.
An Alkyne-Containing Anti-AIDS Drug

Merck’s reverse transcriptase inhibitor efavirenz 53 is one of a new generation of anti-AIDS drugs.\textsuperscript{10} Disconnection of two structural C–O bonds reveals 54 that is clearly the adduct of an acetylene 56 and the ketone 55. The question is, how do we make 56?

We have not yet met three-membered rings but cyclisation of carbon nucleophiles onto CH$_2$s with a leaving group (X in 57) works well! Now the question is: how do we make the pentynol 58?

The answer is an exaggerated form of starting material strategy. We need a five-carbon compound with some oxygenation and some unsaturation. There is one exceptionally cheap and abundant compound that fits the bill: furfural 59. When breakfast cereals are made, furfural is an abundant by-product and the Quaker Oats company have patents on isolating it but chemists can do so from corn cobs by a simple recipe that gives 165–200 g furfural from 1.5 kg of ground up corn cobs.\textsuperscript{11} Treatment of furfural with aqueous NaOH disproportionate$^{12}$ the aldehyde into equal amounts of the acid 60 and the alcohol 61. No doubt sodium borohydride would do the job better. Catalytic reduction gives the saturated alcohol 62 in 85\% yield.\textsuperscript{13}

We seem not to be getting closer to 58, but 58 would actually result by dehydration of 62. In real life, the alcohol 62 is turned into the chloride and a double elimination with NaNH$_2$ gives 58 after acidification.\textsuperscript{14} Though we saw elimination reactions used to make alkenes in chapter 15, this is the first we have seen to make alkynes.

Now the three-membered ring can be closed, after replacing the OH group by Cl, by treatment with two equivalents of butyl-lithium. The first proton is removed from the alkyne so the cyclisation occurs on the diithium derivative$^{15}$ 64.
If the cyclisation is not worked up, the product is the alkynyl-lithium that can be added directly to 55 to give the alcohol 54. In the Merck synthesis of efavirenz, this step is used to make a single enantiomer of 64 and this chemistry is discussed in *Strategy and Control*.16

Alkynes give us new strategies for making alkenes and ketones with disconnections in different places from those used in chapters 13 and 15.

References

Two-Group C–C Disconnections I: Diels-Alder Reactions

Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Chapter 35: Pericyclic Reactions I: Cycloadditions

The Diels-Alder reaction,\(^1\) e.g. 1 + 2, is one of the most important reactions in organic synthesis because it makes two C–C bonds in one step and because it is regio- and stereoselective. It is a pericyclic reaction between a conjugated diene 1 and an alkene 2 or 4 (the dienophile) conjugated with, usually, an electron-withdrawing group Z forming a cyclohexene 3 or 5.

![Diels-Alder Reaction Diagram]

The disconnection is often best found by drawing the reverse reaction mechanism. You may draw the arrows either clockwise or anticlockwise but one must start from the alkene. It makes sense to draw this arrow first. The disconnection is 5a for the general case and 6 for a specific case, revealing a diene 7 and a dienophile 8. These reagents 7 and 8 need only to be heated together in a sealed tube\(^2\) (because they are volatile) to give 6.

![Disconnection Diagram]

This is a two-group disconnection because it can be carried out only when two features are present in the target molecule: the cyclohexene ring and the electron-withdrawing group outside the ring and on the opposite side to the alkene. The relationship between these features must be recognised. No matter how complicated a molecule may be, if those features are present we should first try a Diels-Alder reaction. Other features, such as the two four-membered rings in 9, shouldn’t distract you. In fact we made diene 10 in chapter 15 and the dienophile 11 will be discussed later. Combining the two does indeed give 9 which was used to make\(^3\) the highly strained benzene 12.

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Stereospecificity

The reaction occurs in one step so there is no chance for either the diene or the dienophile to rotate and the stereochemistry of each must be faithfully reproduced in the product. The two Hs in 3 are cis because they were cis in the starting anhydride 2. The two Hs in 14 are trans because they were trans in the diester 13.

The synthetic attractant sig lure 15 used as bait for the Mediterranean fruit fly has all the features of a Diels-Alder adduct and we need the E-unsaturated ester 16 for the reaction.

In manufacture it is easier to use the cheap methyl ester and exchange the esterifying group after the Diels-Alder reaction.

Stereospecificity of the Diene

The stereochemistry of the diene is also faithfully reproduced in the product but this is not so easy to see. Diene 19 with two E double bonds, adds to the acetylene 20 to give a product 21 with the two phenyl groups cis. This is because the two reagents approach in parallel planes. There are two other ways to work this out, both based on a diagram 23 that looks downwards onto the planes. You might see straightaway that the two marked Hs are cis and therefore the two Ph groups must also be cis. You might prefer to see that both reagents are symmetrical, having a plane of symmetry marked with the dashed line in 23 and that the product must keep the same symmetry. A more detailed analysis of all these questions appears in Ian Fleming’s books.
These two aspects of the Diels-Alder are stereospecific in that the stereochemistry of the product is determined only by the stereochemistry of the reagents and not at all by how favourable one or other pathway may be. We deliberately used an acetylenic dienophile in the last example as it gives rise to no new stereochemistry. But if both diene and dienophile lead to new stereochemistry in the product, we need to consider stereoselectivity as there will be two ways in which the integrity of both reagents can be maintained.

**Endo-Selectivity**

In a classic Diels-Alder reaction, cyclopentadiene 24 combines with maleic anhydride 2 with complete stereospecificity to give either 25 or 26: so the two Hs on 2 remain cis to each other in both 25 and 26. These are called endo- and exo- adducts. This refers to the relationship between the alkene on the diene side and the carbonyl groups from the dienophile. These are much closer in the endo-adduct 25. The result is easy to see when both reagents are cyclic.

The experimental result is that the endo-adduct 25 is kinetically favoured while the exo-adduct is more stable. This suggests an attractive interaction between the carbonyl groups and the middle of the diene. Indeed part of the role of the electron-withdrawing groups in the dienophile is to attract the diene through space. This interaction does not lead to any bonding between these atoms and is a secondary orbital interaction. You may find this easier to see in the 3D diagrams 27 and 28 where dotted lines show the secondary orbital interactions or in the flat diagram 29.
In open chain examples, diagrams in the style of 23 or 29 are usually easier to follow, but the choice is yours. The product from 30 and acrolein is clearly 31: top tip number 1—always draw the mechanism first. But what is the stereochemistry at the circled centres? Putting the diene on top 32 and—top tip number 2—drawing in the hydrogen atoms at the new centres—you should be able to see that the three marked Hs are all on the same side. This is the RHS as drawn in 32 but unfolding (or flattening) the ring makes this the top surface 31a and hence the other groups (two methyl’s and an aldehyde) are on the bottom 31b. Here is another virtue of the Diels-Alder reaction: it generally makes the less stable diastereoisomer.

Disconnection will be needed to discover which geometrical isomer of diene or dienophile is needed for a given product. The imide 33, needed for Weinreb’s cytochalasin synthesis is easily disconnected to the imide 34 and the diene 35. We clearly need either E, E- or the Z,Z-diene to get the two substituents on the same side. But which? All the Hs are on the same side so we need the molecules shown in diagram 36 and hence E,E-35. The synthesis of this diene is discussed in the workbook for chapter 15.

**Regioselectivity**

So far we have used at least one symmetrical component but when both components in a Diels-Alder reaction are unsymmetrical, regioselectivity is an issue. A full explanation is beyond the scope of this book and you are referred to Ian Fleming’s books and Clayden chapter 25. We need a quick way to work out what happens between a given diene and dienophile and the simplest mnemonic is that the Diels-Alder reaction has an aromatic transition state (true: six delocalised π-electrons) and that it is ‘ortho,para’ directing. So in the first reaction, with a 1-substituted butadiene 37, we get the ‘ortho’ product 39 while in the second reaction, with a 2-substituted butadiene 41, we get the ‘para’ product 42. Neither reaction gives the ‘meta’ product 40. Notice that these reactions are catalysed by a Lewis acid SnCl₄. This complexes to the oxygen of the ketone making the enone more polarised and enhancing the regioselectivity.
A slightly more rational way to say the same thing is that we do really know which component supplies the HOMO ('nucleophile') and which the LUMO ('electrophile'). The enone 38 is naturally electrophilic as in 43 and 45, especially when bound to the Lewis acid. If the diene 37 acted as a nucleophile, it would give the more highly substituted allylic cations 44 and 46. The Diels-Alder is not an ionic reaction and 44 and 46 are not intermediates but the HOMO and LUMO that determine the regiochemistry in the imaginary ionic reactions 43 and 45 also determine the regiochemistry of the pericyclic reactions.

Sterespecificity, stereoselectivity and regioselectivity combined in Diels-Alder reactions give unprecedented control and you should now see why it is so important. The analgesic tildine 47, effective in cases of severe pain, is an obvious Diels-Alder product. The regioselectivity is correctly 'ortho' and the endo transition state 51 shows that the trans-enamine 49 is needed. This is the geometry we get when the enamine is made in the normal way from the enal 50 and Me₂NH.
FGI on Diels-Alder Products

The cyclic ether 52 comes from the diol 53 that can be made by reduction of various Diels-Alder adducts such as the anhydride 54.

Be careful not to attempt a synthesis based on the direct disconnection 52a as the unsaturated ether 55 lacks the vital carbonyl group and does not react with 41. However maleic anhydride does react, LiAlH₄ reduction gives the diol 53 and the cyclisation occurs⁹ on treatment with TsCl and NaOH. No doubt the mono-tosylate is formed and rapidly cyclises.

Intramolecular Diels-Alder Reactions

As is usually the case, intramolecular reactions are easier than intermolecular and often do not obey the usual rules. Some do not need the carbonyl group, some show exo rather than endo selectivity, and the cyclisation of 56 gives the ‘meta’ product 58. The mechanism 57 makes it clear that the expected ‘para’ product (cf. 42) cannot be formed. This is a particularly impressive example as the product 58 is a ‘bridgehead’ alkene with a strained geometry.¹⁰ The alkene is cis inside the six-membered ring but trans in the outer 10-membered ring.

Diels-Alder Reactions in Water

In an ideal world all chemical reactions would be carried out in water because solvent is the main by-product of all chemical processes and is difficult to recycle. For many reactions water as solvent is virtually impossible as reagents and/or catalysts are incompatible and/or insoluble in water. But Diels-Alder reactions are faster and more stereoselective in water even though the reagents generally don’t dissolve.¹¹ So cyclopentadiene 24 adds to methyl acrylate 59 with poor endo selectivity in cyclopentadiene as solvent. The selectivity improves in ethanol but is
excellent in water. One explanation is that the reagents cluster in small oily droplets in water and are held closer together than they would be if they were in solution.

\begin{equation}
\begin{array}{ccc}
\text{CO}_2\text{Me} & \rightarrow & \text{CO}_2\text{Me} \\
\text{H} & \text{or} & \text{H} \\
60 (\text{endo}) & \text{and} & 61 (\text{exo}) \\
24 & 59 & \text{endo:exo ratio in solvents} \\
\text{in 24: } & 3.9:1 \\
\text{in EtOH: } & 8.5:1 \\
\text{in water: } & 21.4:1
\end{array}
\end{equation}

References

Strategy VIII: Introduction to Carbonyl Condensations

The next 10 chapters are about the synthesis of carbon skeletons with two functional groups. Compounds such as 1–3 will all be treated as 1,3-disfunctionalised compounds since the important thing is not the type of functional group but the relationship between them. Our logic is that all FGs can be derived from alcohols, ketones (or aldehydes) or acids by substitution and that those three can be interconverted by oxidation or reduction.

Analysis will be by FG1 to reveal the oxygen-based functionality at the right oxidation level and then by C–C disconnection using the relationship between the FGs as our guide. So we shall be using two-group disconnections throughout. The carbon synths used will be the same as those we used for two-group C–X disconnections in chapter 6. Most of the chemistry revolves around the carbonyl group and we need to think first how that group affects the behaviour of molecules.

The carbonyl group is the most important functional group in organic synthesis because it can be naturally electrophilic or nucleophilic at carbon. It hardly needs saying that carbonyl compounds are naturally electrophilic, 4 or 5, at the carbonyl carbon and so react with nucleophiles at that atom 6. If there is a leaving group X, the tetrahedral intermediate pushes it out 7 to regenerate the carbonyl group. The result 8 is acylation of the carbon nucleophile.

The corresponding disconnection is of the newly formed C–C bond 8a. The synths are the acyl cation and a nucleophilic carbon species that might be a metal derivative RM (chapter 13) but will generally be an enolate in the next 10 chapters. And that is how carbonyl compounds are nucleophilic.
Carbonyl compounds such as acetone 10 exist predominantly in the keto form 10 but are in equilibrium with the enol form 11. We shall be more interested in the formation of the enolate anion 13 with base 12 and its reactions at the α-carbon with carbon electrophiles.

The disconnection is of the newly formed C–C bond 14a and is not the same as 8a. The synthons are represented by the enolate anion and a carbon electrophile. We saw alkyl halides in this role in chapter 13 but in the next 10 chapters we shall be mostly interested in combining enol(ate)s with carbonyl compounds.

*Nucleophilic and Electrophilic Synthons*

The synthons 9 and 15 have natural polarity and it will be helpful in the next 10 chapters if you recognise whether synthons such as these and 17 have natural polarity. We have discussed 9 and 15 above and 17 in chapters 6 and 13 where we used α,β-unsaturated compounds 18 as electrophiles. You may find it helpful to use the labels suggested by Seebach. The letters a and d are used for acceptor (electrophilic) and donor (nucleophilic) synthons and a superscript number shows which atom is meant. The carbonyl group is always atom number 1. So the enolate becomes a d² synthon and 9 and 17 are a¹ and a² synthons. If you don’t like these labels, ignore them, they are entirely optional.

So if we wish to make a compound like 19 we can disconnect a C–C bond to reveal two synthons, 20, a d² synthon easily recognised as the enolate of ketone 22, and an a¹ synthon 21 realised in the aldehyde 23. We have rediscovered the aldol reaction.
If we wish to make the diketone 24, disconnection to the same enolate 20 reveals the α3 synthon 25 and we already know that enone 26 is the reagent. Both these syntheses use synthons of natural polarity: the enolate anion of one compound 22 and either a simple carboxyl compound 23 or the conjugated enone 26.

For this reason, our chapters on two group C–C disconnections follow a slightly odd order. First we deal with the odd numbered relationships: the 1,3-diCO 19a (chapter 19) and the 1,5-diCO 24a (chapter 21) and then we turn to the even-numbered relationships 1,2-diCO 27 (chapter 23) and 1,4-diCO 28 (chapter 25) because these will need synthons of unnatural polarity. Finally we shall turn to the 1,6-diCO relationship (chapter 27) as that involves a totally different strategy.

We can summarise this in these three points:

1. Synthesis of difunctionalised compounds with odd numbered relationships needs only synthons of natural polarity.
2. Synthesis of difunctionalised compounds with even numbered relationships needs some synthons of unnatural polarity.
3. All odd numbered acceptor synthons (such as α1 and α3) and even numbered donor synthons (such as d2 and d4) have unnatural polarity.

And add a slogan: Before you do C–C disconnections, COUNT the relationships.

You will notice that all these methods depend on the carbonyl group and interspersed with these chapters will be strategy chapters relevant to them culminating in a general strategy chapter on carbonyl chemistry:

Chapter 20: Strategy IX: Control in Carbonyl Condensations.
Chapter 26: Strategy XII: Reconstructions.
Chapter 28: General Strategy B: Strategy of Carbonyl Disconnections.

**Carbon Acids and the Bases Used to Deprotonate Them**

We shall be using a variety of bases to create the enolate anions used in the next few chapters and it helps if you have some idea of relative base strength. In the table any base can be used to deprotonate a carbon acid lower in the table, that is, the conjugate acid of the base should have a higher $pK_a$ than the carbon acid. Do not try to learn all these numbers but a general idea of the magnitudes will help you. You could refer to Clayden, *Organic Chemistry*, chapter 8 for the basics. Among the carbon acids, the proton(s) in italics are the ones removed by a base. You
should realise that $pK_a$ outside the range of water (pH about 0–15) are determined indirectly and there may not be in agreement about the exact number.

### TABLE 18.1 Carbon acids and the bases used to deprotonate them

<table>
<thead>
<tr>
<th>Carbon Acid</th>
<th>$pK_a$</th>
<th>Base B</th>
<th>$pK_a$ of BH</th>
<th>From</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk-H</td>
<td>~42</td>
<td>BuLi</td>
<td>42</td>
<td>available</td>
</tr>
<tr>
<td>$\text{Ar-H}$</td>
<td>~40</td>
<td>RMgBr</td>
<td>~40</td>
<td>RBr + Mg</td>
</tr>
<tr>
<td>$\text{CH}_2=\text{CHCH}_3$</td>
<td>38</td>
<td>ArLi</td>
<td></td>
<td>PhLi available</td>
</tr>
<tr>
<td>PhCH$_3$</td>
<td>37</td>
<td>NaH</td>
<td>~37</td>
<td>available</td>
</tr>
<tr>
<td>MeSO$_2$CH$_3$ (DMSO)</td>
<td>35</td>
<td>i-Pr$_2$NLi (LDA)</td>
<td></td>
<td>i-Pr$_2$NH + BaLi</td>
</tr>
<tr>
<td>Ph$_3$CH</td>
<td>30</td>
<td>MeSO$_2$CH$_2$O$\cdot$NH$_2$</td>
<td>35</td>
<td>DMSO + NaH Na + NH$_3$(l)</td>
</tr>
<tr>
<td>HC+CH</td>
<td>25</td>
<td>Ph$_3$C$^-$</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$CO$_2$Et</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$COR</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$COAr</td>
<td>19</td>
<td>t-BuOK</td>
<td>19</td>
<td>available</td>
</tr>
<tr>
<td>Ph$_3$P$^+$-CH$_3$</td>
<td>18</td>
<td>EtO$^-$, MeO$^-$</td>
<td>18</td>
<td>ROH + Na(0)</td>
</tr>
<tr>
<td>CICH$_2$COR</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhCH$_2$COPh</td>
<td>16</td>
<td>HO$^-$</td>
<td>16</td>
<td>available</td>
</tr>
<tr>
<td>MeCOCH$_2$CO$_2$Et</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$NO$_2$</td>
<td>10</td>
<td>PhO$^-$, Na$_2$CO$_3$</td>
<td>10</td>
<td>PhOH + NaOH</td>
</tr>
<tr>
<td>EtO$_2$CCH$_2$CN</td>
<td>9</td>
<td></td>
<td></td>
<td>available</td>
</tr>
<tr>
<td>Ph$_3$P$^+$ CH$_2$CO$_2$Et</td>
<td>6</td>
<td>NaHCO$_3$</td>
<td>6</td>
<td>available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AcO$^-$, pyridine</td>
<td></td>
<td>available</td>
</tr>
</tbody>
</table>

**Reference**

Two-Group C–C Disconnections II: 1,3-Difunctionalised Compounds

Background Needed for this Chapter References to Clayden, Organic Chemistry: Chapter 27: The Aldol Reaction; Chapter 28: Acylation at Carbon.

This chapter deals with target molecules of two main types: hydroxyketones 1 and 1,3- or β-diketones 4. Both have a 1,3-relationship between the two functionalised carbons. Both can be disconnected at one of the C–C bonds between the functional groups to reveal the enolate 2 of one carbonyl compound reacting with either an aldehyde 3 or acid derivative 5 such as an ester.

We shall need to understand the formation of enol(ate)s from aldehydes, ketones and esters and it is worthwhile establishing now that these three types of compounds form a graded series of electrophiles whilst their enolates form a graded series of nucleophiles in the reverse direction. Any of these enolates can react with any of the carbonyl compounds.

\[ R^1\text{C} = \text{O} \quad \text{more reactive} \quad R^1\text{C} = \text{O} \]

\[ \text{most electrophilic carbonyl compounds} \quad \text{most stable enols or enolates} \]

\[ R\text{C} = \text{O} \quad \text{more reactive} \quad R\text{C} = \text{O} \]

\[ \text{aldehydes} \quad \text{ketones} \quad \text{esters} \quad \text{most nucleophilic enols or enolates} \]

\[ R^1\text{C} = \text{O} \quad \text{more reactive} \quad R^1\text{C} = \text{O} \]

\[ \text{most stable carbonyl compounds} \]

β-Hydroxy Carbonyl Compounds: The Aldol Reaction

With compounds of type 1, only one of the two C–C bonds is worth disconnecting: the one next to the hydroxyl carbon. A simple example without any selectivity is ketone 6 which disconnects to the enolate 7 and the ketone 8. It is easy to see that 7 is the enolate of 8 so this is a
'self-condensation': we simply need to create a small amount of enolate 7 in the presence of much enolised ketone 8 and the reaction will occur.

Bases like hydroxides or alkoxides are of about the right strength: barium hydroxide is often used. The small amounts of enolate 7 quickly add to the large excess of ketone 8 to give the anion 9 of the product which regenerates the base by taking a proton from water or the alcohol.

Products such as 6 are 'aldols' having OH and CHO groups and this reaction is the aldol reaction. The diol 11 that is used to make Meyers' heterocycle 10 is not an aldol but FGI of the only alcohol that could come from a ketone, reveals an aldol product: in fact the dimer of acetone.

The aldol reaction uses barium hydroxide and the reduction that could be carried out with many reducing agents, works well catalytically.

Wanting to study the photochemistry of a β,γ-unsaturated ketone that could not isomerise to a conjugated ketone, chemists chose 13. The obvious Wittig disconnection revealed the ketoaldehyde 14. Observing the symmetry of the carbon skeleton and the 1,3-relationship, they changed the ketone into an alcohol so that an aldol disconnection revealed two molecules of aldehyde 16.

A small amount of sodium hydroxide was enough for the aldol, and oxidation by CrO₃ in pyridine was chemoselective. You might have supposed that the Wittig with a stabilised ylid
would give the \(E\)-alkene 13 selectively but in fact it gave a 50:50 mixture of \(E\)-13 and \(Z\)-13. This was no problem as they could be separated and the chemists wanted to study the photochemistry of both.

\[
\begin{align*}
16 & \xrightarrow{\text{CHO}} 15; 85\% \text{ yield} \\
14 & \xrightarrow{\text{CHO}} 13; 85\% \text{ yield} \\
16 & \xrightarrow{\text{CHO}} 15; 85\% \text{ yield} \\
14 & \xrightarrow{\text{CHO}} 13; 85\% \text{ yield}
\end{align*}
\]

**The Synthesis of \(\alpha,\beta\)-Unsaturated Carbonyl Compounds**

The impossibility of a conjugated alkene in 15 as well as 13, makes this an exceptional case in aldols of aldehydes. Without the branch at the \(\alpha\)-carbon, the product is more usually a conjugated enal.\(^6\) So the linear isomer 17 of 16 with the same base gives the enal 18 in good yield.\(^7\) The true product of the dimerisation is the anion 19. This is in equilibrium with the enolate that allows an E1cB elimination of water 20 to give the enal 18.

\[
\begin{align*}
17 = \text{PrCHO} & \xrightarrow{1\text{M NaOH}} \text{PrCHO} & 18; 85\% \text{ yield} \\
19 & \xrightarrow{\text{PrCHO}} \text{PrCHO} & 18; 85\% \text{ yield} \\
20 & \xrightarrow{\text{H}_2\text{O}, 60 \degree \text{C}} \text{PrCHO} & 18; 85\% \text{ yield}
\end{align*}
\]

The first disconnection for any \(\alpha,\beta\)-unsaturated carbonyl compound 21 is an FGI reversing the dehydration. We could suggest two alcohols; 22 or 25 but we much prefer the 1,3-diO relationship in 22 to the 1,2-diO in 25 as the synthesis of compounds with odd numbered relationships needs synthons of only natural polarity (chapter 18).

\[
\begin{align*}
\text{R}^1 & \xrightarrow{\text{FGI}} \text{dehydration} \\
\text{R}^2 & \xrightarrow{1\text{M NaOH}} \text{OH} \\
\text{R}^1 & \xrightarrow{1,3\text{-diO}} \text{OH} \\
\text{R}^2 & \xrightarrow{1,3\text{-diO}} \text{OH}
\end{align*}
\]

This sequence is a classical ‘condensation’—two molecules react together with the extrusion of a small molecule (water in this case) but the term is now used of most carbonyl reactions of this sort. Another example is that of lactones such as 26. Disconnection reveals two molecules of the simple lactone 28 and condensation with NaOMe in MeOH gives 26 in \(>66\%\) yield.\(^8\)

\[
\begin{align*}
\text{R}^1 & \xrightarrow{\text{FGI}} \text{dehydration} \\
\text{R}^2 & \xrightarrow{1\text{M NaOH}} \text{OH} \\
\text{R}^1 & \xrightarrow{1,3\text{-diO}} \text{OH} \\
\text{R}^2 & \xrightarrow{1,3\text{-diO}} \text{OH}
\end{align*}
\]

Having got the idea, you might not want to be bothered with the rehydration step as it is easy to see the hidden carbonyl group where the alkene is and the half of the molecule with the carbonyl group must be the enolate in real life. Most people just disconnect the alkene and write
the two starting materials in one step. So the lactone disconnection becomes 26a and the general case 21a. This again is a matter of personal choice.

\[
\begin{align*}
\text{26a} & \xrightarrow{1,3\text{-diO}} \text{28} + \text{28} \\
\text{21a} & \xrightarrow{1,3\text{-diO}} \text{23} + \text{24}
\end{align*}
\]

**Intramolecular Aldol Reactions**

Perfect selectivity is the result when symmetrical dialdehydes or diketones cyclise with five- and six-membered rings being preferred to the rest. The linear diketone 29 cyclises to the cyclohexene 30: it doesn’t matter which of the identical α-positions enolises as it will always attack the other ketone.⁹ Cyclisation of cyclocdecadiene 31 is even more impressive: there are four equivalent enolisable α-positions but all give¹⁰ the same product 32.

\[
\begin{align*}
\text{29} & \xrightarrow{\text{H}_2\text{SO}_4} \text{30}; 85\% \text{ yield} \\
\text{31} & \xrightarrow{\text{Na}_2\text{CO}_3} \xrightarrow{\text{H}_2\text{O}} \text{32}; 96\% \text{ yield}
\end{align*}
\]

**1,3-diCarbonyl Compounds**

When we come to 1,3-dicarbonyl compounds 4 the principle is the same but we now have a choice: the keto-ester 35 could be disconnected 35b to the enolate 36 of acetone and diethyl carbonate 37 and this synthesis would work but we prefer 35a as that gives us the enolate of ethyl acetate 34 and ethyl acetate itself 33—another self condensation.

\[
\begin{align*}
\text{33} & \xrightleftharpoons{\text{1,3-diO}} \text{34} \\
\text{35} & \xrightleftharpoons{\text{1,3-diO}} \text{36} + \text{37}
\end{align*}
\]

There is now a reason for choosing one particular base: ethoxide ion. It will produce a small amount of the enolate 34 that will react with unenolised ester 40 to give the product 35, regenerating the base. That is useful, but the real reason we use the same base as the esterifying alcohol (i.e. ethoxide with an ethyl ester) is that if it attacks as a nucleophile 38 instead of as a base 39 it merely regenerates ethyl acetate. Reacting ethyl acetate with sodium ethoxide in ethanol gives ethyl acetoacetate 32 in 60% yield.¹¹ This ketoester is therefore available cheaply and is used as a starting material in many syntheses (chapter 13).
Intramolecular reactions are very favourable here as elsewhere and the cyclic ketoester 41 can be disconnected to the symmetrical diester 42. The cyclisation works well. In these reactions the proton between the two carbonyl groups of the product (marked in 41) is removed by the ethoxide formed in the reaction to give the stable enolate 43. This is easily demonstrated by adding an alkyl halide in the work-up when products 44 are formed.

Since β-ketoesters like 41 and 44 can be decarboxylated easily, it makes sense to use this efficient cyclisation wherever we can. You might first think of disconnecting cyclic ketone 46 to MeNH₂ and divinyl ketone 45 but this looks a rather unstable compound. If we add a CO₂Et group, we can use our 1,3-diCO disconnection to symmetrical 48 and only then revert to the 1,3-diX disconnection as both starting materials 46 are available.

The synthesis is just that, though NaH was used for the cyclisation and the decarboxylation accomplished by hydrolysis of the ester and heating with 20% HCl.

Looking Forward

Most of the examples in this chapter have been of molecules without selectivity. They have indeed all been self condensations. We hope this has established the basic disconnections and the chemistry but we must now turn to examples where selectivity is needed. So the ketone 46 was made to study aldol reactions with aromatic aldehydes. They found that, in acid or base, the enone 52 was the main product with the best yield from HCl in EtOH. The product 52 was isolated as its HCl salt. In this case it is easy to see that only the ketone can enolise, that the aldehyde is more electrophilic than the ketone and that the geometrical isomer shown is the more stable. Such considerations are the substance of the next chapter.
References

1. Vogel, page 798.
10. Ref 2, table VI, page 125.
Strategy IX: Control in Carbonyl Condensations

**Background Needed for this Chapter** References to Clayden, *Organic Chemistry:* Chapter 27: The Aldol Reaction; Chapter 28: Acylation at Carbon.

The last chapter introduced some good disconnections based on carbonyl compounds as both nucleophiles and electrophiles but avoided all questions of chemo- or regioselectivity. These reactions are so important that you need to understand how to control these issues. All the chief difficulties crop up in the synthesis of the conjugated enone 1.

![Chemical structure diagram](image)

This all looks very sound and we met examples in the last chapter. We want the ketone 2 to form an enolate and to combine 4 with the aldehyde 3 to give the anion of an aldol that would almost certainly dehydrate to the target molecule 1.

![Chemical structure diagram](image)

But will any of this happen? We want the ketone 2 to form the enolate, but won't the aldehyde 3 form an enolate more easily? We want the enolate to form on the less substituted side of the ketone, but won't the conjugated enolate be more stable? We want the enolate to attack the aldehyde, but might it not instead attack another molecule of 2 in a self-condensation? We want a cross-condensation between two different carbonyl compounds. To be satisfied with our plan we need answers to these three questions:

**The Three Key Questions for Successful Cross-Condensations**

1. Which compound will enolise/form an enolate?
2. If it is an unsymmetrical ketone: on which side will it form an enol(ate)?
3. Which compound will act as the electrophile?
Fortunately it is rare that all three questions are important, but, even if they are, methods are now available to deal with all but the most intractable cases. In general the problems arise because of the relative reactivity of the main classes of carbonyl compound. This diagram is not quite the same as the diagram in the last chapter both because we need to add all the acid derivatives and also because we need to emphasise something slightly different.

Since the same compounds are most easily enolised and most electrophilic, they tend to self-condense rather than react with anything else. So that, in the reaction of 2 and 3 under equilibrating conditions, the aldehyde 3 will probably self-condense and ignore the less reactive ketone. This chapter looks at ways to overcome that tendency. We examined self-condensation in chapter 19 so we shall look at other cases now.

Intramolecular Reactions

These are the easiest to control as five- and six-membered rings are preferred. If that is what we want, we should use the equilibrium methods we have met so far and allow the molecule to find its own way to the most stable product. Four different enolates 7, 8, 12 and 13 could be made from the diketone 10 by removal of four different protons. Each could cyclise onto the other carbonyl group to give three-membered rings 9 or 11 or five-membered rings 6 or 14. These alkoxides are all in equilibrium with 10 via the enolates and so the unstable three-membered rings quickly revert to 10. So which compound is formed: 6 or 14?

Only product 16 from intermediate 14 is formed.1 This is partly because 14 contains two fused virtually strain-free five-membered rings while 6 has strained bridged rings (these are by
no means impossible: we saw them in chapter 17) but mainly because the E1cB elimination we saw in chapter 19 can occur only on 14. Elimination of water from 6 would give an impossible bridgehead alkene. We can draw the full mechanism more realistically as 13a to 16.

So to summarise: cyclisations to strained three- and four-membered rings are normally reversible and stable five- or six-membered rings are usually preferred, especially if elimination of water makes a stable conjugated product.

**Cross-Conjugations I: Compounds that Cannot Enolise**

If a compound cannot enolise because it has no protons on the \( \alpha \)-carbon atoms then it can take part in a carbonyl condensation only as the electrophile. This will be useful only if it is strongly electrophilic (to avoid self-condensation of the other compound, see point 3 above) so you will see mainly aldehydes and acid chlorides in this list.

<table>
<thead>
<tr>
<th>Carbonates</th>
<th>Chloroformates</th>
<th>Aromatic aldehydes</th>
<th>Formic acid derivatives</th>
<th>( t )-Alkyl derivatives</th>
<th>Oxalates</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Carbonates" /></td>
<td><img src="image2" alt="Chloroformates" /></td>
<td><img src="image3" alt="Aromatic aldehydes" /></td>
<td><img src="image4" alt="Formic acid derivatives" /></td>
<td><img src="image5" alt="( t )-Alkyl derivatives" /></td>
<td><img src="image6" alt="Oxalates" /></td>
</tr>
</tbody>
</table>

Carbonates are useful for adding the CO\(_2\)Et group to make stable enolates of the kind we met in chapter 13 and will meet again soon. Here is a case where disconnecting one carbon atom reveals an available starting material 24. Only the ketone 24 can form an enolate and the carbonate is more electrophilic than the ketone. The ideal base is ethoxide ion to avoid ester exchange, but stronger bases such as NaH work well too.\(^2\)

![Diethyl carbonate](image7)

This method is useful for aryl-substituted malonates 27 where the normal alkylation of the malonate anion 26 is impossible as S\(_{N}\)2 reactions fail on unactivated aryl halides. For \( \text{Ar} = \text{Ph} \) reaction of 28 with NaH and diethyl carbonate gives\(^3\) 27; \( \text{Ar} = \text{Ph} \) in 86% yield.

![Diethyl carbonate](image8)

Aromatic aldehydes condense well with aliphatic ketones such as acetone to give either the mono- 31 or di-adducts 29 depending on conditions.\(^4\) In an excess of acetone, 31 is the main
product but in ethanol with two equivalents of benzaldehyde, the diadduct 29 is the only product. This 29 is dibenzylidene acetone or dba, an important ligand for palladium.

\[
\begin{align*}
\text{Ph} & \quad \text{EtOH} & \quad \text{NaOH, 20-25 °C} \\
\text{2} & \quad \text{PhCHO, EtOH} & \quad \text{PhCHO in Me}_2\text{CO} \\
\text{29: 93% yield} & \quad \text{30} & \quad \text{31: 77% yield}
\end{align*}
\]

Further selectivity is needed if the enol component is an unsymmetrical ketone. Some selectivity can be achieved by choice of acid, favouring the more substituted enol, or base, favouring kinetic enolate formation on the less substituted side. The acid 32 was used at a very early stage of Woodward and Eschenmoser’s synthesisac of vitamin B_{12}. Standard \(\alpha,\beta\)-unsaturated carbonyl disconnection revealed unsymmetrical ketone 33 and unenolisable but very electrophilic glyoxylic acid 34 available as its hydrate. In acid solution reaction occurred very selectively indeed.

\[
\begin{align*}
\text{32} & \quad \text{enone} & \quad \text{CO}_2\text{H} \\
& \quad \text{C-C} & \quad \text{33} + \text{OHC-CO}_2\text{H} \\
& \quad \text{glyoxylic acid} & \quad \text{32: 82% yield}
\end{align*}
\]

By contrast, Woodward’s synthesisb of the supposed structure 36 of the antibiotic patulin, which later turned out to have the isomeric structure 35, required intermediate 37 drawn both to resemble 36 and in a more normal way. Woodward then made the correct structure 35.

\[
\begin{align*}
\text{35: correct patulin} & \quad \text{36: supposed patulin} & \quad \text{37} \\
\text{MeO} & \quad \text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Disconnection of the 1,3-diC\text{O} relationship 37a gave the unsymmetrical ketone 38 and the unenolisable, symmetrical, and very electrophilic (again two carbonyl groups joined together: very electrophilic) oxalate 23; \(R = \text{Me}\). Now enolate formation needs to occur on the methyl group rather than the more substituted side. The answer was to use base.

\[
\begin{align*}
\text{37a} & \quad \text{1,3-diC\text{O}} & \quad \text{23; R = Me} \\
\text{MeO}_2\text{C} & \quad \text{OMe} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

This is thermodynamic control. The initial products 37 and 41 are converted into the stable enolates 40 and 42 by the methoxide released in the reaction. The enolate 40 is more stable than 42 as it has one fewer substituents.
Formaldehyde: the Mannich Reaction

One obvious candidate for an electrophilic but non-enolisable compound is formaldehyde CH$_2$=O but it is simply too electrophilic to be well controlled. A trivial example is its reaction with acetaldehyde and hydroxide ion. The first aldol gives the expected product 43 but a second gives 44 and a third follows. Now hydroxide adds to another molecule of formaldehyde and delivers a hydride ion 45 in the Cannizzaro reaction (the other product is formate ion HCO$_2^-$) to give ‘pentaerythritol’ 46, a useful compound in polymer chemistry for cross-linking but not much use to us. We need to moderate the unruly behaviour of this useful one-carbon electrophile.

![Chemical diagram](http://www.chem4all.vn)

We need a formaldehyde equivalent that is less electrophilic than formaldehyde itself and will therefore add only once to enol(ate)s. The solution is the Mannich reaction. Formaldehyde is combined with a secondary amine to give an iminium salt that adds 47 to the enol of the aldehyde or ketone in slightly acidic conditions to give the amino ketone (or ‘Mannich base’) 48. If the product of the aldol reaction 50 is wanted, alkylation on nitrogen provides a good leaving group and E1cB elimination does the trick.

![Chemical diagram](http://www.chem4all.vn)

Sometimes the hydrochloride of the Mannich base eliminates on heating and the vinyl ketone 53 can be made this way. If base is needed, it may be that even sodium bicarbonate NaHCO$_3$ is strong enough as was the case in Whiting’s synthesis of the acetal 54. Sequential 1,1- and 1,2-diX disconnections take us back to the enone 56, and obvious Mannich product

![Chemical diagram](http://www.chem4all.vn)

The Mannich reaction gave a base that was methylated without isolation to give the salt 58. Elimination with NaHCO$_3$ gave the enone, nucleophilic epoxidation with HO$_2^-$ gave the epoxide
that was hydrolysed to the diol 55. Finally, the acetal was made with acetone in acid solution in 72% yield.

Cross-Conjugation II: Specific Enolates

We need now to look at situations where both compounds might enolise and see how specific enolates can be used to control which compound does so (chemoselectivity) before looking at how we control which side of an unsymmetrical ketone forms the enolate (regioselectivity). We met two specific enol equivalents in chapter 13: β-dicarbonyl compounds and lithium enolates and they are the keys to this section.

β-Dicarbonyl Compounds as Specific Enols in Carbonyl Condensations

Attempts to react enol(ate)s of esters with aliphatic aldehydes are doomed as the aldehyde will simply condense with itself. If the ester is replaced by a malonate 60, there is so much enol(ate) from the β-dicarbonyl compound that the reaction is good. This style of aldol reaction is often called a Knoevenagel reaction and needs only a buffered mixture of amine and carboxylic acid. The enol reacts with the aldehyde 61 in the usual way and enolisation of the product 62 usually means that dehydration occurs under the conditions of the reaction.

If the product 63 is hydrolysed and heated in acid, decarboxylation occurs to give the unsaturated acid and re-esterification gives the ester that might have been the product from condensation of ethyl acetate and acetaldehyde.

If the original reaction is carried out under more vigorous conditions with malonic acid 67, the decarboxylation occurs during the reaction to give the unsaturated acid in one step. This is a simple way to make substituted cinnamic acids 68.

ArCHO + CH₂(CO₂H)₂ \xrightarrow{\text{piperidine}} \quad \text{Ar} \quad \text{CO₂H} \quad 68 

Ar = 2-furyl 
91-92% yield
Any combination of two carbonyl or other electron-withdrawing groups will do this reaction. Compound 69 was needed for a barbiturate synthesis. As cyanide is very anion-stabilising, disconnection gives the ketone 70, whose synthesis will be discussed in chapter 30, and the nitrile 71. The synthesis was straightforward once the right conditions had been found.\(^\text{12}\)

\[
\begin{array}{c}
\text{CONNH}_2 \\
\text{C-C} \\
\text{CN} \\
\text{aldol} \\
\text{CONNH}_2 \\
\text{C-C} \\
\text{CN} \\
\text{NH}_2\text{OAc} \\
\text{HOAc, reflux} \\
\text{separate water} \\
\end{array}
\]

\[
\begin{array}{c}
\text{69} \\
\text{70} \\
\text{71} \\
\text{74% yield} \\
\end{array}
\]

**Lithium Enolates**

Lithium enolates of esters 72 can be made direct from the ester itself with the strong hindered bases LDA or LiHMDS [(Me_3Si)_2NLi] and react cleanly with even enolisable aldehydes and ketones, e.g. 74, to give aldols 75 in high yield.\(^\text{13}\)

\[
\begin{array}{c}
\text{O} \\
\text{OEt} \\
\text{LDA, THF, \(-78^\circ C\)} \\
\text{or (Me_3Si)_2NLi} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{OEt} \\
\text{OEt} \\
\text{Li} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{CHO} \\
\text{76} \\
\text{73} \\
\end{array}
\]

\[
\begin{array}{c}
\text{OH} \\
\text{CO}_2\text{Et} \\
\text{77; 94% yield} \\
\end{array}
\]

One difference between this method and the malonate method is that lithium enolates add direct to the carbonyl group of enals 76 while malonates do conjugate addition. Further, malonate adducts such as 62 normally dehydrate under the reaction conditions while lithium enolates normally give the aldol product 77 without dehydration.

\[
\begin{array}{c}
\text{Ph} \\
\text{CHO} \\
\text{76} \\
\end{array}
\]

\[
\begin{array}{c}
\text{OH} \\
\text{CO}_2\text{Et} \\
\text{77; 94% yield} \\
\end{array}
\]

One of the most important contributions of lithium enolates is the stereoselectivity. Very hindered esters such as 78 form the ‘trans’ enolate and give high selectivity\(^\text{14}\) in favour of the *anti* aldol 80. These stereoselective aldols are discussed in *Strategy and Control*.

\[
\begin{array}{c}
\text{78} \\
\text{LDA, THF, \(-78^\circ C\)} \\
\text{79; ‘trans’ favoured} \\
\end{array}
\]

\[
\begin{array}{c}
\text{RCHO} \\
\text{80; 92:8 anti:syn} \\
\end{array}
\]

Another important contribution is to the regioselectivity of enolate formation from unsymmetrical ketones. As we established in chapter 13, ketones, particularly methyl ketones, form lithium enolates on the less substituted side. These compounds are excellent at aldol reactions even with enolisable aldehydes.\(^\text{15}\) An application of both thermodynamic and kinetic control is in the synthesis of the gingerols, the flavouring principles of ginger, by Whiting.\(^\text{16}\)

\[
\begin{array}{c}
\text{MeO} \\
\text{31; gingerol-6} \\
\end{array}
\]

\[
\begin{array}{c}
\text{MeO} \\
\text{83} \\
\end{array}
\]

\[
\begin{array}{c}
\text{82} \\
\text{aldol} \\
\end{array}
\]
Gingerol-6 81 is an obvious aldol product and disconnection reveals an unsymmetrical ketone 82 and an enolisable aldehyde. We get no favourable answer to any of the three questions at the start of this chapter: control is needed. The ketone 82 could be made in many ways but FGA to the enone 84 allows a second aldol disconnection and reveals vanillin 85 and acetone as very cheap starting materials.

The first aldol needs no control: only acetone can enolise and the aldehyde 85 is more electrophilic than acetone. Aldol reaction under equilibrating conditions gives 84 in good yield and the alkene can be reduced catalytically. The ketone 82 also contains an acidic phenol so that must be protected before the next aldol and a silyl group is the answer 86.

The lithium enolate 87 forms almost exclusively on the methyl side – less than 4% of the other isomer could be detected – and reaction with the aldehyde 83 followed by deprotection in aqueous acid gives gingerol.

Wittig Reagents as Specific Enolates

In many ways the simplest route to an unsaturated carbonyl compound is by Wittig reaction with a stabilised ylid or a phosphonate ester (chapter 15). In his leukotriene work, Corey used the stabilised ylid 90 in a reaction with the sugar deoxyribose, a hemiacetal 88 that is in equilibrium with the aldehyde 89. Drawing the ylid as an enolate 90 makes the point that the formation of 91 is essentially an aldol condensation with Ph₃PO rather than water being lost. It is a great advantage that the ylid is so stabilised as no protection of the three OH groups is needed, unlike our last example, and the Wittig reaction may even be carried out in acid solution.
Wittig reagents can represent enolates of unsymmetrical ketones. From Corey’s work on arachidonic acid metabolites comes the coupling between the aldehyde 92 and the phosphonium salt 93. This is very impressive as both components have multiple functionality and there is no loss of stereochemical integrity even though the Wittig reaction is done in aqueous NaOH.

\[
\begin{align*}
92 & \quad R & \quad \text{CHO} \\
93 & \quad \text{Ph}_3\text{P} & \quad \text{O} & \quad \text{O} & \quad \text{H}_2\text{O} \\
& \quad \text{NaOH} & \quad \text{R} & \quad \text{O} & \quad \text{Me}_3\text{CO}_2\text{Me} & \quad 94; R = n\text{-Pentyl}
\end{align*}
\]

**Enamines as Specific Enols**

Among the best enol equivalents for aldehydes are enamines. They are stable compounds, easily made from aldehydes 95 and secondary amines, reacting with electrophiles in the same way as enols 96 to give iminium salts 97, hydrolysed to substituted aldehydes 98.

They are useful for ketones too. Disconnection of the enone 99 reveals an aldol reaction between cyclopentanone 74 and the enolisable ketone 100. Control is needed solely to prevent self-condensation of the aldehyde.

\[
\begin{align*}
99 & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{O} & \quad 74 \\
& \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{O} & \quad 100 \\
99; 86\% \text{ yield}
\end{align*}
\]

The enamine 102, made with the cyclic secondary amine morpholine 101, does the job admirably. The immediate product is the conjugated enamine 103 rather than an imine, but this is easily hydrolysed to the enone 99 with aqueous acid.

\[
\begin{align*}
74 & \quad \text{cat H}^\oplus \\
101 & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{O} & \quad 102 \\
100 & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{O} & \quad 103 \\
99; 86\% \text{ yield}
\end{align*}
\]

Acylation is a good way to 1,3-dicarbonyl compounds and an aldehyde example is 104 that requires a specific enol(ate) of aldehyde 105 and an acylating agent such as 106.
This time another cyclic amine, pyrrolidine was used to make the enamine 107 and acylation occurred cleanly at carbon in spite of the formation of a quaternary centre. The wide ranging yields are for different Ar groups.\textsuperscript{21} The intermediate is an iminium salt 108 that can be isolated. The equilibrium methods used earlier for 1,3-dicarbonyl compounds would not work here as the product 104 cannot form a stable enolate.

**Cross-Condensation III: Removal of a Product from Equilibrium**

We have already met this in the formation of 16 by dehydration and in the formation of 37 by stable enolate formation. A couple more examples should make the general strategy clear. The unsymmetrical ketone 110 can form an enolate on either side and at first it seems that we shall need a specific enolate to control the aldol reaction. But one product 109 cannot eliminate water while the other 111 can. Under equilibrating conditions 112 is the only product.\textsuperscript{22}

The tricarbonyl compound 113 reacts cleanly with formaldehyde to give the lactone 115 as the first adduct 114 rapidly cyclises to the five-membered ring. The conditions are weak base and piperidine, the last of the three most popular secondary amines used in this chapter. Control is a mixture of intramolecular reaction, stable enolate formation and steric hindrance.\textsuperscript{23}

The lactone reacts regioselectively with benzaldehyde in acid solution at the methyl group rather than with the stable enol. Though 116 may be the first-formed intermediate, it cannot dehydrate while the alternative 117 can and the enone 118 is the only product. This product was needed for an alternative approach to patulin 35.
With the range of methods for controlling carbonyl condensations now available, and we have by no means mentioned them all, it is possible to control almost any reaction. The most important message of this chapter is that you should ask yourself the three questions from the start of the chapter before plunging in to an unconsidered reaction.

References

Two-Group C–C Disconnections III: 1,5-Difunctionalised Compounds
Conjugate (Michael) Addition and Robinson Annelation

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 29: Conjugate Addition of Enolates.

Another odd-numbered relationship means we can still use synthons of natural polarity. The 1,5-diketone 1 disconnects to a d2 synthon, an enolate, and an a3 synthon 2, that you should realise (chapter 6) is represented by the reagent 3. The conjugation in the enone makes the terminal carbon atom electrophilic.

The only new thing in this chapter is the combination of these two reagents so that a C–C bond is made by conjugate addition of an enolate to the enone 5 giving an enolate 6 of the product that gives the 1,5-diketone 1 on protonation.

This raises the regioselectivity question of whether the enolate will add in a conjugate (or Michael) fashion 5 or directly to the carbonyl group. We need to consider which types of enol(ate) and which types of enone (Michael acceptors) are good at conjugate rather than direct addition.

The second point was made in chapter 6 where we said: ‘Very electrophilic compounds such as acid chlorides or aldehydes tend to prefer direct addition while less electrophilic compounds such as esters or ketone tend to do conjugate addition.’ That remains true and the same idea applies to the enolates: very nucleophilic enolates such as lithium enolates tend to prefer direct addition while less nucleophilic enols and enolates such as enamines or 1,3-dicarbonyl compounds tend to do conjugate addition.

Specific Enol Equivalents Good at Michael Addition

1,3-Dicarbonyl Compounds
So if we want to make 9 we have a choice between adding an enolate equivalent of the aldehyde 7 to an unsaturated ester 8 or an enolate equivalent of the ester 11 to an unsaturated aldehyde 10. We prefer the first 9a as the unsaturated ester 8 is more likely to do conjugate addition. An enamine would be a good choice for 7.

However, if we make a small change in the structure by adding two methyl groups 13, our favoured disconnection 13a would be possible only after the discovery of five-valent carbon! We shall have to find a way to use unsaturated aldehydes as Michael acceptors.

Fortunately, we know from the last chapter how to make \( \alpha,\beta \)-unsaturated carbonyl compounds so the disconnection of the enone 3 poses no problems. Both starting materials are ketones: one 4 must provide the specific enolate and the other 16 the enone 3 by the Mannich reaction.

To get conjugate addition we might use a \( \beta \)-ketoester 18 or an enamine for the enolate and we might carry out the reaction using the Mannich salt 19 so that the elimination will be caused by the same base that makes the enolate. Ester hydrolysis and decarboxylation of 20 would give 1.

An example\(^1\) that shows how good these reactions can be is the addition of the cyclopentadione 21 with acrolein in water to give the adduct 23 in 100% yield. This must be a reaction of the enol 22 and, even though the Michael acceptor is an aldehyde and a new quaternary centre is created, no acid or base is needed.
The keto-acid 24 is best disconnected at the branchpoint where the chain joins the ring giving the available cyclohexenone 25 and the enolate synthon 26 best represented by malonate 27.

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad 27 \\
\text{CO}_2\text{Et} & \quad \text{EtOH} \\
\text{EtO}_2\text{C} & \quad 28 \\
\text{EtO}_2\text{C} & \quad 27
\end{align*}
\]

The synthesis\(^2\) uses ethoxide as base to avoid ester exchange and the conjugate addition goes in better yield than the apparently trivial hydrolysis and decarboxylation.

Michael reactions of this sort work best when they follow a catalytic cycle. Malonate anion 28 adds to an enone to give the enolate anion 30 that collects a proton from malonate 27 and forms another molecule of the anion 28 for the next cycle.

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad 27 \\
\text{CO}_2\text{Et} & \quad \text{EtOH} \\
\text{EtO}_2\text{C} & \quad 28 \\
\text{EtO}_2\text{C} & \quad 27
\end{align*}
\]

So when Stevens\(^3\) wanted the amino-diacetal 33 for his synthesis of coccinelline 32, the defence compound ladybirds exclude from their knees, he changed the amine into a ketone 34 with reductive amination in mind so that there would be two concealed 1,5-diCO relationships, more obvious when the acetals are removed 35.

Since 35 is a symmetrical ketone we can use the strategy, introduced in chapter 19, of adding an ester group and disconnecting to two identical molecules, here the aldehydoester 37 still having the 1,5-diCO relationship, and we can use a malonate to make sure we get conjugate addition to acrolein.
The synthesis is straightforward except for the Krapcho method (NaCl in wet DMSO) of decarboxylating one ester in a malonate 39 without hydrolysing the other. After the condensation this was used again to give the ketone 34 and finally the reductive amination used NH$_2$OAc and NaB(CN)H$_3$ as discussed in chapter 4.

Enamines

We met enamines as specific enol equivalents in the last chapter and they are particularly good at conjugate addition. The pyrrolidine amine from cyclohexanone 41 adds to acrylic esters 42 in conjugate fashion and the first-formed product 43 gives the enamine 44 by proton exchange. Acid hydrolysis via the imine salt 45 gives the 1,5-dicarbonyl compound 46.

The unsymmetrical diketones 47 were needed for photochemical experiments. The better 1,5-diCO disconnection 47a is at the branchpoint. The enone 49 can be made by the Mannich reaction (chapter 20).

An enamine 52 was chosen for the synthon 48, using morpholine 51 as the secondary amine.
Among the best specific enol equivalents for Michael addition are silyl enol ethers that are rather beyond the scope of this book but are treated in detail in *Strategy and Control*. So the silyl enol ether 54 of the ester 53 adds to the enone 55 with Lewis acid catalysis to give a reasonable yield of the ketoester 56 considering that two quaternary centres are joined together.\(^6\)

**Michael Acceptors Good at Conjugate Addition**

*Compounds that Resist Direct Attack*

Unsaturated nitro compound and nitriles do not usually suffer nucleophilic attack by enols or enolates and both are good at conjugate addition. The addition of the morpholine enamine 57 of cyclohexanone to 58 demonstrates that the nitro group is more effective than the ester at promoting conjugate addition.\(^7\)

**Less Electrophilic Carbonyl Compounds**

We have already established that RCHO and RCOCl are poor at conjugate addition while ketones and esters are better. An extreme example is the amide 61 that does conjugate addition even with the lithium enolate 60 of cyclohexanone.\(^8\)

**Compounds Activated Towards Conjugate Additions**

If the electrophilic end of the alkene is unsubstituted, it is particularly prone to conjugate additions. Examples include *exo*-methylene lactones 63, ketones 64 and vinyl ketones 65 that are often used
as the Mannich bases 66 since the free vinyl ketones tend to dimerise. So 65; R = Me gives the dimer 67.

Compounds with a Removable Activating Group in the α-Position

Electron-withdrawing groups that can be added to the α-position and removed easily after the new C–C bond is formed, promote conjugate addition. They are activating rather than protecting groups. So the CO₂R group 68 can be removed by hydrolysis and decarboxylation, sulfur-based groups 69 and 70 by reduction with Raney Ni or amalgams, SiMe₃ 71 by fluoride ion and Br 72 by zinc.

Unsaturated Ketones

It may comfort you to know that most α,β-unsaturated ketones will do conjugate addition if the enol(ate) equivalent is carefully chosen.

The Robinson Annellation

Combining aldol and Michael reactions in one sequence is very powerful, particularly if one of the reactions is a cyclisation. The Robinson annelation⁹ makes new rings in compounds like 73 that were needed to synthesise steroids. Disconnection of the enone reveals triketone 74 having 1,3- and 1,5-dicarbonyl relationships. The 1,3-disconnection would not remove any carbon atoms but the 1,5-disconnection at the branchpoint gives a symmetrical β-diketone that should be good at conjugate addition.

The synthesis can be done in stages under very mild conditions. The conjugate addition happens simply in water, as with 23. Amines catalyse the cyclisation and the dehydration of 77 is catalysed by acid.¹⁰ Triketone 74 can be made in one pot if KOH and MeOH are used with an excess of butanone 65; R = Me. Pyrrolidine then catalyses the cyclisation and dehydration.¹¹
Alternatively, Mannich salts\textsuperscript{12} with NaOEt or Mannich bases\textsuperscript{13} with pyridine and HCl can be used. The intermediate 77, not usually isolated, has a cis ring junction, as expected from the intramolecular reaction.\textsuperscript{14}

\[
\begin{align*}
\text{O} & \quad \text{(76)} \\
\text{O} & \quad \text{R = Me} \\
\text{H}_2\text{O} & \quad 66 \quad \text{R}_2\text{NH} \\
\text{R} & \quad \text{74} \\
\text{O} & \quad \text{77} \\
\text{TsOH} & \quad \text{73}
\end{align*}
\]

The new ring need not be fused to an old one and simple cyclohexenones can be made by Robinson annelation usually with the addition of a CO\textsubscript{2}Et activating group. In the disconnection of cyclohexenone 78, you could add the CO\textsubscript{2}Et to form 79 before the second disconnection, as we have done, after the second disconnection or while writing out the synthesis.

\[
\begin{align*}
\text{Ph} & \quad \text{78} \\
\text{Ph} & \quad \text{aldol} \quad \rightarrow \quad \text{Ph} \\
\text{Ph} & \quad \text{79} \\
\text{Ph} & \quad \text{80} \\
\text{Ph} & \quad \text{81; ethyl acetoacetate}
\end{align*}
\]

Chalcones such as 80 are very easily made by an aldol reaction between acetophenone and benzaldehyde: conjugate addition of the enolate of 81 and cyclisation occur all in the same reaction.\textsuperscript{15} The ester 82 is formed as a mixture of diastereomers in high yield: hydrolysis and decarboxylation give 78.

\[
\begin{align*}
\text{Ph} & \quad \text{80} \\
\text{Ph} & \quad + \quad \text{Ph} \\
\text{81; ethyl acetoacetate} & \quad \rightarrow \quad \text{Ph} \\
\text{82; 96% yield} & \quad \text{NaOEt, HOEt} \\
\text{1. NaOH, H}_2\text{O} & \quad \rightarrow \quad 78 \\
\text{2. H}^+ & \quad \text{heat}
\end{align*}
\]

Closely related to the Robinson annelation is the sequence of conjugate addition and acylation used to make ‘dimedone’ 83. Either disconnection of the 1,5-dicarbonyl compound 84 is good but we prefer 84a as the enone 85 is the aldol dimer of acetone (chapter 19) and is readily available.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{84} \\
\text{1,3-dICO} & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{1,5-dICO} & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{83} & \quad \rightarrow \quad \text{84} \\
\text{84} & \quad \rightarrow \quad \text{85}
\end{align*}
\]

The synthesis using malonate is a one-step process with NaOEt in EtOH followed by hydrolysis and decarboxylation in the usual way to give dimedone 83 in 67–85% yield.\textsuperscript{16}

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{85} \\
\text{CH}_2(\text{COOEt})_2 & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{NaOEt} & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{1. NaOH, H}_2\text{O} & \quad \rightarrow \quad \text{TM83}
\end{align*}
\]
Heterocycles Made from 1,5-diCarbonyl Compounds

A family of calcium channel antagonists based on the general structure 88 is widely used to combat high blood pressure. Disconnecting the structural C–N bonds we discover a symmetrical 1,5-diketone 89 so disconnection of either appropriate bond gives the same starting materials: and enone 90 and an acetoacetate ester 91. One of the first was nifedipine\textsuperscript{17} 88; \( R = \text{Me}, \text{Ar} = \text{o-nitrophenyl} \).

\[
\begin{array}{c}
\text{Ar}
\end{array}
\begin{array}{c}
\text{CO}_2\text{R}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{Ar}
\end{array}
\begin{array}{c}
\text{CO}_2\text{R}
\end{array}
\begin{array}{c}
\text{NH}
\end{array}
\begin{array}{c}
\text{2 x C–N}
\end{array}
\begin{array}{c}
\text{enamines}
\end{array}
\begin{array}{c}
\text{enamines}
\end{array}
\begin{array}{c}
\text{2 x C–N}
\end{array}
\begin{array}{c}
\text{enamines}
\end{array}
\begin{array}{c}
\text{88}
\end{array}
\begin{array}{c}
\text{89}
\end{array}
\begin{array}{c}
\text{1,5-diCO}
\end{array}
\begin{array}{c}
\text{90}
\end{array}
\begin{array}{c}
\text{91}
\end{array}
\]

The enone 90 is an aldol product from an aromatic aldehyde and the same acetoacetate 91, raising the possibility that all these reactions might occur at once. We have rediscovered the Hantzsch pyridine synthesis.\textsuperscript{18} The three components are reacted with ammonia (often NH\textsubscript{4}OH or NH\textsubscript{4}OAc) to give 88 in one step.\textsuperscript{19}

\[
\begin{array}{c}
\text{Ar}
\end{array}
\begin{array}{c}
\text{CHO}
\end{array}
\begin{array}{c}
\text{NH}_3
\end{array}
\begin{array}{c}
\text{91}
\end{array}
\begin{array}{c}
\text{90}
\end{array}
\begin{array}{c}
\text{91}
\end{array}
\begin{array}{c}
\text{NH}_3
\end{array}
\begin{array}{c}
\text{NH}_3
\end{array}
\begin{array}{c}
\text{88}
\end{array}
\]

References


Strategy X: Aliphatic Nitro Compounds in Synthesis

Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Chapter 26: Alkylation of Enolates.

In chapter 21 we mentioned nitro compounds as promoters of conjugate addition: they also stabilise anions strongly but do not usually act as electrophiles so that self-condensation is not found with nitro compounds. The nitro group is more than twice as good as a carbonyl group at stabilising an ‘enolate’ anion. Nitromethane ($pK_a \approx 10$) 1 has a lower $pK_a$ than malonates 4 ($pK_a \approx 13$). In fact it dissolves in aqueous NaOH as the ‘enolate’ anion 3 formed in a way 2 that looks like enolate anion formation.

Few aliphatic nitro compounds are wanted as target molecules in their own right but the nitro group is important in synthesis because it can be converted into two functional groups in great demand: amines 7, by reduction, and ketones 5, by various forms of hydrolysis.

The reduction is straightforward: the N-O bond is weak and is reduced by catalytic hydrogenation but the ‘hydrolysis’ needs some comments. Early and violent methods included the Nef reaction\(^1\)—the hydrolysis of the ‘enol’ form 8 in strong acid, probably via the intermediate 10 with liberation of nitrous oxide $N_2O$. 

---

*Organic Synthesis: The Disconnection Approach, Second Edition*  
Stuart Warren and Paul Wyatt  
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Strangely enough other methods use either oxidation or reduction. The anion 8 can be oxidised at the C=N double bond by ozone or KMnO₄ (permanganate). On the other hand, the imine formed by reduction of the N–O bonds, can be hydrolysed to the ketone. It seemed that TiCl₃ was the solution to these problems as the McMurry reaction gives excellent yields of ketones. But the recent surge in price of all Ti(III) salts has made this less attractive.

Nitro compounds can be alkylated and are good at conjugate addition (chapter 21) so the products of these reactions can be used to make aldehydes, ketones and amines. A simple synthesis of octanal shows that these methods can work very well indeed. Alkylation of nitromethane with bromoheptane gives the nitro-compound 11. Formation of the anion 12 and oxidation with KMnO₄ gives octanal in 89% yield. This chemistry gives us the disconnection to an alkyl halide and a carbonyl anion. The anion 12 is an ‘acyl anion equivalent’ and we shall need these in the next chapter.

Reduction of Nitro Compounds

The sequence of alkylation followed by reduction gives an amine and the special advantage of this strategy is that it can lead to t-alkyl amines. The appetite suppressant 15 can be disconnected next to the tertiary centre after the amines are changed to a nitro-compound 16. 2-Nitropropane 18 is available.

The synthesis uses alkylation by a benzylic halide and the reduction of both nitro groups is done catalytically with Raney nickel in the same step.

Other groups beside nitro can be reduced in the same step. So the diamine 19, needed for polyamine manufacture, could come from the unsaturated nitro compound 20 that would in turn come from an ‘aldol’ reaction between the anion of nitromethane 1 and the aldehyde 21. This has a 1,5-diX relationship and acrylonitrile 23 is excellent at conjugate addition (chapter 21) so we can use isobutyraldehyde 24 as a starting material.
In the synthesis we should not wish to make 21 as it would cyclise and, in any case, we'd rather reduce nitrie, nitro and alkene all in the same step by catalytic hydrogenation. The very simple method used for the conjugate addition is possible only because of the slow aldol reaction of the hindered aldehyde 24. The ‘aldol’ 25, also called a Henry reaction, needs a separate dehydration step but the three functional groups in 26 are reduced in one step in good yield.\(^7\)

\[
\begin{align*}
23 + 24 &\xrightarrow{\text{NaOH}} 22 \xrightarrow{67\% \text{ yield}} 25; 80\% \text{ yield} \\
&\xrightarrow{\text{MeNO}_2} 26; 90\% \text{ yield} \\
&\xrightarrow{\text{H}_2, \text{Co/Ni}} \text{TM19} \xrightarrow{95\% \text{ yield}} 
\end{align*}
\]

The ‘nitro-aldols’ can also be converted to ketones. The enantiomerically pure aldehyde 27 (a protected form of glyceraldehyde) reacts with 28 to give the ‘aldol’ 29 as a mixture of diastereoisomers. The protecting group ‘R’ is the very hindered TIPS group (\(i\)-Pr)_3Si. Dehydration by DCC catalysed by Cu(I) gives the nitroalkene 30 as an E/Z mixture.

\[
\begin{align*}
&\text{CHO} \\
&\text{27} \\
&\text{28} \\
&\xrightarrow{\text{DBU, MeCN}} 29; 83\% \text{ yield} \\
&\xrightarrow{\text{CuCl, DCC, MeCN}} 30; 87\% \text{ yield} 
\end{align*}
\]

Reduction of 30 with the mild reducing agent Zn/HOAc at 0°C gives the oxime 31 that can be hydrolysed directly to the ketone 32 without isolation.\(^8\) This ketone was used in a synthesis of compactin.\(^9\)

\[
\begin{align*}
&\text{30} \\
&\xrightarrow{\text{Zn/HOAc, 0°C}} [31] \\
&\xrightarrow{\text{NaHSO}_4, \text{EtOH, H}_2\text{O}} 32; 86\% \text{ yield from 30} 
\end{align*}
\]

Nitro-alkanes are good at conjugate additions too. In a synthesis of an immunosupressant for organ transplants, the spirocyclic amido-ketone 33 was needed. As this is a symmetrical ketone we can use the strategy of adding an ester group and then a 1,3-diCO disconnection 34 to give symmetrical 35. You might have disconnected the amide first but whenever you do it, you should expose an even more symmetrical compound 36. Can we use this symmetry?

\[
\begin{align*}
&\text{33} \\
&\xrightarrow{\text{FGA}} \text{34} \\
&\xrightarrow{1,3\text{-diCO}} \text{35} \\
&\xrightarrow{\text{C-N amide}} \text{36} 
\end{align*}
\]

If we change the amine in 36 to a nitro group 37, three conjugate additions of methyl acrylate to nitromethane become a possibility. Though you need quick thinking to see this, all the disconnections are ones we have seen before.
The synthesis is of course very short. Three equivalents of methyl acrylate add to nitromethane with catalytic (5%) DBU to give the adduct 37 and reduction leads to spontaneous cyclisation of one of the ester groups to give 35. The rest is as planned.

**Diels-Alder Reactions**

Nitroalkenes (see 30) are easily made from nitro-alkanes and aldehydes and take part as dienophiles in Diels-Alder reactions (chapter 17). The products can, as usual, be converted into amines or ketones. The stimulant fencarfarmin 39 disconnects to the obvious Diels-Alder adduct 41 from cyclopentadiene 42 and the nitro-alkene 43.

The synthesis starts as planned and catalytic hydrogenation reduces both the alkene and the nitro group in one step to give 44. In the reductive amination, the imine can be formed and then hydrogenated.

Now, how about making the ketone 47 by the Diels-Alder reaction? Direct disconnection (arrows on 47) leads to a good diene 45 but an unacceptable dienophile 46. This is a ketene and they don’t do Diels-Alder reactions. You will see in chapter 33 what they can do. But if you change the ketone into a nitro group 48, the problem disappears.
This is the work of McMurry so you can expect him to use his reagent (TiCl₃/H₂O) to convert the nitro group into the ketone 47. The stereochemistry of the Diels-Alder adduct 48 is of no interest as both diastereomers give 47.

Summary of Nitro Groups in Synthesis

The nitro group is remarkably versatile and solves otherwise difficult problems. The table is meant to help you see which synthons can be represented by nitro-compounds. Note particularly that the charged synthons all have unnatural polarity and the primary enamine in the Diels-Alder entry could not be made without protection of the amine.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Example</th>
<th>Synthon Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylation</td>
<td><img src="image" alt="Alkylation reaction" /></td>
<td>if reduced</td>
</tr>
<tr>
<td>Nitro ‘aldol’</td>
<td><img src="image" alt="Nitro ‘aldol’ reaction" /></td>
<td>NH₂</td>
</tr>
<tr>
<td>Conjugate addition</td>
<td><img src="image" alt="Conjugate addition reaction" /></td>
<td>NH₂</td>
</tr>
<tr>
<td>Conjugate addition with nitro alkenes</td>
<td><img src="image" alt="Conjugate addition with nitro alkenes reaction" /></td>
<td>NH₂</td>
</tr>
<tr>
<td>Diels-Alder</td>
<td><img src="image" alt="Diels-Alder reaction" /></td>
<td>R⁻</td>
</tr>
</tbody>
</table>

References

5. Vogel, page 600.
Two-Group Disconnections IV: 1,2-Difunctionalised Compounds

Background Needed for this Chapter

References to Clayden, Organic Chemistry: Chapter 20: Electrophilic Addition to Alkenes.

In chapters 19 (1,3-diCO) and 21 (1,5-diCO) we were able to use an enol(ate) as the carbon nucleophile when we made our disconnection of a bond between the two carbonyl groups. Now we have moved to the even-numbered relationship 1,2-diCO this is not possible. In the simple cases of a 1,2-diketone 1 or an \( \alpha \)-hydroxy-ketone 4, there is only one C–C bond between the functionalised carbons so, while we can use an acid derivative 3 or an aldehyde 5 for one half of the molecule, we are forced to use a synthon of unnatural polarity, the acyl anion 2 for the other half. We shall start this chapter with a look at acyl anion equivalents (\( d^1 \) reagents) and progress to alternative strategies that avoid rather than solve the problem.

![Chemical Diagram]

Acyl Anion Equivalents

The simplest reagent for an acyl anion is cyanide ion, one of the few genuine carbanions. After addition to an aldehyde, say, the resulting cyanoxydride 7 can be converted into a range of compounds 6 and 8–10. The cyanide ion represents the synthons shown in frames next to each product.
Despite this versatility, cyanide adds only one carbon atom of course and we need other more general acyl anion equivalents. In chapter 16 we saw how acetylenes can give rise to ketones by hydration. A very simple example is the hydroxy-ketone 11 that could come from the acetylenic alcohol 12 by hydration and hence from acetone with the anion of acetylene acting as the acyl anion equivalent.

The sodium salt of acetylene adds to acetone and alcohol 12 can be hydrated in acid with Hg(II) catalysis.

The cyclohexenone 13 was needed for a synthesis of the boll weevil hormone grandisol. Disconnection with Robinson annelation (chapter 21) in mind gives the rather unstable looking enone 15. No doubt a Mannich method could be used (16; R = NR₂) but any leaving group X in 16 will do.

If we put X = OMe we have a skeleton that could be made by hydration of the symmetrical acetylene 17 and the ethers put in by alkylation of the diol 18. The diol is available because it is easily made from acetylene and formaldehyde.

Alkylation with dimethylsulfate and base gave the diether and the usual hydration with Hg(II) gave the ketone 16; X = OMe.
The Robinson annelation can be carefully completed by the preparation of the enone 15 in acid and combination with the enamine\(^5\) of \(i\)-PrCHO or more simply by combining 16; \(X = \text{OMe}\) with \(i\)-PrCHO in base.\(^4\)

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{HN} \quad \rightarrow \quad \text{enamine} \\
\text{i-PrCHO} & \quad \text{pyrrolidine} \quad \rightarrow \quad \text{enamine} \\
& \quad 15 \quad \text{14} \quad \text{i-PrCHO} \quad \text{base} \quad \rightarrow \quad 16; \quad X = \text{OMe}
\end{align*}
\]

There are many other acyl anion equivalents that are dealt with in detail in *Strategy and Control*.\(^5\) An example of this general approach is phenaglycolol 19 used in the treatment of mild epilepsy. This 1,2-diol could be made in many ways but disconnection of two methyl groups reveals an \(\alpha\)-hydroxy-ester 20 that could be made by addition of cyanide to the ketone 21.

\[
\begin{align*}
\text{Cl} & \quad \text{OH} \\
\text{OH} & \quad \text{Cl} \\
\text{Cl} & \quad \text{19} \\
& \quad \xrightarrow{2 \times \text{C-C}} \quad \text{Grignard} \\
\text{Cl} & \quad \text{Cl} \\
\text{CO}_2\text{R} & \quad \text{O} \\
\text{O} & \quad \text{Cl} \\
\text{1,2-dicO} & \quad \rightarrow \\
\text{Cl} & \quad \text{20} \\
\text{Cl} & \quad \text{21}
\end{align*}
\]

The ketone comes from a Friedel-Crafts reaction, the cyanohydrin was hydrolysed in two stages via the amide 23 and an excess of MeMgI on the ethyl ester 28; \(R = \text{Et}\) gave the diol\(^6\) 19.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{MeCOCl} & \quad \text{AlCl}_3 \\
& \quad \rightarrow \quad 21 \\
\text{1. KCN} & \quad \text{2. H}_2\text{SO}_4 \\
\text{OH} & \quad \text{CONH}_2 \\
\text{Cl} & \quad \text{Cl} \\
\text{20} & \quad \rightarrow \\
\text{ROH, H}^+ & \quad \rightarrow \quad \text{MeMgI} \\
& \quad \rightarrow \quad 19 \\
\text{Cl} & \quad \text{Cl} \\
\text{22}
\end{align*}
\]

*Other Acyl Anion Equivalents*

Cyanide (one carbon) and acetylene (two carbons) are limited and other acyl anion equivalents are more versatile. Dithians are thioacetals of aldehydes that can be deprotonated between the two sulfur atoms by strong bases such as BuLi. Reaction with a second aldehyde gives 27 and hydrolysis of the thioacetal by acid, usually catalysed by Cu(II) or Hg(II), gives the \(\alpha\)-hydroxyketone 4. The disconnection is that shown on diagram 4 and the lithium derivative 26 acts as the acyl anion 2. Unlike previous methods, \(R^1\) does not have to be H or Me.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{S} & \quad \text{SH} \\
\text{HS} & \quad \text{BF}_3 \\
\text{24} & \quad \rightarrow \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{BuLi} \\
\text{25} & \quad \rightarrow \\
\text{S} & \quad \text{R}^1 \\
\text{26} & \quad \rightarrow \\
\text{S} & \quad \text{R}^2 \\
\text{OH} & \quad \text{R}^2\text{CHO} \\
\text{thioacetal} & \quad \text{hydrolysis} \\
\text{4}
\end{align*}
\]

When Knight and Pattenden\(^7\) wanted to make a group of natural products from lichens, including ‘vulpinic acid’ used by Eskimos to poison wolves, they needed the ketoacid 30 and
could have used, say, cyanide for the synthon 29 on some acylating agent but chose instead to use a dithian as a reagent for 31 and carbon dioxide as 32.

The dithian 33 was made from the available aldehyde, acylated with CO₂ to give 34 and the dithian hydrolysed with Cu(II) catalysis to give the α-ketoacid 30 all in excellent yield. Dithians are easy to make, stable and easy to use, but the deprotection can be tricky.

An alternative was used by Baldwin in the work that led to his famous rules for cyclisation. He needed to study the cyclisation of the hydroxy-ene 36 and an obvious aldol disconnection led back to the α-hydroxy-ketone 37. The same disconnection requires the addition of an acyl anion equivalent 39 to cyclohexanone and Baldwin chose the lithium derivative 40 of a vinyl ether.

These compounds are the opposite of the dithians: much easier to hydrolyse but more difficult to make and use. t-BuLi was needed for the deprotonation and the rest of the synthesis was straightforward. Note the high yield in the deprotection and that the aldol is unambiguous: only the ketone 37 can enolise and the aldehyde is more electrophilic.

Methods from Alkenes

Seeing the diol 19 you might first have thought of hydroxylating an alkene and, if so, that was a good idea. Alkenes react with many electrophiles to give 1,2-difunctionalised compounds. So the 1,2-diol 43, at a more reduced oxidation level than we have considered so far, would easily come from the alkene 44 by dihydroxylation with OsO₄. No disconnection so far, but we might
first think of a Wittig reaction, and then the disconnection is across the alkene, equivalent to the bond between the OH groups in 43. Further disconnection reveals that we would be coupling an alkyl halide 47 with an aldehyde 45. There are of course many other ways to make alkenes (chapter 15) that would use different disconnections.

Epoxides give rise to many 1,2-difunctionalised compounds such as 48 with control over stereochemistry. Reactions of the epoxide 49 from 44 give the anti stereochemistry in 48 in contrast to the syn stereochemistry in 43. Other compounds made from alkenes include 1,2-bromides and bromohydrins from reaction with bromine alone or bromine and water.

An example is the study by Lamber\(^9\) of the influence of aromatic rings and neighbouring electron-withdrawing groups on SN2 reactions. He needed the bis-tosylate 50. This comes from the diol 51 and now he had a choice. He could epoxidise an E-alkene or dihydroxylate a Z-alkene. He chose the latter as Z-52 could be made by a Wittig reaction.

He made both starting materials from esters of the corresponding aryl acetic acids 53 and 56 by reduction and substitution (in the case of the phosphonium salt). This gave added flexibility as either component can be used as the phosphonium salt 55 or the aldehyde 54. He used the unusual reducing agent REDAL [NaAlH\(_2\)(OCH\(_2\)CH\(_2\)OMe)\(_2\)] instead of DIBAL to make the aldehyde 54.

PhLi gave the ylid from 55 and the Wittig reaction with 54 did indeed give Z-52. These days we should probably use catalytic OsO\(_4\) for the dihydroxylation but his mixtures [1. AgOAc, I\(_2\), HOAc, H\(_2\)O, 2. KOH, EtOH] also gave the diol 51 and TsCl in pyridine gave the bis tosylate 50. This chemistry is explained in the workbook.
α-Functionalisation of Carbonyl Compounds

We used this strategy in chapter 6 under two-group C–X disconnections where bromination of ketones was the usual functionalisation. More relevant here are conversions of carbonyl compounds into 1,2-dicarbonyl compounds by reaction with selenium dioxide SeO$_2$ or by nitrosation. So acetophenone 57 gives the ketoaldehyde$^{10}$ 58 with SeO$_2$. These 1,2-dicarbonyl compounds are unstable but the crystalline hydrate 59 is stable and 58 can be reformed on heating. Since aromatic ketones such as 57 would certainly be made by a Friedel-Crafts reaction the disconnection 58a is not between the two carbonyl groups and offers an alternative strategy.

Nitrosation of the enol of 60 in acid solution and tautomerisation of the nitroso compound 61 gives the oxime 62. Hydrolysis of the oxime 62 gives the diketone 63.

Examples of α-Functionalisation of Carbonyl Compounds

Metaproterenol 64 is an adrenaline analogue used as a bronchodilator.$^{11}$ The amine might be inserted by reductive amination on the aldehyde 65 and this might be made by α-functionalisation of the available ketone 66.

The phenols need to be protected as their methyl ethers 67 and functionalisation by SeO$_2$, as described earlier in this chapter, gives the keto-aldehyde 68. To get 65 we should have to reduce the ketone in the presence of the aldehyde but the workers at Boehringer discovered a shortcut: reductive amination using hydrogenation reduced both the imine (from i-PrNH$_2$ and the aldehyde) and the ketone to give 69 and hence, by deprotection, metaproterenol 64. Notice that the aldehyde in 68 is more electrophilic than the conjugated ketone so it forms the imine needed for reductive amination.
The triester 70 was needed to study pericyclic reactions with electron-rich (a) and electron poor (b) alkenes. The α, β-unsaturated carbonyl disconnection reveals an enolisable ester 72 (X is some activating group such as CO₂R) and a very electrophilic keto-diester 71. The synthesis of the allyl ester 72 is all right but the tricarboxyl compound 71 with two 1,2-diCO relationships, is a challenge.

\[
\begin{align*}
\text{Me}_3\text{C} & \quad \text{O} \\
\text{b} & \quad \text{a} \\
\text{Me}_2\text{C} & \quad \text{O} \\
70 & \quad \text{aldol} \quad \text{Me}_3\text{C} \\
\text{O} & \quad \text{O} \\
\text{Me}_2\text{C} & \quad \text{71} \\
\end{align*}
\]

Nitrosation of malonate 73 with N₂O₄ (and hydrolysis of the oxime) gave 71. A Wittig reaction was chosen for the coupling which makes sure that no reaction occurs at the esters.

\[
\begin{align*}
\text{Me}_3\text{C} & \quad \text{O} \\
\text{Me}_3\text{C} & \quad \text{O} \\
73 & \quad \text{N}_2\text{O}_4 \quad \text{Me}_3\text{C} \quad \text{O} \\
\text{Me}_3\text{C} & \quad \text{O} \\
71 & \quad \text{72; } X = \text{Ph}_3\text{P} \\
\text{Ph}_3\text{P} & \quad \text{O} \\
\text{Ph}_3\text{P} & \quad \text{base} \quad \text{70}
\end{align*}
\]

**Strategy of Available Starting Materials**

Since the 1,2-relationship is difficult to set up by making the bond between the two functionised carbons, we may choose not to do what we did in the synthesis of 50 and 71. We can instead buy the 1,2-relationship by using a starting material that already contains it. A simple example would be the diol 74 in which we might recognise the bones of lactic acid 75. We therefore need to disconnect both phenyl groups, 74a thinking of the addition of PhMgBr or PhLi to an ester of lactic acid 76 with the remaining OH group protected.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Ph} & \quad \text{Ph} \\
\text{74} & \quad \text{75; lactic acid} \\
\text{HO} & \quad \text{OH} \\
\text{Ph} & \quad \text{Ph} \\
\text{74a} & \quad \text{2 } \text{C-C} \\
\text{RO} & \quad \text{76} \\
\text{OH} & \quad \text{protect?}
\end{align*}
\]

In practice, lactic acid dimerises on heating to give the double lactone 77 with both OH groups protected and treatment of this ‘lactide’ 77 with an excess of PhMgBr gives the diol 13 74.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{75; lactic acid} & \quad \text{heat} \\
\text{77} & \quad \text{excess PhMgBr} \\
\text{HO} & \quad \text{OH} \\
\text{Ph} & \quad \text{Ph} \\
\text{74}
\end{align*}
\]
Available compounds with a 1,2-relationship include many simple ones 78–90 whose trivial names may help you find them in suppliers’ catalogues. The amino acids 83 are the constituents of proteins and are available with \( R = \) alkyl, aryl, and various functionalised groups.\textsuperscript{14}

\[
\begin{align*}
78; \text{oxalic acid} & \quad 79; \text{glyoxal as aqueous solution} & 80; \text{glyoxyl acid (as } \text{H}_2\text{O) } & 81; \text{glycolic acid} & 82; \text{pyruvic acid} & 75; \text{lactic acid} & 83; \text{amino acids} \\
84; \text{butane dione} & 85; \text{chloroacetyl chloride} & 86; \text{benzoin} & 87; \text{bencil} & 88; \text{glycol} & 89; \text{ethanolamine} & 90; \text{ethylene diamine}
\end{align*}
\]

We have also made useful starting materials in this chapter such as 11 and 50. When the true structure of bullatenone 91 was discovered, the synthesis needed enone 92. This is an enol ether and can be made from the aldehyde 93 and hence from 11 that we made earlier in the chapter.

\[
\begin{align*}
91 & \quad \Rightarrow \quad \begin{array}{c} 92 \quad \text{enol ether} \end{array} & \quad \begin{array}{c} 93 \quad \text{CHO OH} \end{array} & \quad \text{1,3-diCO} \quad \text{HCO}_2\text{Et}^+ & \quad 11
\end{align*}
\]

No control is needed in the first step as only the ketone 11 can enolise and the formate ester HCO\(_2\)Et is more electrophilic.\textsuperscript{15} The product is isolated as the hemiacetal 94 that dehydrates to 91 on distillation.

\[
\begin{align*}
11 \quad \text{NaH} \quad \text{HCO}_2\text{Et} \quad \text{NaH} \quad \text{HCO}_2\text{Et} \quad \text{distil} & \quad 92; 59\% \text{ yield}
\end{align*}
\]

The Benzoin Condensation

If an \( \alpha \)-hydroxyketone 95 is symmetrical the disconnection we started with 4 offers an intriguing possibility: could the acyl anion 96 be made from the aldehyde 97? The answer is ‘yes’ providing \( R \) has no enolisable hydrogens, especially if it is aromatic. So, treating benzaldehyde with catalytic cyanide ion gives 98 in one pot.\textsuperscript{16}

\[
\begin{align*}
95 \quad 1,2\text{-diCO} & \quad 96 \quad \text{cat. NaCN} \quad \text{EtOH} & \quad 98; 90\% \text{ yield}
\end{align*}
\]
Cyanide adds to the aldehyde 99 forming 100 which exchanges a proton to give a cyanide-stabilised anion that adds 101 to a second molecule of benzaldehyde. Exchange of a proton allows the release of the cyanide 102 so that it can be used again.

This reaction – the benzoin condensation\(^\text{17}\) – is the nearest we have come to realising the simplest strategy of acyl anion and carbonyl electrophile in one step. One important group of reactions that make 1,2-difunctionalised compounds is the subject of the next chapter on radical reactions. A more modern version of this reaction, not needing cyanide, is described in chapter 39.

References

Strategy XI: Radical Reactions in Synthesis

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 39: Radical Reactions.

We have so far discussed only ionic and pericyclic reactions and rightly so for they are more important in synthesis than the third type: radical reactions.\(^1\) However, some radical reactions are useful and it is appropriate to put them here as many of them lead to 1,2-difunctional compounds.

Functionalisation of Allylic and Benzylic carbons\(^2\)

Ionic routes to allylic 4 and benzylic 6 alcohols include reduction of the ketones 3 and 5 as these are easily made by aldol reactions and Friedel-Crafts acylation. The alcohols can be converted into electrophiles by tosylation or conversion into bromides.

Radical reactions give direct routes to allylic and benzylic halides from hydrocarbons and these reactions add functionality to previously unfunctionalised carbon atoms. The reagent is a bromine radical, that is, an atom of bromine having an unpaired electron. Bromine molecules can be decomposed by light with homolytic cleavage of the weak Br–Br bond 7 and the bromine radicals can then abstract hydrogen atoms 8 from the activated positions next to an alkene or a benzene ring so that the intermediate carbon-centred radical 9 is stabilised by conjugation. The last step is the capture of a bromine atom from a molecule of bromine and it is important that this also releases a new bromine radical to start the reaction again. This is a radical chain process.

The reaction may not even need light: just refluxing \(p\)-nitrotoluene 11 with bromine in petrol ether gives a moderate yield of the benzylic bromide 12. Benzyl chloride 14 can be
made direct from toluene 13 with sulfonyl chloride activated by the radical initiator dibenzoyl peroxide.⁵

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{Me} \quad \xrightarrow{\text{Br}_2} \quad \text{O}_2\text{N} \\
11 & \quad \text{12; 57% yield} & \quad \text{13} & \quad \text{SO}_2\text{Cl}_2 \quad \xrightarrow{\text{cat. (PhCO}_2\text{)}_2} \quad \text{Cl} \\
\end{align*}
\]

Bromine is often replaced by NBS 15 in these reactions, as in the double bromination⁴ of 16. NBS provides a low concentration of bromine and initiates the reaction by thermal cleavage of the weak N–Br bond (see workbook for details).

NBS
\[
N\text{-Bromo-Succinimide}
\]

NBS
\[
\begin{align*}
\text{N} & \quad \text{I} \quad \text{O} \quad \text{O} \\
15 & \quad \text{Me} & \quad \text{O} \quad \text{O} \quad \text{Br} \\
16 & \quad \text{Br} \quad \text{O} \quad \text{O} \quad \text{Br} \\
17 & \quad \text{NBS} \\
\end{align*}
\]

Allylic bromination normally uses NBS as bromine itself would add to the alkene. Thus cyclohexene gives the dibromide 18 with Br₂ but the allylic bromide with NBS. Bromine radicals abstract one of the marked H atoms from 19 and the intermediate allylic radical 21 is delocalised so we don’t know which end of the allylic system⁵ ends up attached to Br.

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{Br}_2} \quad \text{H} \\
18 & \quad \xrightarrow{\text{H, H}} \quad \text{NBS, CCl}_4 \quad \xrightarrow{\text{Br}} \quad \text{20} \\
19 & \quad \xrightarrow{\text{cat. (PhCO}_2\text{)}_2} \quad \text{21} \\
\end{align*}
\]

A Synthesis of Biotin

When Confalone was planning his synthesis⁶ of biotin 22, the coenzyme that carries CO₂ round the body, he observed the continuous chain of nine carbon atoms and wondered if seven of them could come from a cycloheptene. Notice that the detached two are joined to the right heteroatoms: C-8 to N and C-9 to S.

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{Br}_2} \quad \text{H} \\
18 & \quad \xrightarrow{\text{H, H}} \quad \text{NBS, CCl}_4 \quad \xrightarrow{\text{Br}} \quad \text{20} \\
19 & \quad \xrightarrow{\text{cat. (PhCO}_2\text{)}_2} \quad \text{21} \\
\end{align*}
\]

One reason for the nitro group was to use conjugate addition 23a of the thiol 25 to nitroethylene 24. Now it is clear that allylic functionalisation of cycloheptene 27 is the first step. In the
retrosynthetic analysis we call this FGI (Functional Group Interconversion) as it cannot occur without an allylic or benzylic substituent.

\[
\begin{align*}
\text{O}_2\text{N} & \quad 1,3\text{-diX} & \quad \text{O}_2\text{N} \\
S & \quad 23a & \quad \rightarrow \\
& & \quad \text{24} \\
& & \quad \text{HS} \\
& & \quad \text{25} \\
& & \quad \text{FGI} \\
& & \quad \text{Br} \\
& & \quad \text{26} \\
& & \quad \text{FGI} \\
& & \quad \text{27}
\end{align*}
\]

NBS was used for the allylic bromination and protection was needed for the thiol nucleophile to avoid over-reaction (chapter 5). The reactive nitroalkene 24 was introduced by elimination from 2-nitroethyl acetate.

\[
\begin{align*}
\text{27} & \quad \xrightarrow{\text{NBS}} & \quad \text{26; 60% yield} & \quad \text{AcSH} & \quad \text{Et}_3\text{N} & \quad \text{AcS} \\
& & \quad 28; 71\% \text{ yield} & \quad \text{NaOH} & \quad \text{EtOH} & \quad \text{25; 100\% yield} \\
& & & \quad \text{NO}_2 & \quad \text{2-nitroethyl acetate} & \quad \text{23; 99\% yield}
\end{align*}
\]

**Carbon–Carbon Bond-Forming Reactions**

Some radical reactions are used industrially on a large scale including radical-induced polymerisations but these are beyond the scope of this book. A few simple molecules are also made this way including the diene 29 needed for the manufacture of pyrethroid insecticides. As the molecule is symmetrical, disconnection in the middle gives two identical halves providing we make them radicals and not cations or anions. The reaction is carried out at ICI by mixing butene 31 and the allylic chloride 32 at very high temperature.\(^7\)

\[
\begin{align*}
\text{29} & \quad \xrightarrow{\text{C-C radical}} & \quad \text{30} & \quad \text{30} & \quad \text{31} \\
& & & \quad \text{31} & \quad \text{500 °C} \\
& & & & \quad \text{29}
\end{align*}
\]

**The Pinacol Reaction**

The same idea allows us to make symmetrical 1,2-diols 33 by the pinacol reaction. Again we avoid cations and anions by making both halves radicals. These are generated by addition of electrons from metals to aldehydes and ketones. So an electron from sodium adds to acetone to give a radical anion 35 that might dimerise to give 33.

\[
\begin{align*}
\text{33} & \quad \xrightarrow{\text{C-C radical}} & \quad \text{34} & \quad \text{35} \\
& & & \quad \text{35} & \quad \text{Na} \\
& & & & \quad \text{Na} \\
& & & & \quad 2\times \text{?}
\end{align*}
\]

One popular way to perform the reaction is to use magnesium amalgam as this avoids the formation of anions: indeed the magnesium atom holds the two radicals together 36 so that the dimer
37 is formed intramolecularly. Hydrolysis gives the stable hexahydrate 38 and, if necessary, this can be dehydrated to pinacol 33 itself. Pinacol is the old name for this diol but the name is now mainly used for the reaction.

\[
\text{acetone} \quad \xrightarrow{\text{Mg/Hg, benzene}} \quad \xrightarrow{\text{Mg, Hg}} \quad \xrightarrow{\text{H}_2\text{O}} \quad \xrightarrow{\text{heat}} \quad \text{pinacol} 33
\]

Other electron-donating systems include zinc dust and Me₃SiCl, that gives the silyl ethers\(^8\) such as 40, or samarium iodide that gives similar dimers of aromatic aldehydes in excellent yield.\(^9\) These reactions usually favour the anti-isomers 40 and 42.

\[
\text{phenylCHO} \quad \xrightarrow{\text{Zn dust, Me}_3\text{SiCl, dioxane}} \quad \text{ArOSiMe}_3 \quad \text{ArOSiMe}_3 \quad \text{ArOSiMe}_3 \quad \text{ArOSiMe}_3
\]

\[
\text{phenylCHO} \quad \xrightarrow{\text{Sml}_2, \text{THF}} \quad \text{ArOH} \quad \xrightarrow{\text{1. HCl, H}_2\text{O}} \quad \text{ArOH}
\]

Example: Dienoestrol

The synthetic oestrogen dienoestrol 43 might be made\(^10\) by dehydration of the symmetrical diol 44 and hence by pinacol dimerisation of the ketone 45. Successful pinacol with magnesium metal gave 44 that could be dehydrated with AcCl in Ac₂O.

\[
\text{AcO} \quad \xrightarrow{\text{FGI dehydration}} \quad \text{ArOH} \quad \xrightarrow{\text{C-C pinacol}} \quad \text{AcO}
\]

The Acyloin Reaction

The acyloin reaction is a similar radical dimerisation but at the ester oxidation level.\(^11\) At first it looks just like a pinacol: electrons are added to the carbonyl groups to give 47, the radicals combine to give a new C–C bond and the ethoxide groups are lost 48 to give the 1,2-diketone 49.

\[
\text{CO}_2\text{Et} \quad \xrightarrow{\text{Na}} \quad \text{O}_2\text{Et} \quad \xrightarrow{\text{C-C pinacol}} \quad \text{CO}_2\text{Et} + 2\text{EtO}^-\]

That is just the start. If the diester 46 can accept electrons, the \(\alpha\)-diketone 49 will do so more avidly giving a new diradical 50 that forms a C–C \(\pi\)-bond 51 and, on work-up, the ene-diol 52.
that is the less stable tautomer of the α-hydroxyketone \(\text{53}\), also called an ‘acyloin’ and hence the name of the reaction.

However, even this is not the end as, if the reaction is done in this way, those two molecules of ethoxide released from \(\text{48}\) catalyse an intramolecular Claisen ester condensation \(\text{54}\) and the main product is the ketoester \(\text{55}\).

The solution\(^1\) is to carry out the reaction in the presence of \(\text{Me}_3\text{SiCl}\). This does two things. The more obvious is that the enediol dianion \(\text{51}\) is trapped as the silyl enol ether \(\text{56}\), a useful intermediate, but the more important thing is the removal of the basic ethoxide ions as the neutral silyl ether \(\text{EtOSiMe}_3\).

So, if the ester is enolisable, use the \(\text{Me}_3\text{SiCl}\) method. If it isn’t enolisable you don’t need to. The α-diketones \(\text{57}\) were needed for the synthesis of tetronic acids. Changing the oxidation level of one ketone reveals a symmetrical acyloin \(\text{58}\) derived from the esters \(\text{59}\).

These esters \(\text{59}\) are very enolisable so the silicon method must be used.\(^2\)

By contrast, the α-hydroxyketone \(\text{61}\) is an acyloin derived from a diester \(\text{62}\) that has no α-Hs, cannot enolise, and will not need the silicon treatment. Simple C–S disconnection reveals a chloroester \(\text{63}\).
You may be surprised to know that the chloroacid 65 can be made from available pivalic acid 63 by photochemical chlorination. This is again a radical reaction, chlorine radicals abstracting one of the nine hydrogens from the t-butyl group as there are no others. Though the chloride in 65 is rather unreactive, it combines well with sulfide anions and the acyloin goes in good yield without any silicon.\textsuperscript{14}

Making 1,2-Difunctionalised Compounds

We end this chapter with a review of ways one might approach making diaryldiketones such as 16. It helps that \(\alpha\)-hydroxyketone 67 or diol 68 can be oxidised to the diketone\textsuperscript{15} 16.

To put you out of your misery, the original authors\textsuperscript{4} made 67 by a benzoin condensation\textsuperscript{16} and oxidised it to the dione\textsuperscript{17} 16.

But how else might they have done it? Perhaps equally obvious is to use the pinacol reaction to make the diol 68 and oxidise both alcohols. We shall now broaden the discussion by writing Ar for the substituents as many of the reactions have not in fact been done with \(o\)-tolyl substituents. Two of the best yielding methods are Mg in the presence\textsuperscript{18} of \(Me_3SiCl\) and samarium iodide where the colour change from blue Sm(III) to yellow Sm(II) is characteristic.\textsuperscript{19}
The diol 70 could also be made by dihydroxylation of the alkene 73 that might be made by a Wittig reaction from the phosphonium salt 72. As the stereochemistry of neither the alkene 73 nor the diol 70 is relevant to the synthesis of 71, no control is discussed.

You might also have considered the addition of an acyl anion equivalent, such as the lithium derivative of the dithian 74 to ArCHO (chapter 23). There are obviously many other methods but these are the most likely.

References

5. Vogel, page 578.
Two-Group Disconnections V: 1,4-Difunctionalised Compounds

Background Needed for this Chapter: Reference to Clayden, *Organic Chemistry*: Chapter 26: Alkylation of Enolates.

The problem of unnatural polarity also arises in making C–C disconnections for the synthesis of 1,4-difunctionalised compounds. If we start with 1,4-diketones 1, disconnection in the middle of the molecule gives a synthon with natural polarity 2, represented in real life by an enolate 4, and one of unnatural polarity, the a² synthon 3 represented by some reagent of the kind we met in chapter 6 such as an α-haloketone 5.

\[
\begin{align*}
1 &\xrightarrow{1,4\text{-diCO}} 2 + 3 \\
\text{synthons} &\Rightarrow 4; \text{enolate} \quad 5 \\
\text{enolate} &\quad \text{synthon}
\end{align*}
\]

You might think you could escape this problem by choosing the alternative disconnection 8, but this is not so. We have more choice here: we can use the a³ synthon 7 with natural polarity, in real life an enone, but then we shall have to use the acyl anion equivalents 6 that we met in chapter 23. Reversing the polarity gives us the naturally polarised electrophile, an a¹ synthon 9 represented by an acylating agent and the homoenolate, or a³ synthon 10 with unnatural polarity.

\[
\begin{align*}
6 &\xrightarrow{a} 7 \\
\text{acyl anion} &\Rightarrow 8 \\
&\Rightarrow b \quad 9 \\
\text{acylating agent} &\quad \text{enolate}
\end{align*}
\]

Reactions of Enol(ate)s with Reagents for a² Synthons

A simple example would be the keto-ester 11. We should prefer to disconnect the bond at the branchpoint and that suggests the synthons 12 and 13. The reagent for 13 can be the bromoester 15 but we shall need to choose our enolate equivalent carefully. It should not be too basic as the marked protons in 15 between Br and CO₂Et are rather acidic.

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Stuart Warren and Paul Wyatt
Lithium enolates and the like are not good choices but enamines are excellent. The morpholine enamine 18 is cleanly alkylated by the bromoester 15 and hydrolysis gives¹ the keto-ester 11.

Another good choice is the easily made β-ketoester² 19 (compound 41 in chapter 19) as such stabilised enolate anions are not very basic.

A Synthesis of Methylpenomycin

The antibiotic methylpenomycin 21 was synthesised via the key intermediate 22. Aldol disconnection reveals a diketo-ester with a 1,4-relationship and an obvious disconnection next to the branchpoint 23. The starting materials 24 and 25 are available.

There might be some doubt about the cyclisation of 23 but the more highly substituted alkene is preferred in cyclisations under thermodynamic control. Only 22 is formed: none of the alternative 26 can be found.³
4-Hydroxyketones

If we do the same disconnection at the alcohol oxidation level 27 the reagent for the \( \alpha^2 \) synthon might be an epoxide 29. More reactive enolates such as lithium enolates are now all right.

![Chemical structure](http://www.chem4all.vn)

The useful synthetic intermediate 30, from which methyl cyclopropyl ketone can be made, comes from the 4-hydroxyketone 31, disconnected to the enolate of acetone 32 and ethylene oxide.

![Chemical structure](http://www.chem4all.vn)

Though we could use the lithium enolate of acetone, there is an advantage in using ethyl acetoacetate 24. The intermediate 34 cyclises under the reaction conditions and the stable lactone 35 is isolated. Treatment with HBr opens the lactone and decarboxylation gives \(^4\) 30. This two-step sequence requires only mild conditions.

![Chemical structure](http://www.chem4all.vn)

Conjugate Addition of Acyl Anion Equivalents

We have met the acyl anion or \( \delta^1 \) synthon in chapter 23 but for the disconnection 8 on 1,4-diketones we need a \( \delta^1 \) reagent that will do conjugate additions on enones such as 36. Sadly that eliminates dithians from consideration as they are too basic (hard) and tend to add direct to carbonyl groups.

![Chemical structure](http://www.chem4all.vn)

However, the simplest one-carbon \( \delta^1 \) reagent, cyanide ion, does do conjugate addition well so the disconnection is successful if \( R^1 \) in 1 is OH or OR.
The anti-convulsant phenazimide 37, being an imide, comes from a dicarboxylic acid 38 with a 1,4-relationship between the two carbonyl groups. Changing one to cyanide we get back to cinnamic acid 40 as the available starting material.

In practice cyanide added only slowly to cinnamic acid so a second electron-withdrawing group (another cyanide) was needed and the cyanide 42 was used successfully.\(^5\)

**Nitroalkanes as \(d^1\) Reagents**

Nitroalkane anions are very stable and hence excellent at conjugate addition (chapter 22). Quite weak bases such as amines are enough to give the anion of 44 and hence the nitro-ketones 45. Reduction gives the amino-ketones 46 that cyclise to give imines, reduced under the reaction conditions to pyrrolidines 47.

A dramatic example is the synthesis of the ant pheromone monomorine 48 already discussed in chapter 8. A bold double C–N disconnection gives the amino-diketone 49 and hence, after FGI of \(\text{NH}_2\) to \(\text{NO}_2\), the 1,4-disconnection we have just described.

1-Nitropropane adds to the protected enone 52 with catalysis by the base tetramethylguanidine and catalytic hydrogenation completes the first reductive amination 54. Hydrogen adds to the imine on the same side as the H atom already there.\(^6\)
Now the acetal can be hydrolysed to give the free amino-ketone and hence the enamine 55 that is reduced by the alternative reagent (chapter 4) sodium cyanoborohydride again stereoselectively so that all three H atoms in 48 are on the same face of the bicyclic structure.

The alternative transformation of a nitroalkane into a ketone (chapter 22) is well illustrated by a one-pot process where alumina is used to catalyse the conjugate addition and an oxidative process with H₂O₂ is used to form the ketone. Overall yields are good, e.g. R¹ = Bu, R² = Et, 90% yield.

**Direct Addition of Homoenolates (d³ Reagents)**

The same disconnection but of the opposite polarity requires some acylating agent for synthon 9: this is no problem as we have various acid derivatives at our disposal. But the nucleophilic synthon 10, a d³ synthon or homoenolate, is another matter. There is no stabilisation of the anion as drawn but if it were to cyclise to the oxyanion 56, it would be rather more stable and there is evidence—trapping with silicon to give 57 for example—that this can occur.

The simplest way to make such a derivative is to treat a β-halocarbonyl compound 59, easily made from the enone 58 by conjugate addition, with zinc metal to give a species that we might write as 60 but perhaps should be 61 or even 62. Whichever is correct, it is nucleophilic at the β-carbon atom and the polarity of the enone 58 has been reversed.

One well defined compound in this series is the cyclopropane 64 made from chloropropionate esters 63 and sodium in the presence of Me₃SiCl. On treatment with ZnCl₂, the ring is opened and a zinc homoenolate 65 with internal coordination is formed. This reacts with
acylating agents to give 1,4-dicarbonyl compounds\textsuperscript{10} such as 66. These reactions are catalysed by Pd(0).

\[
\begin{align*}
\text{Cl} & \quad \text{OR} & \quad \text{Na} & \quad \text{Me}_3\text{SiCl} & \quad \text{ZnCl}_2 & \quad \text{R'COCl} & \quad \text{CO}_2\text{R} \\
63 & & & & & & \\
\text{OR} & \quad \text{SiMe}_3 & \quad \text{ZnCl}_2 & \quad \text{Et}_2\text{O} & \quad \text{ClZn} & \quad \text{CO}_2\text{R} \\
64 & & & & & & \\
\text{O} & \quad \text{O} & \quad \text{R} & \quad \text{CO}_2\text{i-Pr} \\
65 & & & & & & \\
\text{O} & \quad \text{SiMe}_3 & \quad \text{Me}_3\text{SiCl} & \quad \text{ZnCl}_2 & \quad \text{Et}_2\text{O} & \quad \text{O} \\
66 & & & & \end{align*}
\]

If aldehydes are used as the electrophiles, a kind of homoaldol reaction occurs in the presence of Me\textsubscript{3}SiCl to give the protected γ-hydroxyesters 67 in good yield. The zinc salt (ZnCl\textsubscript{2} or ZnI\textsubscript{2}), used to make 59 also acts as a Lewis acid for the reaction.

\[
\begin{align*}
\text{O}-\text{i-Pr} & \quad \text{ZnCl}_2 & \quad \text{Et}_2\text{O} & \quad \text{ClZn} & \quad \text{RCHO}, \text{Me}_3\text{SiCl} & \quad \text{CDCl}_3 & \quad \text{CO}_2\text{i-Pr} \\
64; R = \text{i-Pr} & & & & & & \\
65; R = \text{i-Pr} & & & & & & \\
\text{O} & \quad \text{SiMe}_3 & \quad \text{Me}_3\text{SiCl} & \quad \text{ZnCl}_2 & \quad \text{Et}_2\text{O} & \quad \text{O} \\
67 & & & & \end{align*}
\]

An improved version uses (i-PrO\textsubscript{3})\textsubscript{2}TiCl as a catalyst: under these conditions the substituted homoenolate 69 reacts with benzaldehyde to give the lactone 70 with good stereoselectivity in favour of syn-70. The regioselectivity suggests that a cyclopropane is not involved.\textsuperscript{11} A more extensive treatment of homoenolates is given in Strategy and Control.\textsuperscript{12}

\[
\begin{align*}
\text{I} & \quad \text{OEt} & \quad \text{Zn/Cu} & \quad \text{I} & \quad \text{Zn} & \quad \text{PhCHO} & \quad \text{Ph} \\
68 & & & & & & \text{70}; 94\% \text{ yield} \\
\text{O} & \quad \text{Et} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
69 & & & & & & \\
\text{O} & \quad \text{Et} & \quad \text{O} & \quad \text{Ph} \\
70 & & & & & & \\
\end{align*}
\]

**Strategy of Available Starting Materials with a 1,4-diCO Relationship**

Just as with 1,2-diCO compounds, we can buy the 1,4-relationship rather than make it. Any supplier's catalogue will reveal a wide variety of such compounds: we shall mention only a few. There are simple disubstituted butanes such as the diol 71, the diamine 72, the dihalides 73 and succinic acid 74.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
71 & & \\
\text{H}_2\text{N} & \quad \text{NH}_2 \\
72 & & \\
\text{X} & \quad \text{X} & \quad \text{HO}_2\text{C} & \quad \text{CO}_2\text{H} \\
73; \text{X} = \text{Br}, \text{Cl} & & & & \\
74 & & & & \\
\end{align*}
\]

There are some important cyclic compounds such as the lactone 75, succinic anhydride 76, furan 77, and many substituted furans, particularly furfuraldehyde 78, a by-product of breakfast cereal manufacture, and its reduction product 79 and maleic anhydride 80.

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
75 & & & & & & \\
76 & & & & & & \\
77 & & & & & & \\
78 & & & & & & \\
79 & & & & & & \\
80 & & & & & & \\
\end{align*}
\]

And finally some unsaturated compounds, cis-butenediol 81, butynediol 82, fumaric acid 83 and levulinic acid 84. And many more.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
81 & & \\
\text{HO} & \quad \text{HO} \\
82 & & \\
\text{HO}_2\text{C} & \quad \text{CO}_2\text{H} \\
83 & & \\
\text{O} & \quad \text{CO}_2\text{H} \\
84 & & \\
\end{align*}
\]
A simple but surprising example of using an available starting material is the synthesis of 1,7-difunctionalised heptan-4-ones 86 and 88, each having two 1,4-diX relationships. The dihaloketone 86 was made from the aldol dimer 85 of butyrolactone 75, as described in chapter 19, where compound 85 was compound 26. The two 1,4-diX relationships in 86 can be seen in the intermediate 85 which has lost CO₂ on its way to 86.

The ketodiester 88 was made from furfural 78 by a Wittig reaction and treatment of the product 87 with acidic methanol. The central carbon atom in 88 can be seen as an enol ether in 87. You might like to try to draw a mechanism for this extraordinary reaction which is described in detail in the workbook.

The FGA Strategy

Butyne diol 91 is just one example of a compound that can be made by reactions of acetylene with carbonyl electrophiles (chapter 16). Reaction in turn with two different aldehydes and reduction of the triple bond leads to unsymmetrical 1,4-diols 92.

Reaction with an aldehyde at one end and CO₂ at the other followed by reduction gives lactones. The cyclisation to the five-membered ring 95 occurs spontaneously on hydrogenation.

Analysis of the final products of these two reactions suggests rather unhelpfully that acetylene is acting as the 1,2-dianion of ethane 96. It is probably better to think of them as examples of the FGA strategy.
References

Strategy XII: Reconnection

Synthesis of 1,2- and 1,4-diCO Compounds by Oxidative C=C Cleavage

We had to be careful in chapter 25 when we wanted to add bromoketones 4 to enolates 3 to make the 1,4-dicarbonyl compound 5. We could not use a lithium enolate because it would be too basic. No such difficulties exist in the reaction of enolates with allylic halides such as 2. Any enol(ate) equivalent will do as there are no acidic hydrogens and allylic halides are good electrophiles for the $S_N2$ reaction.

But this does not make 5; instead it makes 1 with an extra carbon atom. So what we need are oxidative methods to convert 1 into 5 by cleavage of the alkene. There are many ways to do this. The most obvious is ozone that gives aldehydes from a disubstituted alkene 6 with reductive work-up or acids with oxidative work-up.

Dihydroxylation with catalytic osmium tetroxide and stoichiometric oxidant such as NMO ($N$-methylmorpholine-$N$-oxide) gives diols that can be cleaved to the same aldehydes with sodium periodate or lead tetra-acetate. It is also possible to combine either KMnO$_4$ or catalytic OsO$_4$ with an excess of NaIO$_4$ and complete the operation in one pot.

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So, disconnection of 11 by the methods of chapter 25 gives an enolate from the ester 8 but also a bromoaldehyde 12, a type of compound best avoided. But if we replace O by C 10 we can disconnect to allyl bromide 9—a satisfactory electrophile in every way. You might like to call this an FGA, and we shan’t quarrel with that, but read on . . .

Malonate was used in the synthesis,\(^2\) and it makes sense to add the more reactive alkyl group last: in this case the allyl group. The oxidative cleavage was done with ozone.

These methods are compatible with a range of functional groups in spite of the vigorous nature of the reagents. In his synthesis of brevianamide B, Williams\(^3\) ozonised the allyl group in the heterocycle 15 to give the aldehyde 16 in amazingly good yield. The allyl group had been put in as an electrophile added to an enolate.

In his synthesis of the polyether antibiotic X-506, Evans\(^4\) needed the triol 20 with two of the OH groups protected. He added an allyl group as a nucleophile to open the epoxide 17 at the less hindered end and then protected the two OH groups as an acetal 19 before the third was introduced by ozonolysis and reduction. These two examples emphasise the versatility of the allyl group.

But what are we to call the retrosynthetic transformation of 11 into 10? It isn’t a disconnection: rather an extra carbon atom has been added. So we call this operation a reconnection: joining the target molecule back up to something to reveal the precursor. So, consider the synthesis of the cis-enone 21, a structure found in insect pheromones, perfumes and flavourings. A Wittig
reaction would make the cis-alkene from the phosphonium salt 22 but the ketoaldehyde 23 would need protection, perhaps as the acetal 24.

The problem is how to protect the ketone rather than the aldehyde and the answer is like that for 20: protect it when the aldehyde isn’t there. Reconnection to the alkene 25 achieves this and the ketone 26 can be made by reaction of some enolate 27 with allyl bromide.

The synthesis\(^5\) follows this pattern with ozone and reductive work-up with dimethyl sulfide ensuring that the aldehyde is not further oxidised and deprotection of 30 taking place after the Wittig reaction.

We have used a simple allyl group so far but, as the other half of the alkene is lost in the cleavage reaction, it doesn’t matter much what it is. So, with \(\alpha,\beta\)-unsaturated carbonyl compounds 31 and 34, which give rise to 1,2-diCO compounds 32, 33 or 35, it is convenient to use aldol reactions to make the alkene, and, say benzaldehyde is easier to use than formaldehyde.

The extraordinary polycyclic tetraketone staurose 36 was made\(^6\) from 37. The 1,2-diCO relationship in 37 is an ideal candidate for reconnection in this style.
Aldol disconnection 38a reveals a methyl ketone with two 1,4-diCO relationships that could be made by double alkylation of some enolate 27 of acetone with ethyl bromoacetate 40.

\[
\begin{array}{c}
\text{Ph} & \text{O} & \text{CO}_2\text{Et} \\
\text{CC}_2\text{Et} & \xrightarrow{\text{aldol}} & \text{O} & \text{CO}_2\text{Et} \\
38a & \xrightarrow{\text{1,4-diCO}} & \text{O} & \text{C}_\text{O}_2\text{Et} \\
& & \text{Br} & \text{CO}_2\text{Et} \\
& 2 \times 40 & & 2 \times 40
\end{array}
\]

The synthesis used benzyl acetoacetate 41 for the double alkylation so that the benzyl ester 42 could be specifically cleaved by hydrogenation to give 39. Condensation with unenolisable benzaldehyde is unambiguous (chapter 20) and ozone does the rest.

\[
\begin{array}{c}
\text{O} & \text{CO}_2\text{Bn} \\
\xrightarrow{2 \times \text{NaH}} & \text{2 x } 40 \\
2 \times 40 & \xrightarrow{2 \times 40} \\
41 & \xrightarrow{\text{H}_2} & \text{PhCHO} \\
& \xrightarrow{\text{Pd/C}} & \text{39} \\
& \xrightarrow{\text{base}} & \text{38} \\
& \xrightarrow{1. \text{O}_3} & \text{37}
\end{array}
\]

A Dramatic Example of FGA

The saturated hydrocarbon 43 is a pheromone from an ant. We have an obvious problem in designing a synthesis for this compound—there are no functional groups of any kind. A less obvious problem is how to relate the two stereochemical centres when they are 1,7-related.

\[
\begin{array}{c}
\text{43; (11R,17S)-11.17-dimethylhentiacontane}
\end{array}
\]

The solution to the second problem is to start with two enantiomerically pure compounds derived from nature and that suggests adding an alkene between the two chiral centres 44 as that could be made by a Wittig reaction from, say, 45 and 46.

\[
\begin{array}{c}
\text{FGA} & \text{R}^1 \\
\xrightarrow{11} & \text{17} \\
\text{R}^2 & \text{Wittig} \\
\xrightarrow{44} & \text{R}^1 \xrightarrow{45} \text{PPh}_3 + \text{OHC} \\
& \text{R}^2 & \text{46}
\end{array}
\]

The choice of which way round to do the Wittig may appear arbitrary but it isn’t. Pempo and his group\(^1\) chose citronellal 47 and citronellol 48, two related natural terpenes from citronella oil, as starting materials with the right stereochemistry at the one chiral centre. If you imagine a Wittig reaction between the phosphonium salt 49 and some suitable aldehyde, you will see that the central part of the molecule would be right.

\[
\begin{array}{c}
\text{47; (R)-citronellal} & \text{48; (R)-citronellol} & \text{49}
\end{array}
\]

\[
\begin{array}{c}
\text{CHO} & \text{OH} & \text{PPh}_3
\end{array}
\]
However, the aldehyde cannot be citronellal as the stereochemistry would be wrong. In addition, both terminal alkenes must be oxidised away so that the rest of the molecule may be attached. So this is what they did: the left-hand half of the molecule was assembled from citronellol 48 by oxidation to the aldehyde 50 and the remaining seven carbon atoms added by a Wittig reaction. The product is mainly Z-51 but this is irrelevant as the alkene will disappear. The phosphonium salt is ready for coupling to the right-hand half.

Citronellal is combined with the straight chain Grignard. This gives a 1:1 mixture of diastereoisomers—not separated—which are blocked as tosylates before the alkene is cleaved with ozone. Wittig reaction of the resulting aldehyde 56 with the phosphonium salt 53 from the other half of the molecule gives the Z-alkene 57. The new alkene is also cis (it was trans in 44) but this doesn’t matter. The tosylates are reduced off with LiAlH4/NaH and both alkenes hydrogenated to give our pheromone 43 in 78% yield. The only poor step is the second Wittig reaction but this accomplishes so much by joining the two halves of the molecule together so we can live with that.

The point of this synthesis is that the workers recognised that oxidative cleavage of citronellal and citronellol would give two-ended fragments that could be used to make the core of the pheromone with the right stereochemistry. We shall see in the next chapter that this reconnection strategy is vital for the synthesis of one important group of compounds: 1,6-diC10s.

References
Two-Group C–C Disconnections VI: 1,6-diCarbonyl Compounds

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 37: Rearrangements (The Baeyer–Villiger Rearrangement).

We come to the last of our chapters on two-group C–C disconnections and it has been left to the last for a good reason. If we try to start in the same way as we have with the other chapters of this kind, with a generalised 1,6-dicarbonyl compound 1 and disconnect in the middle we might be relieved to see an α synthon 2 easily recognised as an enone in real life, but the δ synthon 3, with unnatural polarity, caused us problems in chapter 25 and now we should need a reagent for 3 that does conjugate addition. Though there are a few ways to do this, it has not been a popular strategy. Disconnecting elsewhere is no help as the true difficulty is that the two carbonyl groups are too far apart for this approach.

\[
\begin{array}{c}
\begin{align*}
\text{O} & \text{R}^1 \text{1} \text{2} \text{3} \text{4} \text{5} \text{6} \text{R}^2 \\
\text{O} & \rightarrow \text{1,6-diCO?} \rightarrow
\end{align*}
\end{array}
\]

Chapter 26 introduced the strategy of reconnection and that is indeed the main strategy for the synthesis of 1,6-diCO compounds. But there is a big difference from what we have seen before. We no longer trim off some atoms at the far end of the alkene to be cleaved. Instead we reconnect intramolecularly so that the marked atoms C-1 and C-6 form a ring 4 and the bond between these atoms must be made weaker than any other bond in the molecule. Irenically we can do this by making it a double bond 5.

\[
\begin{array}{c}
\begin{align*}
\text{O} & \text{R}^1 \text{1} \text{2} \text{3} \text{4} \text{5} \text{6} \text{R}^2 \\
\text{O} & \rightarrow \text{reconnect} \rightarrow
\end{align*}
\end{array}
\]

No atoms are lost in the cleavage reaction so that cheap cyclohexene 6 is used to make adipic acid 7 for nylon manufacture. Any of the oxidative cleavage methods from the last chapter could be used: Vogel\(^1\) has a recipe using concentrated nitric acid on cyclohexanol 8 that presumably goes by dehydration to the alkene 6 followed by oxidation, and other methods are probably used industrially.

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Ketoacids with a 1,6-relationship are easily made from cyclohexanone 9 by addition of an organo-lithium or Grignard reagent, dehydration of the tertiary alcohol 10 and oxidation of the cyclohexene 11 to form 12.

The bicyclic ketone 13 was made from the simpler enone 14 that also had to be made. Aldol (α,β-unsaturated carbonyl compound—still our first choice) disconnection reveals the keto-aldehyde 15.

This is a 1,6-dicarbonyl compound so reconnection to the cyclohexene 16 is needed. Top tip: write the numbers 1–6 both on the target molecule 15 and on the starting material 16 to make sure you put the substitents on the right atoms. Now FGI and removal of the methyl group reveals a simple cyclohexanone 18.

The synthesis of 18 is discussed in the next chapter. The synthesis of 14 is a classic of its kind: the alcohol 17 is not isolated but dehydrated directly to the cyclohexene 16 and the oxidative cleavage is done by ozone. The intramolecular aldol is unambiguous as the alternative is a seven-membered ring.
The Diels-Alder Route to 1,6-diCarbonyl Compounds

This last example makes it clear that we shall normally have to make the cyclohexenes we need for oxidative cleavage and one of the best routes to such compounds is the Diels-Alder reaction (Chapter 17). A generalised example would be ozonolysis of the alkene 21, the adduct of butadiene and the enone 20. The product 22 has a 1,6-relationship between the two carboxylic acids. Since Diels-Alder adducts have a carbonyl group outside the ring (the ketone in 21) the cleavage products 22 also have 1,5- and 1,4-diCO relationships and would be a matter for personal judgement which of these should be disconnected instead if you choose that alternative strategy.

Heathcock required diester 23 for his synthesis of the antibiotic pentalenolactone.\(^3\) Reconnecting the esters gives the cyclohexene 24. We must change the two ether groups into carbonyl groups and one obvious starting material is 25, the Diels-Alder adduct of butadiene and maleic anhydride 26.

The synthesis followed this pattern with the ethers 24 being made immediately after the reduction of 25 and the esters made with diazomethane CH\(_2\)N\(_2\) after oxidative cleavage.

The bicyclic double lactone 27 was used by Eschenmoser as a precursor for all four heterocyclic rings in his synthesis\(^4\) of vitamin B\(_{12}\). Disconnection of both lactones reveals a ketone 29.
The ketone 29 in fact has 1,4-, 1,5- and 1,6-relationships and if we redraw it 29a to see the 1,6-relationship clearly, being careful to get the stereochemistry right, we can reconnect to the cyclohexene 30 and hence, by Diels-Alder disconnection, find the reactive dienophile 31. The methyl and CO₂H groups are cis in 30 and so must be cis in 31.

The dienophile 31 can be disconnected in two ways as there is a carbonyl group at each end of the alkene. Controlling disconnection 31a might be difficult as both components can enolise, but 31 is unambiguous except for the regiochemistry of enolisation of the ketone.

An aldol reaction in acid solution ensures that the more substituted enol is formed and the aldehyde is by far the most electrophilic of all the carbonyl groups. The Diels-Alder reaction gives the free acid 30 which was resolved with a chiral amine and each enantiomer used for a different part of the B₁₂ molecule. The slightly unusual reagent Cr(VI) was used for the alkene cleavage and acetal formation occurred spontaneously under the acidic conditions.

Cyclohexenes from Other Sources

One advantage of making 1,6-dicarbonyl compounds by cleavage of cyclic alkenes is that stereochemistry may be fixed in a ring that wouldn't be fixed in an open chain compound. The natural terpene (+)-2-carene 35 has a cis fused three-membered ring – no other arrangement is possible. Cleavage of the alkene with ozone gave the keto-aldehyde 36 with unchanged stereochemistry. This was just what McMurry needed to make a series of compounds such as 37 with the same stereochemistry.
The sequence of cyclohexene cleavage and aldol reaction on the dicarbonyl product gives ring-contracted cyclopentenes. This proved particularly valuable when Iwata\(^6\) wanted to make suberogoric acid \(41\) that has three five-membered rings awkwardly joined around a quaternary carbon atom. So crowded are these compounds that they are difficult to draw clearly. Ozonolysis of the synthetic cyclohexene \(38\) gave the unstable dialdehyde \(39\) that cyclised by an aldol condensation to \(40\) and hence could be oxidised to \(41\).

Oxidative Cleavage by the Baeyer–Villiger Reaction

Cyclohexanones may be cleaved oxidatively by peroxyacids to give seven-membered ring lactones. This is the Baeyer–Villiger rearrangement: a migration from carbon to oxygen that has the effect of inserting an oxygen atom into the ring.\(^7\) The lactone already has a 1,6-dio relationship but this is more obvious in the hydroxy-acid \(44\). This reaction is used widely in industry.\(^8\)

The disconnection is to extrude the oxygen atom. There is a danger here. Such disconnection of both lactones \(45\) and \(47\) leads to the same cyclohexanone \(46\) and both cannot be right. The one that works is \(45\) because the migration step prefers the more highly substituted migrating group \(48\) as the developing positive charge on the left-hand part of the molecule can be shared more.

So when the hydroxyketone \(49\) was needed for a pheromone synthesis, it was made by nucleophilic displacement on the lactone \(50\) by an organo-lithium compound. This lactone is of the right kind (cf. \(45\)) to be made by a Baeyer–Villiger rearrangement from the cyclohexanone \(51\) and this can be made by total reduction of the phenol \(52\) (chapter 36).
Catalytic reduction of the phenol gave a mixture of diastereoisomers of 53 and pure 51 could be separated from the reaction mixture after oxidation. The Baeyer–Villiger and the opening of the ring with n-octyl-Li worked well.9

Other Approaches

There is of course no need to use reconnection if you prefer another strategy but you are advised to try disconnection first. Disconnection of the 1,3-dicarbonyl relationship in the spiro-diketone 54 reveals a 1,6-dicarbonyl compound that could no doubt be made by oxidative cleavage of 58. But various authors10 preferred to ignore the 1,6-dicarbonyl relationship and simply disconnect to the enolate of cyclopentanone 56 and a bromoester 57.

We discussed making 57 from the lactone 59 in chapter 25 and we have used the ketoester 60 in chapters 19 and 25. Alkylation of 60 gives 61, reaction with concentrated HCl gives the acid corresponding to 55 and polyphosphoric acid (PPA) catalyses the cyclisation to 54.

References

General Strategy B: Strategy of Carbonyl Disconnections

This chapter links the carbonyl disconnections of the last 10 chapters with the general principles established in chapter 11. We shall find some new principles but the main idea is to discover why, in designing the synthesis of a particular molecule, some disconnections prove more helpful than others.

We could look at every possible C–C carbonyl disconnection and decide which we prefer. For any even moderately complex molecule, this can be an exhausting process and we shall do it for just one target molecule. Thereafter we shall choose disconnections as we go along and go back to the target only if that strategy proves poor. Pratt and Raphael\(^1\) needed the keto-diester 1 for a synthesis of the anti-tumour compound vernolepin. Our first disconnection is easy as the \(\alpha,\beta\)-unsaturated carbonyl unit suggests the classic aldol \(1a\) disconnection to 2.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{1} & \quad \text{1a} \\
\end{align*}
\]

\[
\text{\textalpha,\textbeta-unsaturated carbonyl compound} \xrightarrow{\text{intramolecular aldol}} \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{2}
\]

Compound 2 has 1,3-, 1,4-, 1,5- and 1,6-dicarbonyl relationships. Disconnecting the 1,3-diCO in the two possible directions 2a and 2b gives a one- or two-carbon fragment and enolates 3 and 4 that would be very difficult to control. There is in any case little simplification in either of these disconnections so we shall not pursue this strategy.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{1,3-diCO} & \quad \text{1,3-diCO} \\
\text{3} & \quad \text{2a,b} \\
\text{O} & \quad \text{O} \\
\text{CO} & \quad \text{CO} \\
\text{+ CO(OEt)\text{2}} & \quad \text{+ MeCO}_2\text{Et} \\
\end{align*}
\]

The 1,4-diCO disconnection 2c looks promising as the required enolate 6 is of a stable 1,3-dicarbonyl compound and the electrophile is available bromoacetate 5. Much will depend on how easy it is to make 6.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{1} & \quad \text{1,4-diCO} \\
\text{2c} & \quad \text{Br} \\
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{4} & \quad \text{6} \\
\end{align*}
\]

---

*Organic Synthesis: The Disconnection Approach, Second Edition*  
Stuart Warren and Paul Wyatt  
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The 1,5-diCO disconnection \(2d\) also looks promising as the required enolate \(6\) is again stable and the electrophile is the available enone \(8\). At the moment there is little to choose between these disconnections \(2c\) or \(2d\) but the ease of making of \(6\) or \(7\) may be decisive.

Finally we can investigate the 1,5-dicarbonyl approach by reconnection \(2d\) to give a cyclohexene that seems destined for synthesis by a Diels-Alder reaction from isoprene \(11\) and the enone \(10\) that can probably be made by a Mannich reaction on ethyl acetoacetate.

So we have three promising approaches. But the reactions in the first two are the same: they are just done in the reverse order. So the sensible thing is to try one of those so that the starting materials can be used for the other if necessary. Pratt and Raphael found that the 1,5-diCO strategy via enolate \(7\) was successful. The others may be successful too. Note that the final cyclisation of \(2\) required only weak acid and weak base.

The Synthesis of a Lactone

Where there are structural C–X bonds in the target molecule, it makes sense to disconnect them first as we can then see the carbon skeleton displayed and count the relationships between the functional groups. So the lactone \(14\) has the carbon skeleton of \(15\) and this compound has 1,3- and 1,4-diCO relationships \(15a\).
We can continue both strategies by disconnections at the branchpoint, each needing simple aryl ketones 16 and 18, but 15b requires a homoenolate reagent for the d^3 synthon 19 and we should rather avoid that, while 15c needs a simple enolate 17 and we prefer that.

The keto-acid 16 is going to be made by a Friedel-Crafts reaction and the best reagent is succinic anhydride 22 so that the disconnection is outside the 1,4-diCO system as explained in chapter 25. The starting material 21 can be made by methylation of 20 with dimethyl sulfate and the enolate chosen for the last step was the organo-zinc derivative (Reformatsky reagent) of methyl bromoacetate. The methyl ester protecting group used in 23 disappears during lactonisatıon.²

Synthesis of a Symmetrical Cyclic Acetal

The keto-acetal 24 was needed for a prostaglandin synthesis.³ Disconnection of the acetal 24a reveals the symmetrical carbon skeleton 25 having 1,4- and 1,5-diCO relationships. There is another 1,4-diCO relationship between the two alcohols.

None of these relationships looks very promising, in part because any C–C disconnection would destroy the symmetry. We can get round this problem by using a trick that appeared first in chapter 19. We add an extra functional group (CO₂Me) to give us a 1,3-diCO relationship that can be disconnected 26 without destroying the symmetry.
This new intermediate 27 has all the 1,4- and 1,5-diCO relationships of 25 but it also has a 1,6-diCO relationship 27a that can be reconnected to 28 again without destroying the symmetry. An adjustment of functionality gives an obvious Diels-Alder adduct 29 of butadiene and maleic anhydride 30.

Since the two hydrogen atoms in maleic anhydride 30 are cis, they must also be cis in the adduct 29. Reduction and protection are needed before the oxidative cleavage so that the difference between the left- and right-hand halves of the molecule is preserved. Hydrolysis of the ester in 33 and decarboxylation in acid gave 24.

**Synthesis of a Spiro Enone**

Corey needed the spiro-enone 34 for his synthesis of gibberellic acid. The obvious enone disconnection reveals a keto-aldehyde 35 with a 1,4-relationship between the carbonyl groups and disconnection at the branchpoint suggests some enol(ate) equivalent of the aldehyde 36 and the bromoketone 37.

The planning for this synthesis involves the repeated disappointment of rejection of good-looking strategies. For example, the aldehyde 36 has a 1,5-diCO relationship but cannot easily be made by conjugate addition as that would require conjugate addition of an acyl anion equivalent. One alternative might be to use an allylic bromide 39 (reconnection strategy — chapter 26) and the enolate of ethyl acetoacetate 40.
But this strategy is doomed too as the allylic bromide will almost certainly react at its less hindered end on the vinyl group. However, we might choose the alternative branchpoint disconnection 38a and consider conjugate addition of some vinyl-metal (copper?) derivative to the enone 41 that could be made by some aldol process from the ketone 42 and an enol(ate) of acetone 43.

\[
\begin{align*}
38a & \xrightarrow{\text{C-C}} \text{one-group} & 41 & \xrightarrow{\text{aldol}} & 42 \quad + & 43
\end{align*}
\]

The ether 42 can obviously be made from the hydroxyketone 44 and, as we shall see in chapter 36, a good way to make 1,4-difunctionalised cyclohexanes is by reduction of a cheap aromatic compound such as quinol 45.

\[
\begin{align*}
42a & \xrightarrow{\text{ether}} \text{C-O} & 44 & \xrightarrow{FGL \text{ reduction}} & 45; \text{quinol}
\end{align*}
\]

This approach requires a basic kind of chemoselectivity (chapter 5) to distinguish the two phenolic hydroxyl groups in 45 so that one may be alkylated and one oxidised. Trial and error revealed that the best way was to reduce completely first and benzylate to give a mixture of unreacted diol 46, mono-ether 48 and diether 47. This is the statistical method (chapter 5) that is expected to give about 50% of 48 and 25% of 46 and 47. Fortunately these can easily be separated and recycling 46 directly and 47 after debenzylolation gives a good conversion. Oxidation of 48 then gives 42. In any case, the benzylolation is an early step in the synthesis and can be carried out on a large scale with such cheap materials.\(^5\)

\[
\begin{align*}
45; \text{quinol} & \xrightarrow{\text{H$_2$, Ni}} & 46 & \xrightarrow{\text{Na}} & 47 & \xrightarrow{\text{BnO}} & 48 & \xrightarrow{\text{CrO$_3$}} & 42
\end{align*}
\]

Corey chose a Wittig-style (HWE) reaction to control the 'aldol' process and copper-catalysed addition of vinyl Grignard for the conjugate addition. Oxidation with NaIO$_4$ and catalytic OsO$_4$ gave the keto-aldehyde 35 which cyclised cleanly under equilibrating conditions.

\[
\begin{align*}
49 & \xrightarrow{\text{EtO}_2\text{P}} \text{O} & 41 & \xrightarrow{\text{MgBr}} & 38 & \xrightarrow{\text{NaO}_4 \text{ cat. Cu$_2$I$_2$}} & 35 & \xrightarrow{\text{NaOH \text{ cat. OsO}_4}} & 34
\end{align*}
\]
The Synthesis of Piquindone

Our final example is the heterocyclic diketone 50, an intermediate in the Hoffmann-La Roche synthesis of piquindone 51, an anti-psychotic agent.6

![Chemical structure of 50 and 51](image)

We might first think of removing the structural heteroatom—the ring nitrogen. With reductive amination in mind we might consider imines from 52 or amides from 53. But these compounds have four different carbonyl groups and obviously problems of selectivity arise.

![Chemical structures of 50a, 52, and 53](image)

It might be better to start on the carbonyl disconnections immediately. The most obvious come from the 1,3-dicarbonyl relationship 50b, c and suggest two keto-ester starting materials 54 and 55.

![Chemical structures of 54, 55, and 50b,c](image)

These two intermediates 54 and 55 each have a 1,5-diCO relationship that can be disconnected in two ways. Both 54b and 55b disconnect a ring bond and give unsimplified starting materials 56 and 59. But the others 54a and 55a achieve some simplification and suggest simple cyclic enones 57 and 60 in combination with enol(ate)s of acetone 58 or an acetate ester 61. These are much more promising and we shall come back to them.

![Chemical structures of 56 to 61](image)
Incidentally, the 1,5-diCO relationship is present in the target molecule 50 too and attempts to disconnect it 50d,e reveal a most unpromising 10-membered ring 62 or a more promising diketone 63. Continuing the analysis of 63 would lead us back to 57 or 60.

Returning to 57 and 60, the α,β-unsaturated carbonyls suggest aldol-style disconnections to 64 and 65. You may by now be reminded of something we saw in chapter 19: compounds like 64 and 65 with 1,3-diX relationships between nitrogen and a carbonyl group. There the carbonyl groups were both esters: here one must be an aldehyde and the other either an ester or a ketone.

We could presumably make 57 from 67 (compound 44 in chapter 19) by reduction and elimination. Addition of, say, acetoacetate anion should give 63.

In fact, it isn’t necessary to make 57 as, when R=Me, it is the natural alkaloid arecoline. However, when the synthesis was continued by attempted conjugate addition of the enolate of methyl acetoacetate to 57 only very low yields (12–18%) of products could be found. The problem turned out to be the base-catalysed rearrangement of 57 into the aromatic pyridone 71.

Using 60 and malonate solved this problem. The intermediate 72 and the diketone 50 could be isolated and characterised but it was better in the manufacturing process, to continue with
the formation of the drug 51 in the same process. The drug has potent and selective dopamine antagonist activity.

There remained the synthesis of 60. An old synthesis\(^7\) used essentially the strategy we have outlined via 65: alkylation of MeNH\(_2\) with the chloro-acetal 74, conjugate addition of 75 to butenone 76 and cyclisation in acid solution. It was very low yielding. One reason is the poor amine synthesis by alkylation (chapter 8) and another is presumably that the acetal 77 hydrolyses to the aldehyde 65 but control in the cyclisation is poor.

The workers at Roche chose to make 60 by a completely different strategy inspired by the availability of a pyridine 78 with the same skeleton. Protection and methylation gave the pyridinium salt in very high yield and reduction and hydrolysis gave 60. The paper\(^5\) describing the search for a good synthesis of 51 is worth longer study.

**Summary of General Approach to the Design of Syntheses**

1. Convert all FGs to those based on oxygen (OH, CO etc.) by FGI or C–X disconnection so that the carbon skeleton is exposed.
2. Identify the relationships between the functional groups. This means counting!
3. Adjust oxidation level if necessary and disconnect using reactions from chapters 18–28.
4. Continue to examine all possible relationships (e.g. by counting both ways round a ring) until a good synthesis emerges.
5. If necessary, add extra FGs or activating groups to make reactions possible.
6. If a bad step must be included, try to make it the first step.
References

Strategy XIII: Introduction to Ring Synthesis: Saturated Heterocycles

Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Chapter 42: Saturated Heterocycles and Stereoelectronics.

Cyclisation Reactions

This chapter is about intramolecular reactions and, in particular, about making heterocycles by cyclisation reactions. At the end of the last chapter we mentioned that the synthesis of 76 by reaction of the primary alkyl chloride 74 with MeNH$_2$ was likely to give a poor yield (numbers from chapter 28). The problem is that the product 75 is also a nucleophile and will react at a similar rate with 74 as does MeNH$_2$. The reaction is *intermolecular* and so bimolecular.

![Chemical structure](http://www.chem4all.vn)

We hope you would not be surprised that the very similar reaction of 2 gives exclusively the pyrrolidine 3. The reaction 4 is now *intramolecular*—a unimolecular cyclisation in fact—and is greatly preferred to any bimolecular processes. In fact 2 cannot be prepared as the free amine: its salts, e.g. the hydrochloride, are stable but neutralisation with base liberates 2 which promptly cyclises to 3.

![Chemical structure](http://www.chem4all.vn)

This chapter is about the advantage that cyclisations have over intermolecular reactions and therefore about the simplicity of heterocyclic synthesis. We need to look first at some details. It is not true that all cyclisations are favourable. A general cyclic amine synthesis shows that there is a large difference in the rates of formation of rings of different sizes.$^1$ Five-membered rings
are formed fastest, then six- and three-membered while four-membered rings are formed very slowly and seven-membered rings quite slowly.

This is partly to do with the ease of the cyclisation mechanism and partly to do with the stability of the ring being formed. Three- and four-membered rings are unstable because of 'strain', that is the angles between the bonds are significantly less than the tetrahedral angle of about 109°. Five- six- and seven-membered rings are unstrained and stable with six-membered rings being the most stable as they can have a chair conformation. So cyclisation 6 to give three-membered rings is favourable because the favoured conformation is right for cyclisation and the nucleophilic N is close to the electrophilic C. Cyclisation to give four-membered rings is unfavourable because the favoured conformation 9 cannot cyclise and the conformation 10 that can cyclise has eclipsed bonds. Both cyclisations are unfavourable because the products and hence the transition states are strained.

Five-membered ring formation is very favourable as the conformation needed 4 is reasonable and transition state and product are unstrained. If you make a molecular model of a long chain and fold it round you will find that the atoms that approach each other have a 1,5-relationship. Folding a chain 12 to form a six-membered ring takes the nucleophile past the electrophile 12a and only when the chain folds up in a chair-like fashion can cyclisation 13 occur.

So to summarise: kinetic and thermodynamic factors affect cyclisation to different extents depending on the ring size and on the reaction. Table 29.1 gives a general indication.

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Kinetic Factors</th>
<th>Thermodynamic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>very favourable</td>
<td>unfavourable (strain)</td>
</tr>
<tr>
<td>4</td>
<td>unfavourable</td>
<td>unfavourable (strain)</td>
</tr>
<tr>
<td>5</td>
<td>favourable</td>
<td>favourable</td>
</tr>
<tr>
<td>6</td>
<td>moderately favourable</td>
<td>very favourable</td>
</tr>
<tr>
<td>7</td>
<td>moderately favourable</td>
<td>moderately favourable</td>
</tr>
</tbody>
</table>
Thermodynamic factors can be divided into enthalpic and entropic components. The difference between five- and six-membered rings is shown in the formation of lactones 16 and 18 from hydroxyacids 15 and 17. Enthalpy favours the six-membered ring as the transition state is more stable but entropy favours the five-membered ring as there is a higher chance that 15 will be in a favourable conformation for cyclisation.

\[
\begin{align*}
\Delta H^\ddagger &\approx 80 \text{ kJ mol}^{-1} & \Delta S^\ddagger &\approx -48 \text{ J deg}^{-1} \text{mol}^{-1} \\
\Delta H^\ddagger &\approx 52 \text{ kJ mol}^{-1} & \Delta S^\ddagger &\approx 108 \text{ J deg}^{-1} \text{mol}^{-1}
\end{align*}
\]

The difference between the most kinetically favoured cyclisations is easily seen in the type of base needed to cyclise chloro-alcohols to three- and five-membered cyclic ethers (epoxides and THFs). Chloroethanol 19 cyclises only as the oxyanion: specific base is needed, i.e. a strong enough base to remove the OH proton completely. By contrast, 4-chlorobutanol cyclises by general base catalysis: the proton is removed during the cyclisation 21 and weak bases will do.\(^1\)\(^2\)

This means that three-membered rings can easily be made but tend to decompose under the conditions of their formation, that four-membered rings are difficult to make, that it is often difficult to stop five- and six-membered rings forming and that seven-membered rings can usually be formed when needed.

### Three-Membered Rings

You are already familiar with the simple formation of epoxides 26 by the action of peroxyacids such as \(m\)CPBA on alkenes 27. They can equally well be made by cyclisation of chloro-alcohols 25 as in the Cornforth addition of a Grignard reagent to an \(\alpha\)-chloroketone and cyclisation in base.\(^3\)

The nitrogen heterocycles, aziridines, can be made by displacement of an alcohol by an amine after activation. In their synthesis of the antitumour and antibiotic compound 30, whose active region is the aziridine, J. P. Michael and group opened the cyclic sulfite 28 with azide ion. Reaction occurred at the allylic position and with inversion. Activation of the alcohol as a mesylate gave 29 and reduction of the azide to an amine was followed by base-catalysed cyclisation, again with inversion.\(^4\)
Four-Membered Rings

Though these are the least favourable cyclisations, they do happen and are usually preferred to intermolecular reactions where there is no alternative, i.e. no more favourable ring can be formed. Upjohn’s analgesic and anti-depressant tazadoline 31 contains a four-membered cyclic amine, an azetidine. Simple disconnection of C–N bonds gives 32 (where $X$ is a leaving group) and then the enone 33, the aldol product from cyclohexanone 34 and benzaldehyde.

Rather surprisingly this strategy works. It was better to use the diketone 36 (rather than 33), made by acylation of the morpholine enamine 35 of 34 and reductive amination of with 3-aminopropanol to give 37 that is dehydrated in acid to the amine 38. A Mitsunobu-like treatment with Ph$_3$P·Br$_2$ converts the OH to Br whereupon cyclisation of 32; $X = Br$ gives 31.

They offer an even more surprising alternative in which reductive amination with benzylemine with reduction of the other ketone and cleavage of the N-benzyl bond followed by dehydration gives the simple amine 40. Now reaction with 1,3-dibromopropane gives 31, presumably again via 32; $X = Br$. 
When a four-membered heterocycle is cis-fused on the side of another ring, as with syn-44, which we met in chapter 12, cyclisation of the syn-monosylate 42 in base is very efficient as the, usually unfavourable, conformation 10 is now the only possible one and the nucleophile and electrophile are perfectly arranged 43 for cyclisation. This observation took on a new importance when the anti-cancer compound taxol® was discovered as it also has a cis-fused oxetane.  

![Chemical structure](http://www.chem4all.vn)

**Five-Membered Rings**

These are the most favourable of all and the precursors, such as the hydroxy acids, e.g. 15, cannot usually be isolated, though the carboxylate salts are stable. The only important thing is to get the oxidation level of the precursor right. Using cyclic amines as examples, a fully saturated ring 45 would come from an alkylation reaction on 46; X = a leaving group. Imines 47 or enamines 49 would come from aldehydes or ketones 48.

![Chemical structure](http://www.chem4all.vn)

Lactams 50 come from acid derivatives 51. Compounds such as amino esters 53 are not stable as the free amine but are usually isolated as salts such as the hydrochloride 52. When treated with base, 52 gives the free amine 53 which promptly cyclises to the lactam 50.

![Chemical structure](http://www.chem4all.vn)

For examples, we shall include sulfur heterocycles. The unsaturated ring 54 does have a double bond but it is not next to the heteroatom: it is an allylic rather than a vinylic sulfide. So two disconnections at the alcohol oxidation level suggest the doubly allylic starting material 55. As it happens, we made the diol 56 in chapter 16 so we simply have to turn the OH groups into leaving groups and cyclisation with Na₂S gives the heterocycle.  

![Chemical structure](http://www.chem4all.vn)

When Metzner⁷ wanted to make the C₂ symmetric sulfide 57 he looked no further than the diol 58 which was available as a single enantiomer by asymmetric reduction. Conversion into a bis-mesylate 59 (not isolated) and double displacement with Na₂S gave the thiolane 57. The first
displacement must be intermolecular but the second is intramolecular so it is much faster than reactions with other molecules of 59. Both displacements go stereospecifically with inversion.

A combination of C–C and C–X disconnections can lead to a short synthesis. The sulfide 60 was needed by Woodward as an intermediate in a synthesis of biotin. Immediate C–S disconnections lead to an unlikely and very reactive compound 61. If instead the 1,3-diCO disconnection 60a is done first, the same C–S disconnections can be done to give simple starting materials.

Woodward chose to do the conjugate addition second because thiolacetic ester 63 was available. The diester 62 cyclised under equilibrating conditions to give 60.

A compound with two heteroatoms in the ring 66, needed for a synthesis of mannicone 65, illustrates the other two oxidation states. Disconnecting both C–N bonds noting that C-1 is at the acid oxidation level while C-3 is an enamine and so at the ketone oxidation level gives the keto-ester 67 and hydrazine 68. Where two heteroatoms are joined in a ring, it is usually better not to disconnect the bond between them but to look for a starting material containing both.

Now the 1,3-diCO relationship can be disconnected in two ways. One 67b would require a condensation between two esters that is difficult to control but the other 67a will be regioselective for reasons we explained in chapter 20.
The synthesis\(^\text{10}\) is straightforward: the condensation is indeed regioselective and it doesn’t matter which way round hydrazine reacts or indeed which carbonyl compound reacts first. The enamine will form so as to be in conjugation with the remaining carbonyl group.

\[
\begin{array}{c}
\text{CO(OEt)}_2 \\
\text{NaH}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{EtO}_2\text{C}
\text{EtO}_2\text{C}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{H}_2\text{N} \text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{69}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{67}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{66}
\end{array}
\]

**Six-Membered Rings**

The same methods work well with six-membered rings so we shall look at a few instructive examples. A dramatic demonstration of the advantages of intramolecular reactions comes in the synthesis of tetramethyl piperidone \(72\). Removal of the nitrogen with conjugate addition of ammonia to the dienone \(73\) opens the possibility of a double aldol disconnection to reveal three molecules of acetone.

\[
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{2 x 1,3-diX}
\text{2 x C-N}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{3 x acetone}
\end{array}
\]

\[
\begin{array}{c}
\text{72}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{73}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{acetone}
\end{array}
\]

Treatment of acetone with ammonia and the mild dehydrating agent calcium chloride at room temperature gives the piperidone \(72\) in one step.\(^\text{11}\) Presumably the acetone dimerises and trimerises but the incipient polymerisation is nipped in the bud by the capture of one or more of these intermediates by ammonia and the formation of the only possible stable six-membered ring heterocycle \(72\). The yield (48%) seems poor but excess acetone is recovered in the isolation and the yield is 70% if that is taken into account. In any case, making 430 g of \(72\) from 1 kg acetone is a cheap process with so much ‘added value’.

\[
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{NH}_3
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{acetone}
\end{array}
\]

\[
\begin{array}{c}
\text{74}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{73}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{72}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{76}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{77}
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{78}
\end{array}
\]

The morpholine derivative \(75\) has an obvious amide disconnection to \(76\) and a less obvious 1,2-diX disconnection at the ether to \(77\). This is obviously an epoxide \(78\) adduct with ammonia.
But supposing things are not so simple. The compound 79, with a subsituent on the other carbon atom and required as a single enantiomter, starts the same way but when we get to 81 we cannot go further using an epoxide.

Fortunately 81 is phenylalaninol—the alcohol from the amino acid phenylalanine. The workers decided to acylate at nitrogen first and so used chloracetyl chloride to make 77 which cyclised on treatment with base.

This compound 79 was needed to make a coenzyme analogue 86. Alkylation on oxygen by Meerwein's reagent gave the activated imino-ether 84 which reacted with phenylhydrazine to give the hydrazone salt 85. Now insertion of a single carbon atom as an orthoester HC(OMe)₃ gave the triazolium salt 86. Note that the two bonded nitrogen atoms are added at once and that addition of a single carbon atom in a cyclisation reaction works superbly well.₁²

With two heteroatoms in the six-membered ring, it is again useful to identify a compound containing both. The nucleic acid base uracil 87 contains a molecule of urea 88 in its structure but removing that leaves an awkward synthet 89. The question is; how are we to add to the enone and get the double bond back? The solution is to use the acetylenic acid 90. Heating 90 and 88 together in acid gives uracil in 65% yield.₁³

Seven-Membered Rings

Seven-membered nitrogen-containing heterocycles, especially those fused to benzene rings, are important in drug design. The famous tranquillisers Librium® 91 and Valium® are based on
such a ring system with two nitrogens 91. In the search for similar compounds,\textsuperscript{14} workers at Hoffmann-La Roche chose analogue 92. Disconnection of two of the ring C--N bonds (it doesn’t alter things if you disconnect more) reveals the oxime 93 of an aromatic ketone and chloroacetyl chloride 94.

![](http://www.chem4all.vn)

In practice the oxime 96 of the amino ketone 95 can be used in the cyclisation reaction to make an intermediate 97 that can be alkylated with various alkylating agents to give 92. The more nucleophilic amine is acylated and cyclisation to the less nucleophilic oxime nitrogen gives 97.

![](http://www.chem4all.vn)

Compounds such as 98 with only one nitrogen in the ring are more interesting synthetically and are needed for an anti-HIV drug.\textsuperscript{14} Initial C=C disconnection is followed by a C--N disconnection between the ring and the nitrogen 99. This is possible because nucleophilic aromatic substitution (S\textsubscript{N}Ar) works well on aryl fluorides with ortho or para electron-withdrawing groups\textsuperscript{15} such as the aldehyde in 100.

![](http://www.chem4all.vn)

We have already explained that compounds like 101 are unstable and cyclise rapidly to the lactam. So the workers at Takeda used the lactam 102 as the starting material. Opening the lactam with NaOH gave the anion 103 of 101 that added to 100 to give 99 and hence that aldol product 98 in base. Cyclisation to a seven-membered ring is preferred to intramolecular reactions.

![](http://www.chem4all.vn)

The related benzazapinones 105 can be made by formation of C--N bonds in two different ways.\textsuperscript{16} Amide formation from compounds like 104 is not surprising but reductive amination
between the amide nitrogen and the aldehyde in 106 is a testament to the efficiency of cyclisations even when a seven-membered ring is the product.

When workers at GlaxoSmithKline wanted to make 107 as an intermediate in the synthesis of a drug for the treatment of osteoporosis, they chose the double disconnection 107 because they already had a way of making single enantiomers of the diacid 108.

Imine formation of the diester 110 with the amine 109 and Lewis acid catalysis gave 111 and completion of the reductive amination with NaBH(OAc)₃ gave the free amine that cyclised on refluxing in toluene. Though the cyclisation required these relatively vigorous conditions, it still demonstrates the preference for seven-membered ring synthesis over intermolecular reactions or, in this case, an eight-membered ring.

References
2. B. Capon, Quart Rev., 1964, 18 64.
Three-Membered Rings

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 40: Synthesis and Reactions of Carbenes.

Chapters 30–37 are concerned with the synthesis of carbocyclic rings. The disconnections are therefore of C–C rather than C–X bonds and the choice is correspondingly greater. We start in this chapter with three-membered rings and work our way upwards to six-membered. But the principles, particularly of cyclisation, remain the same as in chapter 29.

Cyclopropanes by Alkylation of Enolates

Three-membered rings are kinetically favoured but thermodynamically unstable so that they are often destroyed under the conditions of their formation. Since most carbonyl condensations are reversible, they are generally not good routes to three-membered rings. But the alkylation of enol(ate)s is usually irreversible so that these can be excellent methods.

Cyclopropyl ketones 1 can be made by cyclisation of some derivative of the γ-hydroxy-ketone 2. Notice that we are proposing to make a three-membered carbocyclic ring from an easily made three-membered heterocyclic ring.

Since we have already made compounds like 2 in chapter 25 from β-keto-esters, it makes sense to use the same strategy here. Addition of ethylene oxide 3 to the enolate of 5 gives the lactone 6 directly and treatment with HBr accomplishes decarboxylation and formation of the bromide 7 in one pot.1 Vogel2 uses the chloroketone to make 1; R=H in 82% yield by this method with NaOH for the base.
A more dramatic example is the synthesis of cis-chrysanthemic acid 11, the basis of most modern insecticides, from didealone 8, whose synthesis we discussed in chapter 21. Methylation between the two carbonyl groups gives 9, with the complete skeleton of 11—a little reorganisation of the atoms is needed. Treatment with bromine and base gives the inevitably cis-fused bicyclic dione 10 and a further three simple steps produce chrysanthemic acid.³

Some explanation is needed! Treatment of 9 with base and bromine must produce the potassium enolate of the bromoketone that cyclises 12 to form the three-membered ring. Reduction presumably gives the exo-alcohol 13 whose tosylate can fragment with hydroxide 14 to give 11.

A much less promising cyclisation gives the biologically patterned insecticide permethrin⁵ 17. The enolate of the ester in the starting material 15 must cyclise by displacement of chloride at a tertiary centre. Cyclisation to form three-membered rings can be remarkably favourable.

The simple bicyclic amines 18 are drug candidates with Merck for treatment of pain.⁶ Disconnection to one of the amino alcohols 19 suggests that the anion of the nitrile 23 might be used to make two C–C bonds in the cyclopropane by alkylation of epichlorhydrin 22 both at the epoxide and at the chloride. If this sequence works, it can give only the stereochemistry required.

The workers at Merck were able to go from start to finish in a single vessel. Base treatment of 22 + 23 led to attack at the epoxide end of 22 to give the anion 24. This is in equilibrium with the carbanion stabilised by Ar and CN and cyclises to an epoxide that gives a 15:85 mixture of the diastereoisomers 25 and 20. Reduction with borane gave a mixture of the amino alcohols
which was converted into a mixture of the chlorides 26 as their hydrochloride salts. Raising the pH to > 8.5 gave enough of the free base of 26 to cyclise to 18. The two drugs bicifadine (Ar = p-tolyl) and DOV21947 (Ar = 3,4-dichlorophenyl) were formed in acceptable overall yield for this multi-step operation. The trans compound obviously cannot cyclise and was removed by crystallisation.

Carbene Insertion into Alkenes

The cyclisation methods we have used so far all depend on the simple disconnection 27a into a carbonyl group and an alkylating agent in the same molecule 28. But the same general class of molecule 27 can be made a very different way that is revealed by disconnection of two C–C bonds 27b to suggest an alkene 29 and a carbene 30.

Carbenes have divalent carbon with a lone pair and hence only six electrons in the outer shell of the carbon atom. They are normally electrophilic and can form two bonds at once with a π-system. One way to make carbenes is by loss of nitrogen from diazocompounds such as diazoketones 33. The formation of very stable nitrogen is initiated by heat or light and compensates for the formation of the unstable carbene 30. Diazoketones are easily made by acylation of diazomethane with an acid chloride 31. Loss of a very acidic proton from the diazonium salt 32 gives 33. Normally the diazoketone and the alkene are combined and treated with heat or light.

This will obviously be easier if both reactive centres are in the same molecule so disconnection of the tricyclic ketone 34 reveals a diazoketone 35 that can be made from the acid 36. The
branchpoint disconnection would require a $d^3$ reagent.

This strategy did not appeal to Ruppert and White who preferred to make 36 by a chain extension route. A Reformatsky reagent gave 39 and dehydration and alkylation of malonate gave 36. Treatment with oxalyl chloride (COCl)$_2$ followed by reaction with diazomethane gave 35 which duly cyclised to 34 with copper catalysis.

---

**Carbenes by $\alpha$-Elimination**

You will be familiar with $\beta$-elimination that leads to alkenes (chapter 15) but $\alpha$-elimination gives carbenes. The simplest example is dichlorocarbene 44 made by treatment of chloroform 42 with base. The carbanion 43 decomposes by loss of chloride ion to give the neutral but unstable carbene 44 that should be released in the presence of the alkene. So cyclohexene 45 gives the dichloro-cyclopropane 46 using NaOH as the base and an ammonium salt as a phase-transfer catalyst.\(^{10}\)

A more interesting example is the aryl-cyclopropane 47. Removing the carbene we must put back the HCl lost in the $\alpha$-elimination to reveal 48. An example is with the benzylic chloride 49 that gives the bicyclic compound 47 in good yield and with high diastereoselectivity (10:1) in favour of the *endo* isomer shown. The strong and very hindered base 50 is used.\(^{11}\)
Metal Complexes of Carbenes

Some metals form stable complexes of carbenes, a notable example being rhodium. Treatment of the diazocompound with catalytic rhodium acetate gives the cyclopropane 52 via the carbene complex 53. Notice that the carbene inserts in only the less hindered of the two alkenes.\(^\text{12}\) This style of chemistry is treated in more detail in *Strategy and Control*.

\[
\text{N}_2 \quad \xrightarrow{\text{cat } \left[ \text{Rh(OAc)}_2 \right]_2} \quad \text{O} \quad \xrightarrow{52; 71\% \text{ yield}} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{O}
\]

\[
\begin{align*}
51 & \quad \text{52; 71\% yield} \\
53 & \quad \text{52; 71\% yield}
\end{align*}
\]

Metal Carbenoids

Related to metal complexes are metal carbenoids such as those formed when zinc reacts with di-iodomethane. In early examples, such as the efficient cyclopropanation of cyclohexenone 54, the zinc was activated by some copper.\(^\text{13}\) The active reagent is the zinc α-complex 56. One might suppose an α-elimination 57 would occur to give the carbene, but this is apparently not so. The active reagent 56, nearly but not quite a carbene, is known as a carbenoid.

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{CH}_2\text{I}_2} \quad \text{O} \\
54 & \quad 55; 90\% \text{ yield} \\
56 & \quad \text{CH}_2 + \text{Znl}_2
\end{align*}
\]

A better version involves diethyl zinc as the source of the metal and again, simple alkenes such as 58 can be converted into cyclopropanes.\(^\text{14}\) The active reagent is probably 60.

\[
\begin{align*}
58 & \quad \text{59; 86\% yield} \\
59 & \quad \text{59; 86\% yield} \\
60 & \quad \text{60}
\end{align*}
\]

However, this method really hit the headlines when it was used on allylic alcohols 61 and became known as the Simmons–Smith reaction.\(^\text{15}\) If there is stereochemistry at the alcohol 63, the cyclopropane is formed on the same side as the OH group 64 suggesting that the alcohol guides the zinc carbenoid into the alkene.

\[
\begin{align*}
\text{R} \quad \text{CH}_2\text{I}_2 \quad \text{Zn/Cu} \quad \text{R} \\
61 & \quad \text{62} \\
63 & \quad \text{64}
\end{align*}
\]

In their synthesis of the anti-leukaemia compound steganone, Magnus, Schultz, and Gallagher used the allylic alcohol 65 to make the cyclopropane 66. The extra carbon atom was incorporated into the eight-membered ring of steganone.\(^\text{16}\)
An example with stereochemistry comes in the synthesis of halicholactone by Takemoto.\textsuperscript{17} The diene 67 (the various R groups are protecting groups) gives only one cyclopropane: the allylic alcohol alone reacts and the cyclopropane appears on the same face of the alkene as the allylic OH group 68.

All these methods using carbenes, metal complexes of carbenes or carbenoids are stereospecific in that the geometry of the alkene is faithfully reproduced in the stereochemistry of the cyclopropane so \textit{trans}-67 gives \textit{trans}-68 specifically. They can also be stereoselective, particularly the Simmons–Smith on allylic alcohols: thus the cyclopropane in 68 is on the same side of the alkene as the OH group in 67. We now come to a widely used method that is not stereospecific on the alkene.

\subsection*{Sulfonium Ylid Chemistry}

The simplest sulfur ylids are formed from sulfonium salts 69 by deprotonation in base. These ylids react with carbonyl compounds to give epoxides.\textsuperscript{18} Nucleophilic attack on the carbonyl group 70 is followed by elimination 71 of dimethylsulfide 72 and formation of the epoxide 73. You should compare diagram 71 with diagram 23 in chapter 15. The phosphonium ylid reacted by formation of a P–O bond and an alkene in the Wittig reaction. The sulfonium compound reacts by formation of a C–O bond 71 as the S–O bond is much weaker than the P–O bond. The sulfonium salt 69 can be reformed by reaction of 72 with MeI.

So what has this got to do with cyclopropanes? If sulfur ylids react with enones either the epoxide 74 or the cyclopropane 76 may be formed.\textsuperscript{19} The general rule is that sulfonium ylids from 69 give epoxides but sulfoxonium ylids give cyclopropanes 76.
The sulfoxonium ylid 78 is more stable and is therefore liable to do conjugate rather than direct addition (chapter 21). The intermediate eliminates dimethyl sulfoxide 79 to give the cyclopropane 76. The intermedoiate is long lived and the single bond that was the alkene can rotate so the geometry of the alkene is lost. In this case we expect the more stable trans cyclopropane to be formed by choice.

These reactions may show considerable selectivity. Corey and Chaykowsky19 give an example with the terpene carvone 80. The ylid 78 is made with NaH and reacts only with the enone and not with the unconjugated alkene. The product is one diastereoisomer 81 as the ylid has added to the opposite side of the ring to the only substituent. It also has retained the stereochemistry of the cis alkene but that is inevitable as 3/6 ring fusion must be cis.

A more complex example comes in the synthesis of halicholactone by Wills.20 A diene 82 is again used and again only the conjugated alkene gives a cyclopropane 83. The reaction stereo-selectively gives a 5:2 ratio of 83 and the other trans cyclopropane with the ring below the chain. Notice that the allylic alcohol is blocked so there is no Simmons-Smith style direction. The geometry of the alkene again appears to be retained but that is by choice. The product is cyclised to give the nine-membered lactone 84 where R is the cyclopropane-containing side chain.

In all these carbene-related methods the disconnection is the same (as in 34 or 47) with a choice over which pair of bonds in the three-membered ring you prefer to disconnect. Or you could think which alkene you would rather make. In most cases we prefer to remove a CH₂ group if possible as the reagents CH₂I₂ or 78 are much easier to come by. However the diazo 34 and simple carbene 47 examples show that this is not a rule.

References

2. Vogel, page 1090.
Strategy XIV: Rearrangements in Synthesis

Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Chapter 37: Rearrangements.

If the carbon framework of a TM is difficult to construct, one strategy is to make a slightly different framework by conventional reactions and rearrange it into the framework we want. Methods involving rearrangement range from simple chain extensions to deep-seated skeletal rearrangements very difficult to analyse.

Diazoalkanes

In the last chapter we met diazoalkanes as sources of carbenes in the synthesis of three-membered rings. These same diazoalkanes are useful reagents for rearrangements via carbenes or carbocations.

Chain Extension with Diazoalkanes: The Arndt–Eistert Procedure

If an acyl diazoalkane 2, made from a carboxylic acid, is treated with heat, light or a metal to give a carbene in the absence of a carbene acceptor, the carbene rearranges 3 by migration of the side chain (R) to give a ketene 4, a strong electrophile that gives derivatives of the homologous carboxylic acid such as the ester 5. The chain length has been increased by one carbon atom. Ketenes are discussed more fully in chapter 33.

\[
\begin{array}{cccccccccccc}
O & C & Cl & \text{CH}_2 & N_2 & \text{O} & \text{N} & \text{N} & \text{heat} & \text{metal} & \text{or hv} & \text{R} & \text{C} & \text{O} & \text{MeOH} & \text{R} & \text{O} \\
1 & & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
& & & & & & & & & & & & & & & \\
\end{array}
\]

This extension, known as the Arndt–Eistert procedure,\(^1\) is useful if the relationship between functional groups is unhelpful in the TM but becomes helpful if the chain is retrosynthetically shortened. Other methods, such as cyanoide displacement, also increase the chain length by one carbon and we saw a chain extension by two carbon atoms in the last chapter. The disconnections are strange: both C–C bonds between R and CO are made in the reaction so we must disconnect both 5a. You might like to think of this as a reconnection strategy (chapter 26) or as an extrusion of a CH\(_2\) group.

---

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In chapter 27 we analysed the synthesis of the bicyclic lactone 7 needed by Eschenmoser for his vitamin B₁₂ synthesis. The next step was a chain extension by the Arndt–Eistert procedure to the ester 9.

The unsaturated ester 10 would be made by dehydration of the tertiary alcohol 11. But this has an unhelpful 1,4-diCO relationship that leads to a homoenolate 13 that we should rather avoid.

Chain extension 11a solves the problem. The homoenolate 13 becomes an enolate 15 with many possibilities.

Smith used a Reformatsky reagent as the enolate equivalent and everything went according to plan, especially the yield on the chain extension step.

Diazooalkanes in Ring Expansion and Contraction

Related to simple chain extension is ring expansion and contraction useful because some ring sizes are easier to make than others. So available cyclohexanone can be expanded into cycloheptanones such as the useful keto-ester 20 with an activated position for enolate reactions. The reagent is ethyl diazoacetate 18 readily available from glycine esters. Addition to the ketone 18 automatically
produces an oxanyion and a diazonium leaving group that collaborate 19 in the migration. The disconnection is again extrusion of a carbon atom.

Disconnection of the bicyclic diketone 21 starts reasonably to reveal 22 but the two carbonyl groups are now 1,6-related suggesting a reconnection strategy (chapter 27). But this is impossible as the bridgehead alkene 23 is too strained to exist. However, if we extrude the carbon atom in the seven-membered ring between the ketone and the branchpoint 22a, we get a new ketoester 24 with a 1,5 relationship that can be made by conjugate addition (chapter 21).

An enamine is ideal for the conjugate addition. We could have used diazomethane for the ring expansion but a better idea is to make it intramolecular by using a diazoketone 28 easily made from the free acid 27 with diazomethane. This time the rearrangement was initiated with Meerwein's salt and only the more substituted carbon atom migrates.

For ring contraction, the diazo group has to be on the cyclic ketone and the reaction resembles the ketene formation at the start of this chapter. The four-membered ring in the natural product junionone 29 is difficult to make but Wittig disconnection suggests a simplier aldehyde 30 and, if we could somehow put the carbonyl group back into the ring using a diazoketone 31, we could start with a simple cyclopentanone 32.
The diazocompound was made with tosyl azide and it proved better to add an activating group (CHO in its end form in 33) for this. Rearrangement in light gave a ketene that picked up methanol to give the ester 34 and the rest is straightforward.\(^5\) Ring contraction of five- to four-membered rings is unusual because of the increased strain but the gain in forming nitrogen compensates.

The Pinacol Rearrangement

In chapter 24 we saw that carbonyl compounds dimerise by a radical reaction when electrons are transferred to them from metals. The typical ‘pinacol’ 37 formed from acetone 36 is important because it rearranges\(^6\) in acid to give a tertiary alkyl ketone 38 known as ‘pinacolone’. The key step is a methyl migration as one of the OH groups is lost 39.

Though restricted by the need for symmetry, this is a useful approach to \(t\)-alkyl ketones which are otherwise difficult to make.\(^7\) The crowded alkenes 40 can be made by dehydration of alcohols 41 and hence from the ketone 42 and RLi or RMgX. As 42 has a \(t\)-alkyl substituent it is a candidate for the pinacol approach.

The easiest way to do the disconnections is to reverse the rearrangement and there are two ways to do this 42a and 42b. Diol 44 can be made by pinacol dimerisation of cyclopentanone 43 while diol 45 would be the product of dihydroxylation of the alkene 46.

In fact Corey\(^8\) chose strategy a using the pinacol dimerisation to make the diol 44 and the pinacol rearrangement to make the spirocyclic ketone 42.
The product 40 was used in a synthesis of the Columbian frog venom perhydro-histrionicotoxin 49 and that also used the Beckmann rearrangement of the oxime 47. Note that only the group anti to the N-O bond migrates and that it does so with retention. You can see that each ring was expanded in this synthesis.

Rearrangements of Epoxides

The limitation of the pinacol is the need for symmetry. This section and the next suggest ways of avoiding this problem. Unsymmetrical epoxides are easily made from alkenes and open with Lewis acid catalysis to give the more substituted of the two possible cations.9 Even such a weak Lewis acid as LiBr opens the epoxide 51 to give the tertiary cation 52 which rearranges by ring contraction to the aldehyde 53. The authors prefer to have the bromocompound 54 as an intermediate.10

A more exciting example is the epoxide 56 of natural α-pinene 55 that rearranges to the unsaturated aldehyde 57 in excellent yield. Epoxide opening to give the more substituted carbocation is followed by rearrangement 59 and then fragmentation 58. Note that the expansion of the strained four-membered ring is preferred to any alternatives.
Semi-Pinacol Rearrangements

One limitation remains that would apply to pinacol rearrangements and unsymmetrical 1,2-diols: only the more highly substituted cation would be formed. We can get round that by selectively functionalising the less substituted alcohol with a sulfonate leaving group. Pinacol rearrangement of the diol 61 would lead to migration of H or Me to the tertiary centre. But if the secondary alcohol is selectively mesylated 62, rearrangement gives the ketone 63 by migration of an R group 64. This sequence was carried out with single enantiomers as the starting material is natural lactic acid.\(^\text{12}\) The disconnections for epoxide and semi-pinacol rearrangements are the same as for the pinacol; just reverse the rearrangement. But it is not straightforward to see that this solution is available.

The Favorskii Rearrangement

The rearrangements we have seen so far are all essentially cationic even though no cationic intermediate may be involved. By contrast the Favorskii rearrangement is anionic—almost every intermediate is an anion. Halogenation of cyclohexanone gives the α-chloroketone 66. Treatment of such compounds with nucleophilic alkoxide gives ring-contracted esters 67. The enolate of 66 cyclises 69 to give an unstable cyclopropanone that reacts immediately with the alkoxide to cleave one of the weak C–C bonds in the three-membered ring.

Cyclopropanone cleavage with elimination 72 can also lead to ring contraction as in the synthesis of the trans acid 74 from natural pulegone\(^\text{13}\) 70. Bromination gives the unstable dibromide 71 that is immediately treated with ethoxide to initiate the Favorskii rearrangement. The product is a mixture of cis and trans isomers of the ester 73 but hydrolysis under vigorous conditions (reflux in aqueous ethanol) epimerises the ester centre and gives exclusively the trans acid 74.

Once again the only reasonable way to ‘disconnect’ such an ester is to reverse the rearrangement in your mind, adding the halide at a reasonable position. So 67 might be made by reversing the Favorskii rearrangement 75 and only when you see the simple starting material 66 can you
appreciate that this looks a good strategy. Another way would be to draw the cyclopropanone 76 from which 67 could be made. But rearrangements are difficult to visualise retrosynthetically.

References

Four-Membered Rings: Photochemistry in Synthesis

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapter 35: Pericyclic reactions I: Cycloadditions.

In chapter 29 we concluded that four-membered rings are uniquely difficult to make: they are strained with ring angles of about 90° and the most favourable conformation of the starting material cannot cyclise. Four-membered rings can occasionally be formed by ordinary cyclisations. The double alkylation of malonate 1 with dibromopropane gives the cyclobutane 2. But Perkin found in his original work on carbocyclic rings¹ that double alkylation of acetooacetate 3 was successful for all ring sizes from three to seven except four. The enol ether 4 was formed instead of a cyclobutane. It is easy to see how the enolate of the intermediate 5 is ideally arranged to form 4 but not to form a cyclobutane.

![Chemical structures](http://www.chem4all.vn)

Photochemical Cycloadditions

So special reactions are often used to make cyclobutanes. In the next chapter we shall see that thermal cycloadditions of alkenes with ketenes give four-membered rings, but the commonest method is photochemical cycloaddition. You are already aware that Diels-Alder reactions (chapter 17) occur easily when a diene 6 and a dienophile 7 are heated together and six-membered rings 8 are formed. Have you ever wondered why four-membered rings 9 are not formed instead? Orbital symmetry allows cycloadditions involving six π-electrons but not those involving four π-electrons.²

![Chemical structures](http://www.chem4all.vn)

The 2 + 2 cycloadditions do occur in the excited state so these are photochemical reactions.³ They work best if one component (usually an enone) absorbs the light to form the excited state.
while the other (usually a simple alkene) reacts in its ground state. Even ethylene reacts with conjugated enones such as 10 under irradiation\(^4\) to give reasonable yields of the cyclobutane 11. The stereochemistry of H and Me at the ring junction is determined partly by the fact that they are already cis in the starting material 10a and partly by the difficulty of making trans 4/6 fused system.\(^5\)

![Chemical diagram showing the photochemical reaction between CH₂ + O to form 11 with 62% yield.](http://www.chem4all.vn)

Both components may be functionalised so disconnection of the middle ring of 12 leads to the greatest simplification suggesting two simple starting materials 13 and 14. Irradiation of the mixture does indeed give\(^6\) a good yield (70%) of 12. The stereochemistry of the B/C ring junction must be cis 12a, as two four-membered rings must be cis fused, but that of rings A/B follows the guidelines of 11. The relative stereochemistry of the two cis junctions, i.e. that of rings A and C, is chosen to give least steric hindrance. There is no endo rule. Because both compounds have the alkene conjugated to a carbonyl, the minor product is the dimer of 14.

![Chemical diagram showing the transformation of 12 into 13 and 14.](http://www.chem4all.vn)

Most cyclobutanes offer a choice between two 2 + 2 disconnections and the choice can often be made by considering the availability of the starting materials. We already know from 11 that compounds like this can be made by irradiation of ethylene with enones, here 15, so we shall focus on the alternative 16b. The starting material for an intramolecular photo-cycloaddition would be dienone 17. It was decided to make this by oxidation of 18 because this alcohol was easy to make.\(^7\)

![Chemical diagram showing the cycloaddition reactions 15 to 16b, and the formation of 18.](http://www.chem4all.vn)

The idea was to add vinyl Grignard 19 to the aldehyde 20 which could be made by allylation of isobutyraldehyde 21. Oxidation to the ketone might be carried out either before or after the cycloaddition.

![Chemical diagram showing the reaction of 18 with CH₂ + MgBr to form 19.](http://www.chem4all.vn)
In fact, the allylation was carried out by the Claisen rearrangement (chapter 35) and the cycloaddition on the alcohol 18 catalysed by Cu(I). The product was a mixture of the major isomer 23 with some of the exo-alcohol (OH up as drawn). This is irrelevant as both alcohols oxidise to the ketone 16. The stereochemistry at the ring junction can only be cis.

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
21 & \quad 20 \\
\text{TsOH} & \quad \text{CuOTf} \\
\Rightarrow & \quad \Rightarrow \\
\text{hv} & \quad \text{hv} \\
19 & \quad 18 \\
\text{82-83\% yield} & \quad \text{83-89\% yield}
\end{align*}
\]

**Regioselectivity**

Only one regioselectivity is possible in the cyclisation of 18 but in intermolecular reactions we need to consider which way round it will go. So the unsymmetrical alkene 24 could add to the very unsymmetrical enone 25 to give 26 or 27. In fact the reaction gives virtually 100\% of 27 without a trace of 26.

![Chemical structures](http://www.chem4all.vn)

Some big steric or electronic factor is clearly at work. Though the alkene 24 is hindered at one end, the enone barely is and it is electronic factors that dominate. The natural polarity of the alkene is to be nucleophilic at the CH\(_2\) group 24a. So in the thermal reaction (that doesn’t happen) it could attack the electrophilic end of the enone 25a. One way to predict photochemical 2 + 2 cycloadditions is to suppose that the excited state of the enone reverses the natural polarity from 25b to 25c and the new electrophilic end now combines with the alkene 24. As the alkene is not excited, it behaves in the normal way 24a. This is of course a simplification but it works.

![Chemical structures](http://www.chem4all.vn)

Intramolecular reactions occur by the same principle if they can, but the contortion required to get the bridged cyclobutane 28 from 29 is too much and the molecule prefers to add the ‘wrong’ way round and give the fused structure 30 instead.

![Chemical structures](http://www.chem4all.vn)

But amazing contortions are possible. Photocycloaddition of the allene 31 unites just one of the allene bonds with the conjugated alkene to give the very strained cyclobutane 32. Diagram
31a should make it clear how this distortion gives 32. This product 32 was perfect for Hiemstra’s synthesis of solanoelepin A 33, an extraordinary compound that is exuded from growing potatoes and causes the potato eelworm to hatch from its cysts.\(^\text{11}\)

![Chemical structures](http://www.chem4all.vn)

**Four-Membered Rings by Ionic Reactions**

The cyclobutene 14 used a few pages back in a cycloaddition was actually made by an ionic reaction from adipic acid 34. Double bromination of the acid chloride and quenching with methanol gives 35 that cyclises\(^\text{12}\) to 14 with NaH. Presumably one enolate is alkylated by the other bromide and then the second enolate eliminates 36 to give 14.

![Chemical structures](http://www.chem4all.vn)

Remarkable syntheses of polycyclic fused systems such as 38 by treatment of simple compounds 37 with base have emerged from Takasu and Ihara.\(^\text{13}\) You might compare the skeleton of 38 with that of 30.

![Chemical structures](http://www.chem4all.vn)

Presumably the silyl enol ether of 37 adds in a conjugate fashion to the unsaturated ester 39 and the intermediate enolate then cyclises onto the cation 40 to give 38. This will happen only if the stereochemistry of 40 is the same as that of the product 38 as the 4/5 and 4/6 ring fusions must both be \textit{cis}. This suggests that the first step is reversible. The formation of the cyclobutane requires that particular relationship between ketone and unsaturated ester so this kind of reaction is less versatile than photochemical cyclisation. Asymmetric versions of these reactions are also known.\(^\text{14}\) Probably the most versatile thermal method to make cyclobutanes uses ketenes and is the subject of the next chapter.
References

Strategy XV: The Use of Ketenes in Synthesis

We met ketenes in chapter 31 where they were intermediates in the Arndt–Eistert chain extension procedure. Now we are going to take a wider view of their value in synthesis. A ketene 1 is very electrophilic at the curious sp carbon atom (marked * in 1) and combines with nucleophiles 2 to give enolates that are protonated at carbon 3 to give acylated compounds 4.

Ketenes are rarely isolated as they dimerise easily. Ketene itself 2 gives the lactone 5 but dimethylketene 6 gives the diketone 7. Other ketenes may give either type of dimer. Only a few ketenes, such as diphenyl ketene, are normally isolated.

Ketenes are normally prepared by the base-catalysed elimination of HCl from an acid chloride 9 or by elimination of chlorine from a chlorosulkyd acid chloride with zinc dust, often assisted by ultrasound. For reactions with nucleophiles, the solution would already contain the nucleophile before the ketene 6 was generated.

[2 + 2] Thermal Cycloadditions of Ketenes

Unlike ordinary alkenes, ketenes do 2 + 2 cycloadditions with themselves—the dimerisation above—and with other alkenes.¹ Reaction of dichloroketene with cyclobutadiene 11 to give the
dichloroketone 12 shows that they prefer $2 + 2$ to $4 + 2$ cycloadditions and also shows off the regioselectivity you would expect: the $sp$ carbon reacts with the most nucleophilic end of the alkene.$^2$ The ‘mechanism’ 13 shows the major orbital interaction as the two reagents approach each other: the reaction may well be a concerted cycloaddition.

Reaction of dichloroketene with cis or trans cyclo-octene suggests that it is a concerted reaction; each gives stereospecifically a different stereoisomer of the adduct: cis-15 gives cis-16 while trans-17 gives trans-18. The marked hydrogen atoms should make this clear. The very reactive trans-cyclo-octene 17 gives a 100% yield so there is no room for any 16 in the product.$^3$

The disconnections for this reaction are, of course, of one of the two sets of opposite C–C bonds in the cyclobutanone. Each will give a ketene and an alkene and a choice has to be made. Adduct 12 is easy: disconnection 12a gives two simple starting materials while disconnection b, though the cyclisation would be intramolecular, gives a starting material of some difficulty. For example, the middle alkene must be cis for the reaction to have a chance.

Others are not so obvious. Cyclobutanone 22 might come from diphenylketene and the diene 21 (disconnection 22a) or from ketene itself and the diene 23 (disconnection 22b). No doubt both dienes could be made but the regioselectivity of both cycloadditions looks in doubt.

The diene 23 would probably react at the less hindered alkene or at the wrong end of the more activated alkene with the two phenyl groups. But the chances of 21 reacting at the right end are much better: it is both the more nucleophilic and the less hindered alkene and the regioselectivity looks right too. This is in fact how it was made: diphenylketene 20 adds to the cis-diene 21 to give 22 in 99% yield.$^4$
Rearrangements of the Products of Ketene 2 + 2 Cycloadditions

Both the Baeyer–Villiger and the Beckmann rearrangement are used on the cyclobutaones formed in these cycloadditions. Dechlorination of adduct 12 with zinc and rearrangement with a peroxo-acid gives a lactone 25 widely used in prostaglandia synthesis. Note that the more substituted carbon migrates and does so with retention of configuration.

An example with regioselectivity in both reactions is the cyclobutanone 27. Addition of dichloroketene, that must be made by the zinc dehalogenation method for good results, to the cyclohexenone 26 gives just one isomer of 27 that can be dehalogenated (zinc again) and oxidised to the lactone 29. Again the more substituted carbon atom migrates with retention.

The Beckmann rearrangement is used in a similar way to produce the lactam 32, an intermediate in the synthesis of swainsonine 33. Stereoselective addition of dichloroketene to the enol ether 30 gave one isomer (∼95:5) of cyclobutanone 31. Beckmann rearrangement with a sulfonated hydroxylamine and dechlorination gave the lactam 32 in 34% yield over five steps from a precursor of 30. Note that the cis-alkene 30 gives the trans cyclobutanone selectively.

Even the diazomethane ring-expansion (chapter 31) works well on cyclobutanones: they seem all too eager to lose their strain by ring expansion. This unusual sequence leads to the cyclopentenone 38 used for various conjugate additions. Presumably CHMe migrates better than CCl₂ giving 36 and the zinc treatment removes just one chlorine atom. The LiBr/DMF treatment must eliminate via the enol(ate) of 37 giving the more substituted alkene 38.
**Ketene Dimers as Acylating Agents**

We mentioned the dimer of ketene 6 itself at the start of this chapter: it is a cyclic enol ether and a good acylating agent. Nucleophiles attack the carbonyl group 39 expelling the enolate 40 of the acetoacetyl derivative 41. The disconnection is shown on 41 and the ketene dimer represents synthon 42.

![Diagram showing the reaction of ketene dimers with nucleophiles](http://www.chem4all.vn)

The heterocycle 43 was needed as an intermediate in a cytochalasan synthesis. Disconnection of the 1,3-diCO relationship between the two ketones reveals the amide 44 that is the acetoacetyl derivative of phenylalanine ethyl ester 45.

![Diagram showing the conversion of 43 to 45](http://www.chem4all.vn)

The synthesis is straightforward: the ester 45 combines with the ketene dimer 6 with catalysis by base providing the base is not in excess. Cyclisation to give a five-membered cyclic amide occurs with more base to give 43 that actually exists as the enol 43a.

![Diagram showing the synthesis of phenylalanine](http://www.chem4all.vn)

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**References**

Five-Membered Rings

Unlike three-, four- or six-membered rings, five-membered rings are often made by standard carbonyl chemistry. This is because five-membered rings are the easiest to make by carbonyl condensations as they have kinetic and thermodynamic advantages over open chain compounds (chapter 29). This chapter gives a selection of such methods and the next chapter looks at some special methods for making five-membered rings.

Five-Membered Rings from 1,4-diCarbonyl Compounds

Cyclopentenones 1 disconnect to 1,4-dicarbonyl compounds 2. Any of the methods in chapter 25 may be used to make these but the regioselectivity of the cyclisation is an important consideration. If $R = \text{Me}$ 3, cyclisation can lead only to 1; $R = \text{Me}$ but, if $R = \text{Et}$ 4, could cyclise to 5 or 6 depending on which ketone forms the enolate. Thermodynamically 6 is favoured as it has a more highly substituted alkene, but it is close.

A simple example is the cyclopentenone 7 because the keto-aldehyde 8 can cyclise only one way as the aldehyde cannot enolate. The best 1,4-dicarbonyl disconnection is probably 8 giving some enolate equivalent 10 of isobutyraldehyde and a reagent for the unnatural synthon 9 such as the bromoketone 11.
In fact the workers who wanted 7 for photochemical addition to alkenes (chapter 32) chose to use propargyl bromide 14 and an enamine 13 of the aldehyde 12. Mercury-catalysed hydration of 15 gave 8 which cyclised to 7 in base.

\[
\begin{align*}
12 & \xrightarrow{R_2NH, H^+} 13 + 14 & 15 & \xrightarrow{1. \text{Hg(II), H}_2\text{O}, 2. \text{NaOH}} 7
\end{align*}
\]

Some molecules are studied for their theoretical interest; one being cyclopentadienone 16. But it turns out that this dimerises instantly by a Diels-Alder reaction and cannot be studied. The simplest cyclopentadienone that can be made is the tetraphenyl compound 17. Aldol disconnection gives 18 but we can now do a second aldol disconnection to reveal the two symmetrical starting materials 19 and 20.

![Chemical structures](http://www.chem4all.vn)

Benzil 20 can be made by the oxidation of benzoin\(^2\) 21 (chapter 23) and it combines with 19 in one step under base catalysis\(^3\) without the need to isolate 18. The problem with these compounds is that 16 has only four \(\pi\)-electrons delocalised round the ring and is anti-aromatic. Clearly four phenyl groups help stability but 17 exists as deep purple crystals showing an unusually small gap between the populated and unpopulated orbitals.

![Chemical structures](http://www.chem4all.vn)

**Cyclopentyl Ketones from 1,6-diCarbonyl Compounds**

We have already seen (chapter 19) the synthesis of cyclopentanone itself 24 via the useful \(\beta\)-ketoester 23 from adipate esters 22. In the same way unsaturated ketones 25 disconnect with an aldol in mind to the 1,6-dicarbonyl compound 26. There may again be regioselectivity questions in the cyclisation.

![Chemical structures](http://www.chem4all.vn)

Thus both unsaturated carbonyl compounds 27 and 30 disconnect to the same 1,6-dicarbonyl compound 28 that reconnects to natural limonene 29. There are two chemo-selectivity problems
here: how do we cleave one alkene in limonene without cleaving the other and how do we control the cyclisation?

\[
\begin{align*}
\text{aldol} & \\
\text{27} & \rightarrow \\
\text{28} & \rightarrow \\
\text{1,6-diCO} & \rightarrow \\
\text{reconnect} & \\
\text{29} & \rightarrow
\end{align*}
\]

It turns out that epoxidation prefers the more substituted alkene in the ring. The epoxide 31 can then be opened to the diol 32 and cleaved with periodate to give 28. The ketoaldehyde 28 was not isolated but cyclised immediately.\(^4\)

\[
\begin{align*}
\text{mCPBA} & \\
\text{29} & \rightarrow \\
\text{31} & \rightarrow \\
\text{32} & \rightarrow \\
\text{32} & \rightarrow \\
\text{28} & \rightarrow
\end{align*}
\]

But what about this cyclisation? In stronger protic bases like KOH in water, all the cyclisations are reversible and the more stable ketone 27 is formed by thermodynamic control. In buffered conditions (weak amine base and weak acid) only the more reactive aldehyde enolises and 30 is formed by kinetic control.

\[
\begin{align*}
\text{27; no yield given} & \\
\text{Et}_2\text{O, shake} & \\
\text{26} & \rightarrow \\
\text{30; 59\% yield} & \text{piperidine} & \text{HOAc}
\end{align*}
\]

**Cyclopentanes from 1,5-diCarbonyl Compounds**

The silicon modification of the acyloin condensation gives excellent yields of five-membered rings. The simple spiro compound 35 provides a perfect illustration. The traditional acyloin without silicon gives a paltry 18\% yield: with Me\(^3\)SiCl present, the yield (of 33) rises\(^5\) to 87\%.

\[
\begin{align*}
\text{33; 87\% yield} & \\
\text{34} & \rightarrow \\
\text{35; 18\% yield} & \text{Na, xylene} & \text{R = Me}
\end{align*}
\]

Even with a spiro four-membered ring, the reaction works well. In a synthesis of the theoretically interesting molecule 39, the silicon acyloin and its hydrolysis gave good yields.\(^6\)

\[
\begin{align*}
\text{36} & \rightarrow \\
\text{37; 84\% yield} & \text{Na, Me}_3\text{SiCl} & \text{toluene} & \text{R = Me}
\end{align*}
\]

\[
\begin{align*}
\text{37} & \rightarrow \\
\text{38; 95\% yield} & \text{HCl} & \text{H}_2\text{O}
\end{align*}
\]
However, the presence of an alkene \textit{exo} to the chain 40 stops the reaction, presumably because the 120° angle holds the ends too far apart. The solution is conjugate addition of an amine 41: the acyloan then works well 42 and the synthesis of the flavouring compound ‘corylone’ 43 is completed simply by a silica column.\textsuperscript{7} Hydrolysis of the silyl enol ethers leads to elimination of Me$_2$NH under the slightly acidic conditions.

![Chemical Structures]

**Synthesis of Cyclopentanes by Double Sequential Conjugate Addition**

In chapter 21 we saw how a conjugate addition, followed by an aldol condensation, gave six-membered rings. Now we can see that conjugate addition followed by another conjugate addition can give five-membered rings. The starting material 45 is easily made by alkylation of malonate with the allylic halide 44. Treatment with base and an unsaturated ketone 46 gives a cyclopentane with high (>50:1) stereoselectivity in favour of the \textit{trans} compound\textsuperscript{8} 47.

![Chemical Structures]

The conversion of 45 and 46 into 47 occurs in one operation. Evidently the anion of 45 adds 48 to the enone 46 and the enolate produced cyclises by a second conjugate addition 49. This type of reaction gives a more highly substituted cyclopentane than we have seen so far.

![Chemical Structures]

The disconnection is of the two 1,5-diCO relationships present in 47: it doesn’t matter (much) which you do first: the second follows. Disconnection \textit{47a} leads us straight back to \textit{51} and hence our starting materials but \textit{47b} needs a little more imagination to see the second disconnection on \textit{50}. This sequence leads to a five-membered ring because there is only one CH$_2$ group between the bromine and the alkene in \textit{44}. If there were two, a six-membered ring would be formed. That is the subject of chapter 36.
References


Background Needed for this Chapter Reference to Clayden, *Organic Chemistry*: Chapter 36: Pericyclic Reactions II: Sigmatropic and Electro cyclic Reactions.

The only pericyclic reactions we have used so far have been cycloadditions: the Diels-Alder reaction in chapter 17 and 2 + 2 cycloadditions in chapter 33. Electro cyclic and sigmatropic reactions are also used in synthesis and, as each is the basis for a synthesis of five-membered rings, they are grouped together here.

Electro cyclic Reactions

An electro cyclic reaction is the formation of a new $\sigma$-bond across the ends of a conjugated $\pi$-system or the reverse. They thus lead to the creation or destruction of one $\sigma$-bond. Hexatrienes 1 can cyclise to six-membered rings 2 in a disrotatory fashion but we shall be more interested in versions of the conrotatory cyclisation of pentadienyl cations 3 to give cyclopentenyl cations 4. The different stereochemistry results from the different number of $\pi$-electrons involved.¹

The Nazarov Reaction

The Nazarov² is probably the most important of reactions like 3. The cation 6 is formed from a dienone 5 by protonation and cyclises to the allylic cation 7. Though this is presumably a conrotatory process, the stereochemistry is usually lost in the formation of the cyclopentenone 9.

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Thus the natural product damascenone 10, responsible in part for the smell of roses, cyclises in acid to the cation 11 that can lose a proton from one side only to give\(^3\) 12. The disconnection for the Nazarov reaction is of the single bond in the five-membered ring opposite the carbonyl group 12a.

The double bond in the ring can be part of a benzene ring so that Nazarov disconnection of 13 reveals an aromatic ketone that can surely be made by a Friedel-Crafts reaction on some derivative of the acid 16.

You might think of using the acid chloride 16; \(X = \text{Cl}\) with a Lewis acid and that might well be successful, but it turns out that reaction of the acid 16; \(X = \text{OH}\) with the ether 15 using polyphosphoric acid as catalyst does both the Friedel-Crafts and the Nazarov in one step. The yield is only 70\% but it is a very short synthesis.\(^4\)

Aromatic heterocyclic compounds such as the \(N\)-tosyl pyrrole 17 can also be used with anhydride catalysis (acid might destroy the pyrrole). Regioselectivity is determined by acylation next to the nitrogen\(^5\) and cyclisation follows.\(^6\)

In other situations, Lewis acids such as \(\text{AlCl}_3\) may be better. Disconnection of the tricyclic compound 21 is best at the middle ring and Nazarov is ideal as it gives a simple dienone 22. Though 22 has two enones, both are in rings so we should rather disconnect a bond between rings to give the synthons 23 and 24.
One reason for choosing this disconnection is because the lithium derivative 26 of dihydro-
pyran 25 is easily made and the enal 27 is the product of cyclisation of hexadienal. Oxidation of 28
(MnO₂ is good for the oxidation of allylic alcohols) and treatment with AlCl₃ gives 21 in high
yield. The remaining alkene in 21 is conjugated with the ether oxygen and the stereochemistry
is inevitably cis for two fused five-membered rings.⁷

![Chemical diagram]

**Sigmatropic Rearrangements**

A sigmatropic rearrangement is a unimolecular reaction 29 in which a σ-bond moves from one
place in a molecule to another. In these reactions there is no net change in the number of
σ-bonds. They are classified by numbering both ends of the old σ-bond ′1′ 29a and numbering
round in both directions to find the new σ-bond 30a. So this reaction 29 is a [3,3]-sigmatropic
rearrangement. The sum of the two numbers gives the size of the cyclic transition state⁶ 31.

![Chemical diagram]

This reaction does not create a ring but there is an important group of sigmatropic rearrange-
ments that make five-membered rings—the vinyl cyclopropane to cyclopentene rearrangement.

**The Vinyl Cyclopropane to Cyclopentene Rearrangement**

On heating, vinyl cyclopropanes 32 isomerise to cyclopentenes⁹ 33. This is a [1,3]-sigmatropic
rearrangement of 32a to 33a having a rather strained four-membered cyclic transition state 34. It
usually requires strong heating, typically >300°C. There is disagreement about the mechanism:
some people think it is concerted 32 and others that a C–C bond in the three-membered ring
splits 32b to give a diradical 35 that can reunitate to give 33.

![Chemical diagram]

So the cyclopropane 36 isomerises at high temperature, no doubt via the [1,3] shift to 37,
formation of the extended enol 38 and movement of the alkene into conjugation follows. The
product 39 was used in a synthesis of the natural product zizaene.¹⁰
The disconnection looks tricky but it is all right if you simply reverse the rearrangement, by drawing the mechanism for the imaginary reverse reaction. There may well be two possible starting materials. Thus cyclopentene 40, needed for a photochemical experiment, could be disconnected as 40a or 40b. There is no obvious way to continue from 41 but 42 has an enone that could be made from aldehyde 43 and some reagent for the enolate of acetone 44.

The aldehyde was made by alkylation of the nitrile 45 and reduction (actually using LiAlH₄, though we might prefer DIBAL), an HWE olefination and conversion of the ester 46 into the ketone 42. Finally, the rearrangement required 400 °C.

If there are heteroatoms in the molecule, the [1,3] shift can be catalysed by acids or Lewis acids. The heterocycle 49, needed for a synthesis of alkaloids from narcissi, is formed from the cyclopropyl imine 48 with HB₃ catalysis. The imine 48 comes from an aldehyde 47 made in the same way as 43.

Lower temperatures are enough with a strong Lewis acid like Et₂AlCl. The cyclopropane 52 comes from available dihydrofuran 50 by rhodium-catalysed carbene insertion. Rearrangement at very low temperatures gives the cyclopentene 53 that actually has three five-membered rings fused together.
[3,3]-Sigmatropic Rearrangements

We used the all-carbon Cope rearrangement 29 to introduce this section but now we want to feature the more useful Claisen rearrangements.\textsuperscript{14} The aliphatic Claisen 54 works for most substituents because an alkene is lost and a much more stable carbonyl group is formed 55. It doesn’t matter whether we have an aldehyde (X = H), a ketone, (X = R), an acid (X = OH), an ester (X = OR) or an amide (X = NR\textsubscript{2}), the reaction works well. The original Claisen rearrangement was the aromatic version 56 that gives an unstable non-aromatic intermediate 57 that quickly loses a proton to restore the aromatic ring and the product is a phenol 58.

The disconnection for the aromatic Claisen is to reverse the rearrangement. This is a little simpler than those we have seen so far as one C–C bond is broken 59 and one C–O bond made. But you must remember to turn the allylic system back to front. This is easily seen if the starting material is drawn as 59a with the dotted line representing a reconnection. The rest is a normal ether disconnection.

The allylic halide needed for the alkylation is easily made by some aldol or Wittig-style reaction to give 63 followed by reduction and conversion of OH to Br. Alkylation of phenols (pK\textsubscript{a} 10) with allylic halides is very easy as a weak base such as carbonate is enough and the Claisen rearrangement merely requires heating.\textsuperscript{15}

The aliphatic Claisen rearrangement is simpler in that there is no rearomatisation at the end but there is an ionic step first as the vinyl ether 67 has to be made and the easiest way to do that is from the allylic alcohol 65 by acetal exchange with another vinyl ether to give 66 and elimination to give 67. All these steps, including the rearrangement occur under the same conditions\textsuperscript{16} and the product is a γ,δ-unsaturated carbonyl compound 68.
The easiest way to see that a Claisen rearrangement might be useful is to look at the relationship between the alkene and the carbonyl group. A simple C–C disconnection suggests that allylation of an enolate 71 with allylic halide 70 would be a good method. But 70 will react at the wrong end of the allylic system so we need a method that turns the allylic system inside out and that is the Claisen rearrangement using 72 as the allylic alcohol.

Just as 65 gave 68, so 72 gives 69 except that we must work at a higher oxidation level, using an orthoester MeC(OEt)₃ to make the ketene acetal 74 and hence the ester 69 rather than the aldehyde 68.

**Stereoselectivity of the Claisen rearrangement**

If the new alkene has geometry, the Claisen rearrangement is very E-selective. Thus the allylic alcohol 75 gives just the E-unsaturated aldehyde 77. The transition state for the rearrangement is a six-membered ring 78 and has a chair conformation 79. All the substituents are hydrogen except for R which will prefer an equatorial position. If you look at the right-hand side of this diagram 79 you will see that the framework of the E-alkene is already in that conformation.

A good illustration is the synthesis of E-84 by Claisen rearrangement of 82 (R is a protecting group). Notice that neither a carbonyl group nor a furan ring interferes with the reaction. The next step in this synthesis of porphobilinogen, the porphyrin precursor, was an intramolecular Diels-Alder reaction between the new alkene and the furan ring.
An important reason for making new molecules is to use them in the construction of organic materials such as highly branched polymers. The tetrabromo compound 89 is one of these and remarkably it can be made by a Claisen rearrangement. The allylic alcohol 85 is made by the usual Wittig-reduction sequence and Claisen rearrangement with ethyl orthoacetate gives the unsaturated ester 86. Hydroboration now gives the lactone 67, reduction of the diol 88, and all the oxygen atoms are then transformed into bromides in a single operation. This compound was used to make tetra-amine and hence ‘dendrimers’—highly branched tree-like polymers.

The Claisen rearrangement can also be used to make amides if the dimethylacetal of DMF 91 is used to make the vinyl ether. So our final example is an introduction to the next chapter on six-membered rings where we shall use Birch reduction as a method of reducing aromatic compounds. Allylic alcohol 90 is made by Birch reduction of the aromatic compound and the Claisen rearrangement 92 has an extra feature. The rearrangement occurs across the top face of the ring so that the product 93 is a single diastereomer. You will notice that the other alkene moves into conjugation with the ester. This product was used in the synthesis of an alkaloid.

References

Six-Membered Rings

There are three general methods of making carbocyclic six-membered rings and each produces rings with a characteristic substitution pattern. The first uses carbonyl condensations and the best of these is the Robinson annelation\(^1\) (chapter 21). The disconnections are aldol 1 and conjugate (Michael) addition 2. The target molecule is a conjugated cyclohexenone.

\[
\text{aldol} \quad 1 \quad \xrightarrow{\text{1,5-diCO}} \quad \text{Michael} \quad 2 \quad \xrightarrow{\text{3,4-diCO}} \quad 3 + \quad 4
\]

The second method is the Diels-Alder reaction (chapter 17). The target molecule 5 also has a carbonyl group and an alkene but now only the alkene is in the ring. The carbonyl group is outside the ring and remote from the alkene. The simplest way to do the disconnection is to draw the mechanism of the imaginary reverse reaction 5a. Start your arrows on the alkene and go whichever way round the ring you prefer 5a or 5b.

\[
5 \quad \xrightarrow{\text{Diels-Alder}} \quad 5a \quad \xrightarrow{\text{Diels-Alder}} \quad 5b
\]

The third is partial or total reduction of an aromatic ring. Any catalogue lists a vast number of available substituted benzene rings. Saturated compound 8 can obviously be made by total reduction of 9 but it may not be obvious that partial reduction (Birch) allows the enone 11 also to be made from 9. Birch reduction is the only new method here so we shall revise the Robinson and the Diels-Alder and concentrate on Birch.

\[
8 \quad \xrightarrow{\text{total reduction}} \quad 9 \quad \xrightarrow{\text{Birch reduction}} \quad 10 \quad \xrightarrow{\text{FGI}} \quad 11
\]
Carbonyl Condensations: The Robinson Annelation

Tremendous improvements have been made in the Robinson annelation in recent times: organic catalysts have been developed, some giving single enantiomers of products (see Strategy and Control) and some, such as 12, giving very fast reactions and complete control over the stereochemistry of the aldol intermediate 13.

Neither starting material need be cyclic. Combination of the acyclic enone 14 and β-ketoester 15 with an amine catalyst gives high yields of 16 and good (>97:3) stereoselectivity. Both 13 and 16 can easily be dehydrated to the enones 1 or 17.

Other Ionic Cyclisations

The Robinson annelation is by no means the only ionic reaction that makes six-membered rings. Six-membered rings form easily so trapping a Nazarov intermediate (chapter 35) makes good sense. The Friedel-Crafts-like disconnection 18 suggests a most unlikely cation 19 until we realise that it would be formed in the Nazarov cyclisation of the dienone 20 whose synthesis is discussed in the workbook.

The catalyst used was TiCl₄ and the complex 21 cyclises in a conrotatory fashion so that the two Hs end up trans in the intermediate 22. Cyclisation to the activated para position of the benzene ring that is already attached to the bottom face of the five-membered ring gives the titanium enolate 23 and protonation puts the ethyl group in the more favourable ‘down’ position, anti to the nearer methyl group.

A similar cyclisation of an alkene derived from geranyl acetate 24 by dihydroxylation and formation of the epoxide 26 leads to a substituted cyclohexane 28. The Lewis acid ZrCl4 is used to open the epoxide and the alkene attacks intramolecularly 27 to give eventually the syn-compound 28 with both substituents equatorial. The alignment of the alkene and the epoxide in a chair conformation 27a is responsible for the diastereoselectivity.6 Note the regioselectivity: the less substituted end of the alkene attacks the more substituted end of the epoxide 27. These are just two examples of the very many ordinary ionic reactions that can be used to make six-membered rings.

The Diels-Alder Reaction

We established in chapter 17 that the Diels-Alder reaction offers exceptional control over all forms of selectivity and so it is one of the most important of all reactions used in synthesis.6 So when Nicolaou needed 29 for a synthesis of columbiasin A, he was prepared to go to some lengths to change 29 into a Diels-Alder substrate. It looks unpromising: neither ring has the alkene nor is there a carbonyl group in the right position. But the ketone in ring A could come from an enol ether 30 and the benzene ring B could come from a quinone by the reverse logic.

Making the Diels-Alder disconnection by drawing the mechanism of the reverse reaction 31a gives a new enol ether 32 and a quinone 33. The enol ether 32 is a derivative of the simple enone 34 and can be made by trapping the kinetic enolate with a suitable silyl group.

Nicolaou preferred7 to use the t-BuMe2Si group for ‘R’ in 32 and found that the Diels-Alder with 32a went with complete regio- and stereo-control. The stereocontrol is not important as the
next step will destroy it but the regiocontrol is important and interesting. The OMe group on the quinone is conjugated with the lower carbonyl group so the ‘para’ orientation is between the \( t\text{-BuMe}_2\text{SiO} \) group and the other carbonyl group. For the same reason the right-hand alkene in the quinone is less electrophilic. It is remarkable that these small factors have such a big effect.

Arematisation to 29 simply requires enolate formation and methylation to give 30. Hydrolysis of the silyl enol ether with CF\(_3\)CO\(_2\)H gave the ketone 29.

A Synthesis of the Guanacastepene Skeleton

The guanacastepenes are antibiotics from a rare Costa Rican fungus and have the basic skeleton 35. This has five-, six- and seven-membered carbocyclic rings but there is a hint of Diels-Alder possibilities about it in that ring C is a cyclohexene. In fact Shipe and Sorensen\(^8\) chose 36 as a key intermediate but no direct Diels-Alder disconnection looks likely. Does it help if we reconnect to the lactone 37?

It does because 37 can be made by a Baeyer–Villiger rearrangement from the ketone 38 as the more substituted centre migrates with retention. We have the carbonyls outside the ring (the two CO\(_2\)Me groups) but we cannot have the carbonyl group on the ring. So we change it to an enol ether 39 and Diels-Alder disconnection reveals two simple starting materials 40 and 41.
The diene 41 was made from the cyclohexenone 42 (easily made by intramolecular aldoi) by kinetic enolate formation and silylation. Diels-Alder reaction followed by hydrolysis of the intermediate 39; R = SiMe3 gave the ketone 38 and Baeyer–Villiger oxidation gave the lactone 37. Notice the very high yields, especially in the rearrangement, leaving no doubt as to the total control over selectivity. Opening of the lactone 37 in acidic methanol gave the key intermediate 36 with ring C complete. The original six-membered ring in 42 has disappeared to be replaced by a new six-membered ring formed by the Diels-Alder reaction.

Reduction of Aromatic Compounds

Total reduction of a benzene ring requires pressure and active catalysts and is more easily done industrially than in the lab. We might choose such a method if substituents that are unhelpfully related in an aliphatic compound such as 43 and 45 may be conveniently related in the aromatic equivalents 44 and 46. This usually means a ‘para’ relationship in the target molecule.

The phenol 44 can obviously be made by a Friedel-Crafts reaction and the amine 45 by reduction of the nitro group in 46 as well as of the benzene ring. Since OH and OEt are both o, p-directing, the syntheses are simple.9

A more interesting case is the antispasmodic drug dicyclomine 50 with its two six-membered rings. Removing the ester group 51 makes it easier to see that one ring could be derived from a benzene ring. If we also change the acid to a nitrile 52, the other six-membered ring can be made by alkylation. Ring B cannot be made by reduction as it has a quaternary centre.
The synthesis is straightforward. The nitrile \( \text{53} \) is alkylated and treated directly with acidic ethanol to give the ester \( \text{54} \) so that the new ester \( \text{55} \) can be made by ester exchange. The reduction of the benzene ring is the last step.\(^{10}\)

\[
\begin{align*}
\text{PhCN} & \xrightarrow{\text{NaNH}_2} \text{52} \quad \text{EtOH} \quad \xrightarrow{\text{H}^+} \quad \text{PhCO}_2\text{Et} \quad \xrightarrow{\text{base}} \quad \text{PhCO}_2\text{Et} \quad \xrightarrow{\text{H}_2, \text{PtO}_2} \text{50} \\
\text{53} & \quad \text{54} & \quad \text{55} & \quad \text{50}
\end{align*}
\]

**Partial (Birch) Reduction of Benzene Rings**

Birch reduction\(^{11}\) is the partial reduction of aromatic rings by solvated electrons produced when alkali metals dissolve (and react) in liquid amines. Typical conditions are sodium in liquid ammonia or lithium in methyamine. These electrons add to benzene rings to produce, probably, a dianion \( \text{57} \) that is immediately protonated by a weak acid (usually a tertiary alcohol) present in solution. The anions in the supposed intermediate \( \text{57} \) keep as far from each other as they can so the final product is the non-conjugated diene \( \text{58} \). It is important to use the blue solution of solvated electrons before it reacts to give hydrogen and Na\( \text{NH}_2 \).

\[
\begin{align*}
\text{Na}^+ & \xrightarrow{\text{NH}_3(l)} \text{Na}^\ominus + e^- \text{((NH}_3)_n \\
\text{56} & \xrightarrow{2e} \text{57} & \xrightarrow{\text{t-BuOH}} \text{58}
\end{align*}
\]

If a benzene ring substituted with an electron-donating group (typically R or RO) is reduced in this way, the dianion now keeps away from the electron-donating group \( \text{60} \) so that the product from anisole \( \text{59} \) is the enol ether \( \text{61} \). Hydrolysis under mild conditions gives the unconjugated enone \( \text{62} \), though more vigorous conditions move the alkene into conjugation.

\[
\begin{align*}
\text{MeO} & \xrightarrow{2e} \text{MeO} \quad \text{t-BuOH} \\
\text{59} & \quad \text{60} & \quad \text{61} & \quad \text{62}
\end{align*}
\]

On the other hand, an electron-withdrawing substituent, particularly a carbonyl group \( \text{63} \), will attract the anion \( \text{64} \) and again we get a non-conjugated product. If the acid \( \text{63} \); R=H is used, the less stable, non-conjugated anion in the intermediate \( \text{64} \); R=H captures the proton from the acid giving the enolate dianion \( \text{66} \) as the immediate product. This can be combined with electrophiles such as alkyl halides as we shall see.

\[
\begin{align*}
\text{RO}_2\text{C} & \xrightarrow{2e} \text{RO}_2\text{C} \quad \text{t-BuOH} \\
\text{63} & \quad \text{64} & \quad \text{65} & \quad \text{63; R=H} & \xrightarrow{2e} \text{66}
\end{align*}
\]

The epoxide \( \text{67} \) obviously comes from the diene \( \text{68} \) and hence by Birch reduction from \( \text{69} \). In the reduction \( \text{68} \) has both anions away from the alkyl substituents but the alternative \( \text{70} \) would be less stable as the dianion.
Sodium in liquid ammonia does the reduction and the more substituted, and hence more nucleophilic, alkene reacts with the peroxycacid to give the target molecule.\textsuperscript{12} Peroxyphthalic acid 71 was used as the oxidant.

\[ \text{Na, NH}_3(l) \rightarrow \text{MeOH} \rightarrow \text{RCO}_2H \rightarrow \text{CO}_2H \]

An Alkaloid Synthesis

Guillou and her team\textsuperscript{13} needed 73 for a synthesis of the cytotoxic alkaloid maritidine 72. Reductive amination looks a good bet with the amine 74 combining with the aromatic aldehyde.

\[ \text{MeO} \rightarrow \text{MeO} \rightarrow \text{MeO} \rightarrow \text{MeO} \]

The amine 74 certainly looks like a product of Birch reduction of the simple \textit{para}-disubstituted benzene 76 via the enol ether 75.

\[ \text{NH}_2 \rightarrow \text{NH}_2 \rightarrow \text{NH}_2 \rightarrow \text{NH}_2 \]

It turned out that the Birch reduction of 76; R\text{=Me} had already been done in 1958 by the standard sodium in liquid ammonia procedure but gave a low yield (\textasciitilde20\%) of the conjugated ketone as the first compound isolated.\textsuperscript{14} Guillou and her team improved on this by using lithium and \textit{t}-BuOH at low temperature to give 78 in nearly quantitative yield.\textsuperscript{15} The reductive amination needed only NaBH\textsubscript{4} in MeOH at room temperature and gave 78\% of the enol ether of 73 from which the synthesis of 72 was completed.

\[ \text{NH}_2 \rightarrow \text{OMe} \rightarrow \text{OMe} \rightarrow \text{OMe} \rightarrow \text{OMe} \]
Reduction of Aromatic Carboxylic Acids

In the last chapter we used 79 in an aliphatic Claisen rearrangement to make an anisatin intermediate. You can now see that 79 was made by Birch reduction of 80. With a Friedel-Crafts in mind, we change the alcohol for a ketone 81 and start with 82.

This plan looks good but in fact the CO₂Me group proved incompatible with the reactions so they made the alcohol 86 without it. Using PPA for the Friedel-Crafts reaction meant that the methyl ester 84 could be cyclised directly. The large reducing agent preferred to approach the flat five-membered ring from the side opposite the methyl group.

The next step is a directed lithiation—this subject is treated in Strategy and Control—to give the acid 88 via the lithiated species 87. Birch reduction moves the two alkenes next to the electron-donating group (the three alkyl groups) and away from the electron-withdrawing group (CO₂H) 79. The rest of the synthesis appears in chapter 35.

Birch reduction of acid derivatives is even more productive if the first-formed enolate (as 66) is used as a nucleophile. Our example also links this chapter with the last as a Cope rearrangement is featured. A group of alkaloids including mesembrine have the bicyclic structure 89. Removing the structural nitrogen atom by standard disconnections (chapters 6 and 8) leaves the carbon skeleton 91 that does not immediately look a Birch reduction product.

The aromatic precursor is 92 reduced and then alkylation of the enolate anion 93 gives 94, which was hydrolysed in aqueous HCl to the ketone 95. In fact the ‘NR₂’ group was chiral and 95 was indeed one enantiomer. So we have added a three-carbon side chain but in the wrong place.
The allyl group is moved to the right position 96 on heating in 1,2-dichlorobenzene by a Cope rearrangement. This occurs because the conjugation of the alkene with the two carbonyl groups in 96 is more effective than that with the aryl group in 95. Ozonolysis liberates the aldehyde 97 and the reductive amination is followed by spontaneous Michael addition to close the five-membered ring 98. All that remains is to remove the amide group from the β-ketoamide 98 by hydrolysis and decarboxylation.

Each of these methods of making six-membered rings has its own special characteristics and taken together they are versatile and powerful. They are not the only ways to make six-membered rings but they are the ones you should consider first for any new problem.

References

General Strategy C: Strategy of Ring Synthesis

This chapter collects ideas from the last eight chapters on ring synthesis and puts them into the context of our general approach to strategy. No grand new principles are needed as we shall use the same guidelines already established in chapters 11 and 28 with one or two extra guidelines for cyclic compounds.

Cyclisation to Control Selectivity

Cyclisations are easy. In chapters 7 and 21 we saw that the type of control needed to make open chain compounds is often unnecessary for cyclisations as intramolecular reactions usually take precedence over intermolecular. If, therefore, a difficult step needs to be used in a synthesis, it is good strategy to make it a cyclisation.

Corey wanted to make the ketone 2 as an intermediate in the synthesis of the marine allomone 1 (a substance exuded by an organism and used by a predator). Disconnection 2a (Friedel-Crafts alkylation) would be easy to realise as it occurs para to the powerful o,p-directing OMe group. But disconnection 2b is more difficult as it must occur meta to OMe. So we should make the formation of bond b a cyclisation and disconnect it first.

The position of the branchpoint in 3 suggests a C–C disconnection with conjugate addition in mind and we can choose between 3a and 3b.

The synthesis starts with ortho-cresol 6 which is methylated and the easy substitution para to the OMe group puts in the aldehyde by a Vilsmeier acylation. A Knoevenagel-style aldol
gives the unsaturated acid 4 and copper-catalysed addition of the Grignard to the methyl ester 9 completes the carbon skeleton. Cyclisation with PPA occurs at the less substituted position para to the methyl group.

Early Disconnection of Small Rings

It is generally good strategy to disconnect a small (three- or four-membered) ring at an early stage or at least consider how the small ring might be made. The special methods needed for small rings often dominate the strategy. So for compound 11, having three- and six-membered rings and two ketones, one protected as an acetal, carbene addition to the alkene 12 looks a good bet and this should immediately suggest a Birch reduction for the six-membered ring.

The methyl ether was chosen for 14 and it turned out that the enol ether 13 could be converted directly to the acetal 12. It is essential to have one ketone protected before the other is introduced. The diazoketone (with copper catalysis) was used to put in the three-membered ring.

Four-Membered Rings and New Reagents for Given Synthons

The tricyclic ketone 15 with four-, five- and six-membered rings must be made by a 2 + 2 photochemical cycloaddition (chapter 32), the small ring again dominating the strategy. There are two such disconnections 15a and 15b, each starting material 16 and 17 having an enone and an isolated alkene. We need not be concerned about the regio- or the stereoselectivity as only one cyclisation is possible in each case.
There is no immediately obvious disconnection of 17 but there is a strategic bond in 16 whose disconnection would make for a short synthesis. Now we have a new problem: neither polarity of disconnection 16a is entirely satisfactory. We can easily think of reagents for 18 (Grignard reagent) or 20 (alkyl halide) but what about 19 and 21? Yet we persist with this strategy because the bond between the ring and the chain is strategic.

\[
\begin{align*}
18 & \quad + \\
19 & \quad \xrightarrow{\text{C--C}} \\
16a & \quad \xrightarrow{\text{C--C}} \\
20 & \quad + \\
21 & 
\end{align*}
\]

At least 19 has the natural polarity of the enone but conjugate addition would lose the alkene so we need to add a leaving group at the site of the plus charge 22. One possibility is an enol ether 23 as these are easily made from 1,3-diketones 24 and a suitable alcohol.

\[
\begin{align*}
19 & \quad \xrightarrow{X} \\
22 & \quad \xrightarrow{\text{RO}} \\
23 & \quad \xrightarrow{\text{ROH}} \\
24 & 
\end{align*}
\]

Ethanol was used to make the enol ether 23; \( R = \text{Et} \), the addition of the Grignard 25 was successful and the cycloaddition went in excellent yield.\(^3\)

\[
\begin{align*}
24 & \quad \xrightarrow{\text{EtOH}} \\
23; \ R = \text{Et} & \\
25 & \quad \xrightarrow{\text{MgBr}} \\
16 & \quad \xrightarrow{\text{hv}} \\
15; \ 92\% \ yield & 
\end{align*}
\]

A more challenging example is the isomeric ketone 26. The same two disconnections reveal two enones 27 and 28. This time the regioselectivity of the \( 2 + 2 \) cycloadditions is ‘wrong’ in both cases but again we are not unduly concerned as they will be intramolecular.

\[
\begin{align*}
26a & \quad \xrightarrow{2+2} \\
27 & \\
26b & \quad \xrightarrow{2+2} \\
28 & 
\end{align*}
\]

We have to choose between making a five-membered ring 28 or a six-membered ring 27 and we shall choose the latter since it offers more possibilities. Disconnection at the branchpoint gives synthon 20 that can simply be an alkyl halide. The nucleophilic synthon 29 could be an enolate providing we move the alkene out of conjugation 30 and this leads back to a Birch reduction product.
Experiments showed\(^4\) that the free acid 32 could be used for the Birch reduction and the product alkylated without work-up. Treatment with aqueous HCl hydrolysed the vinyl ether, decarboxylated the resulting \(\beta\)-ketoacid, and moved the alkene into conjugation 27. As expected, the photochemical cycloaddition gave a high yield of the right positional isomer\(^5\) 26. This chemistry was used by Mander in his synthesis of gibberellic acid.\(^6\)

![Chemical structures and reaction schemes](http://www.chem4all.vn)

**Alternative Disconnections**

We should emphasise that general guidelines on strategy suggest routes that you should try first but are less important than the target molecule under discussion. We have suggested that small rings may dominate strategy so our first disconnection a of the ketone 36 leads to the obvious addition of a carbene to the alkene 37. Unfortunately, the alkene 37 is a tautomer of \(\alpha\)-naphthol and cannot be made. The six-membered ring must be disconnected first 36b.

![Chemical structures and reaction schemes](http://www.chem4all.vn)

Any pair of the three bonds in the cyclopropane ring such as 35a could now be disconnected but none is very favourable. We should much rather use a diazacarbonyl compound such as 42 to make the carbene. That will mean chain extension after cyclopropane formation.

![Chemical structures and reaction schemes](http://www.chem4all.vn)

So, in this instance, cyclopropane formation is the first rather than the last step in the synthesis. Addition of ethyl diazoacetate 42; \(R = \text{Et to styrene} \) 41 gave a mixture\(^7\) of cis and trans isomers of \(40, R = \text{Et. Only the cis isomer will be able to cyclise so separation}\(^8\) of the free acid gave 34% yield of cis-43. Chain extension by the Arndt–Eistert procedure\(^9\) (chapter 31) gave cis-35 and the acid chloride duly cyclised to 36.
Regioselectivity Suggests a Change of Strategy

Raphael	extsuperscript{10} needed the diketone 44 for his synthesis of strigol (a compound that triggers the germination of the parasitic plant witchweed). At first sight a route via electrophilic substitution and the aromatic ketone 45 looks promising. But the regioselectivity is wrong. The OH dominates and directs ortho. Indeed it was already known	extsuperscript{11} that the product of reaction between 46 and 47 was isomeric 48.

A better strategy emerges from disconnection of the six-membered ring 44a. Aldol disconnection reveals a triketone with two 1,4-dicarbonyl relationships 49. An ideal disconnection would correspond to a reagent for the d	extsuperscript{1} synthon 51 that can do conjugate additions to both 50 and 52.

This worked well with nitromethane 53 as the d	extsuperscript{1} reagent. Conjugate addition	extsuperscript{12} to 50 and then 52 gave the diketone 55 that cyclised to 56 in acid. Hydrolysis of the nitro group with TiCl	extsubscript{3} (chapter 22) gave the required ketone	extsuperscript{13} 44.

A Synthesis of the Anticancer Compound Taxol	extsuperscript{®}

Taxol, the anti-cancer compound from yew trees	extsuperscript{14} (Taxol spp.) has two six- and one eight-membered carbocyclic rings 58. Nicolaou	extsuperscript{15} saw that two C–C disconnections would give two simple six-membered ring precursors 57 and 59.
Compound 57 looks like a Diels-Alder adduct but the ketone must be changed 60 and it is much simpler if one alkoxy group is removed 61. Diels-Alder disconnection then gives the known dienophile 62 and a functionalised diene 63.

Nicolaou found that the closely related diene 64 was known from some basic chemistry, already reported from the 1960s, using just aldol, Grignard reagents and elimination.\textsuperscript{16}

This part of the synthesis went very well: the Diels-Alder reaction required a high temperature in a sealed tube but gave an excellent yield of 61.

Hydrolysis and reacetylation gave the ketone 67, which was protected and oxidised with SeO\textsubscript{2} to give the enone 68. Reduction and deprotection gave 57; R\textsuperscript{1}=H. The other starting material 59 was also made by a Diels-Alder reaction as described in the workbook.

\textit{A Synthesis of Sarracenin}

For a remarkable strategy we need look no further than a synthesis of sarracenin 69 by Yin and three Changs.\textsuperscript{17} The rings in 69 are all heterocyclic but the starting material for the synthesis
contains only carbo cyclic rings 73. Sarracenin contains several 1,1-diX relationships and they can be disconnected in any order. So disconnection of the acetal 69 reveals an alcohol, an aldehyde and a hemiacetal 70 that can be disconnected to reveal a second aldehyde and an enol 71. Rewriting the enol as an aldehyde we arrive at a compound with no rings 72 but lots of stereochemistry, better drawn as 72a. There are several 1,5-diCo relationships here but the normal conjugate addition approach to these would make stereochemical control difficult. So it was decided to use the reconnection strategy normally used for six-membered rings (chapter 36). In fact the starting material was 73 where X is a heteroatom.

The synthesis of this starting material 73; X = SMe also uses interesting strategy. The first step was a Diels-Alder reaction between a cyclopentadiene 77 and the dienophile 62 used by Nicolaou in his taxol® synthesis. The diene was made from the anion of cyclopentadiene 74 and ethyl formate, and the enolate 76 transformed into the enol ace late 77. Diels-Alder addition of 62 and hydrolysis of the enol ester gave the adduct 78.

The aldehyde 78 was protected as an acetal 79 and the ketone 80 revealed by hydrolysis. Methylation of the lithium enolate occurred on the less hindered bottom face 81 to set the scene for the remarkable chemistry to come.

Ring expansion by chemistry discussed in the workbook gives 82 whose enolate is sulphenylated 83 and cyclised in acid solution with hydrolysis of the acetal to give 84 and the five-membered rings in 73 start to appear.
Mesylation of the free OH sets up an ideal arrangement for a base-catalysed fragmentation and suddenly the two fused five-membered rings are there. Acid moves the alkene into the more stable position and esterification gives 73. Notice that there are three five- and one seven-membered ring in 84; fragmentation cleaves one five- and the seven-membered ring leaving the two rings that we want. One C–C bond of one of the five-membered rings was made in the original Diels-Alder reaction while the other five-membered ring was the diene.

References

Strategy XVII: Stereoselectivity B

Background Needed for this Chapter References to Clayden, Organic Chemistry:
Chapter 33: Stereoselective Reactions of Cyclic Compounds; Chapter 34: Diastereoselectivity.

This chapter follows on from chapter 12 where we introduced some basic ideas on stereoccontrol. Since then we have met many stereospecific reactions such as pericyclic reactions including Diels-Alder (chapter 17), 2 + 2 photochemical cycloadditions (chapter 32), thermal (chapter 33) cycloadditions, and electrocyclic reactions (chapter 35). Then we have seen rearrangements where migration occurs with retention at the migrating group such as the Baeyer–Villiger (chapters 27 and 33), the Arndt–Eistert (chapter 31) and the pinacol (chapter 31).

We have expanded our collection of stereoselective reactions even more in the making of alkenes by the Wittig reaction (chapter 15), from acetylenes (chapter 16), by thermodynamic control in enone synthesis (chapters 18 and 19) and in sigmatropic rearrangements (chapter 35). We have seen that such E- or Z-alkenes can be transformed into three-dimensional stereochemistry by the Diels-Alder reaction (chapter 17), by electrophilic addition (chapters 23 and 30), by carbene insertion (chapter 30) and by cycloadditions to make four-membered rings (chapters 32 and 33).

With so many methods of stereochemical control now available, it is time to look in general at syntheses where stereochemistry dominates the strategy. This is a very large subject and this chapter deals only with diastereo-selectivity. Our Strategy and Control expands on diastereoselectivity and the synthesis of single enantiomers.

Synthesis of Molecules with Many Chiral Centres

The Prelog–Djerassi Lactone

At the start of the analysis when you have done no more than recognise the PGs and note special features (such as rings) or easy disconnections, note also the number of chiral centres and their relationship to each other. The Prelog–Djerassi lactone 1 is an important intermediate in the synthesis of macrolide antibiotics. It has a six-membered lactone ring and a separate carboxylic acid. More to the point, it has four chiral centres 1a. Three (1–3) are adjacent and one (5) separate. We might say that the three adjacent centres should be easy to control because they are next to each other but that we might have trouble with C-5. Another way to look at it is to say that the three round the six-membered ring (2, 3 and 5) should be easy to control, as the
conformation of six-membered rings is so well understood, but that we might have trouble with C-1. The most obvious disconnection 1b, that of the lactone, doesn’t help much as 2 is now open-chain.

One appealing strategy is to set up C-5 and one of the three adjacent centres initially and then control the other two from that one. One disconnection that leads to immediate simplification 1c uses the 1,3-diX relationship between the functional groups. Aldol disconnection of 3 leads to the nearly symmetrical 4 with a 1,4-diCO relationship. Differentiating the carbonyl groups would be easy with the cyclic anhydride 5 and this was the chosen starting material.²

Since 5 is symmetrical (it has a plane of symmetry and is achiral) it doesn’t matter which carbonyl reacts so the sequence of symmetry breaking with ethanol, formation of the acid chloride 7 and reduction of the acid chloride gives the aldehyde 8 ready for the aldol step.

Bartlett and Adams² chose to use a Wittig reaction to make the alkene 3 in excellent yield and conditions were found experimentally to cyclise 3 to 1. The product was a mixture of 1 and its C-2 epimer but these could be separated by chromatography.

There are many more syntheses of this important compound and interesting strategies include a reconnection of the 1,7-related carboxylic acids 2a to offer a seven-membered ring compound as starting material.³ 10.
The methyl group at C-2 was introduced by cuprate addition to the enone 11 on the face opposite the large TBDMS group and the lithium enolate 12 trapped with Me₂SiCl to give 13. This silyl enol ether was ozonised, reduced, and the silyl group hydrolysed whereupon oxidation gave spontaneous lactonisation to 1 in 12% yield from 11.

A lactone invites a Baeyer-Villiger rearrangement, in this case from the cyclopentanone 14. The more highly substituted group migrates (chapter 27) but which is that? The ambiguity is easily removed by disconnecting the one methyl group that can easily be added by alkylation of an enolate. Now the side-chain carbon must migrate and does so with retention of configuration. This ketone 15 can be made in various ways. A review article has more details and many more syntheses.

Using the Diels-Alder Reaction

A similar stereochemical problem arises with the dialdehyde 16 needed for alkaloid synthesis. Reconnecting the 1,6-diCO relationship 17 and removing the acetal reveals an obvious Diels-Alder adduct 18 from the enone 19 and butadiene. The only substituent on the nearly flat enone 19 is the methyl group and the Diels-Alder reaction does indeed give the right diastereomer.
Stereochemical Control in Folded Molecules

cis-Fused smaller rings (four-, five- and six-membered) have folded conformations rather like a half-opened book. The 4/4 fused system 20 has nearly flat rings and looks just like a book 20a. It has two faces: the inside, concave or endo-face and the outside, convex or exo-face. Reagents much prefer to approach from the outside and it can be difficult to get substitution on the inside. So the 5/4 fused ketone 21 forms an enolate that is alkylated on the outside face. Notice that this means the new substituent is on the same face as the ring-junction hydrogens 22.

![Diagram of stereochemical control in folded molecules]

The anti-cancer compound coriolin 23 has three fused five-membered rings and two epoxides. Notice that the 3/5 and both 5/5 ring fusions are cis. There have been many syntheses of coriolin, most using stereochemistry from folded precursors.\(^7\) We shall feature a couple of examples. Matsumoto’s synthesis involves the hydroboration of alkene 24. The addition of borane is cis 25 and the boron is replaced by OH with retention of configuration to give 26. The hydroboration occurred on the outside of the molecule, on the same face as the ring junction hydrogens.\(^8\)

![Diagram of coriolin synthesis]

Ikegami’s synthesis has two steps of particular interest. Allylation of the enolate of 27 puts the new allyl group on the outside and forces the old methyl group onto the inside 28. The planar enolate is an intermediate. The final step puts on both epoxides on the outside of the molecule from the dieneone 29 mainly through complexation of VO\(^+\) with one of the free OH groups.\(^9\) This also makes both the right-hand 5/5 and the 5/3 cis fused.\(^10\)

![Diagram of Ikegami's synthesis]

We discussed the synthesis of tricyclic 30 in chapter 32 (compound 12 there) but did not discuss how the stereochemistry of the ring junctions was proved. Rings A/B form a folded system so, when the ketone is reduced with NaBH\(_4\), we expect the reagent to approach from the exo-face, on the same side as the ring junction H atom. In fact the lactone 32 was isolated.\(^11\) This
compound could be made only if the OH was on the same side of the molecule as the CO₂Me group so 31 must have the structure predicted and 30 must have the structure shown.

When we come to two six-membered rings fused together 33, it is not so obvious that there is an inside and an outside, but if both rings have the chair conformation 33a there is an inside and an outside. Even if there is only one ring-junction substituent 34 there is still a distinction.

A clear example is the catalytic reduction of the Robinson annelation product 36. Hydrogen adds to the top face of the alkene to give the cis-fused system 35. The point is that the alkene must sit on the catalyst surface and that is much easier on the top face (cf. 34). The axial methyl group at the ring junction is small compared with the other ring. But if the reagent approaches on the other ring next to the axial methyl group, as in borohydride reduction to give 37, it can attack from the bottom face.

A Synthesis of Copaene

The strange terpene copaene 38 has two six-membered rings with a four-membered ring trapped between them. Heathcock chose to put in some functionality 39 to help disconnections. Approaches based on 2 + 2 photochemical cycloadditions are unlikely to help: starting materials will be 10-membered rings with two trans alkenes 40.
A disconnection of just one of the bonds in the four-membered ring might use the enolate of the ketone to displace a leaving group X 41 and we have a much more helpful cis-decalin 41a.

With X and OH next to one another, an epoxide 42 looks a good bet. This would have to come from an alkene 43 and there must be a possibility of getting this from the Robinson annelation product 36 whose reduction we have just been discussing.

Both reductions (of C=O and C=C in 36) are needed and 37 was chosen as the starting material. Tosylation provided the leaving group 44 and the hydrogenation gave the expected selectivity. The equatorial tosyl group is more-or-less in the plane of the alkene and has little effect. Elimination can go only one way and we have 43 in a few steps.

The ketone had to be protected before epoxidation (avoiding the Baeyer–Villiger reaction?) and epoxidation then occurred on the outside of the folded molecule 47.

The epoxide evidently could not be used as the leaving group for the cyclisation so it was opened with benzylxide anion 48 and activated by tosylation 49. After deprotection, enolate cyclisation gave 50 from which copaene was made. There are two possible enolates from 49: the other would also give a four-membered ring if it cyclised but it is too far away.
The epoxide must open the epoxide to give a trans diaxial product 48a by attacking the less hindered end of the epoxide. This is inevitably from the endo face but attack at the other end of the epoxide would have to be from right inside the fold. Being a cis decalin, the product can equilibrate to the equatorial conformer 48b and the arrangement for cyclisation is perfect 51.

**Summary of Stereoselectivity on Folded Molecules**

Reagents, whether electrophilic or nucleophilic, prefer to approach the 'outside' or 'exo' face of folded molecules. These are cis-fused four-, five-, or six-membered rings. If a substituent is needed on the 'inside' or 'endo' face, it must be added first, that is disconnected second 54, as in the synthesis of the ketone 54. If there is only one substituent and it is endo, R² can be H.

**The Synthesis of Juvabione**

Juvabione 55 is a juvenile hormone mimic produced by the balsam fir as a defence against bugs. It prevents the larvae metamorphosing into adults. It has a six-membered ring and two adjacent chiral centres, one on the ring and one outside. The only obvious disconnection is of the unsaturated ester that gives a tricarbonyl compound 56 with a 1,6-diCO relationship. Reconnection leads back to juvabione but the other gives a different cyclohexene 57. No doubt this compound could be made but it does not suggest any way of controlling the stereochemistry.
A more drastic series of disconnections removes the isobutyl side chain 55a and then replaces the unsaturated ester with a ketone that appears to be on the ‘wrong’ carbon atom.\(^\text{13}\)

\[
\begin{align*}
\text{55a; } R &= \text{r-Bu} \\
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & \overset{\text{acylation}}{\longrightarrow} & \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} & \overset{\text{FGI}}{\longrightarrow} & \begin{array}{c}
\text{O} \\
\text{X}
\end{array}
\end{align*}
\]

The reason for this becomes plain when you see that the new 1,6-diCO relationship does allow a very interesting reconnection. Adjustment of the oxidation state allows a reconnection to a lactone 61 that should be the product of a Baeyer–Villiger rearrangement on the ketone 62.

\[
\begin{align*}
\text{59} & \overset{\text{FGI}}{\longrightarrow} \text{50} \overset{\text{1,6-diO}}{\longrightarrow} \text{52} \overset{\text{Baeyer-Villiger}}{\longrightarrow} \text{62}
\end{align*}
\]

Now all three chiral centres are in a rigid framework 62a making it easier to control them. An alkene was introduced and you might think Schultz and Dittani were going to do an aldol disconnection 63 next. The diketone 64 is symmetrical and might well cyclise to 63.

\[
\begin{align*}
\text{62} & \overset{\text{FGA}}{\longrightarrow} \text{62a} \overset{\text{aldol}}{\longrightarrow} \text{63} \overset{\text{enolate}}{\longrightarrow} \text{64}
\end{align*}
\]

However, that was not how they made 63. They preferred a method we met in chapter 37 where a cyclohexenone was used in alkylation. Here there will be three alkylations of the enol ether 68, one with a nucleophile and two with electrophiles. So the disconnections cleave a C\(_3\) side-chain in two alkylations 63a and 66 with a nucleophilic addition of a methyl group in between.

The first few steps used 67; X = I, Y = Cl to ensure faster reaction at one end. The intermediate 66; X = Cl did not cyclise in good yield, but replacing Cl with the better leaving group I ensured an excellent cyclisation. Note that although we said in chapter 37 that such enol ethers had to be symmetrical, this alkylation of 68, followed by addition of MeMgBr and rearrangement gives only one isomer of 65.
The hydrogenation of 63 occurred quantitatively and with high stereoselectivity (25:1 in favour of 62). The regioselectivity was similarly good in the Baeyer-Villiger rearrangement (12:1) in favour of 61 over the isomeric lactone. Attempts to convert the lactone directly to 60; X = i-Bu gave only low yields.

Cleavage of the lactone with methanol and protection of the OH group with the bulky t-BuMe₂Si group gave 69 which did react cleanly with i-BuMgCl to give the ketoae 70 in 90% yield from 61. Now the transformation of 70 into juvabione follows Ficini’s synthesis.¹⁴

Protection of the free ketone 70 as the acetal and desilylation with fluoride give the alcohol 71, which was oxidised to the ketone 72 with Cr(VI) in the form of pyridinium chlorochromate (PCC).

The new ketone can be used to add the ester group regioselectively to the less hindered side (though this is not important) and the ketone is reduced to a mixture of epimers of the alcohol 73. Tosylation and elimination give the conjugated alkene by the E1cB mechanism so that the stereochemistry of the OTs group is irrelevant. Deprotection gives juvabione 65.
You may well think that this is a long synthesis but other shorter ones fail to control the stereochemistry. The shortest\textsuperscript{15} gets quickly to the enone 75 by Diels-Alder and HWE reactions but the stereoselectivity of the reduction is only moderate.

\[
\text{\begin{array}{c}
\text{\textbf{74}} \\
\text{CO}_2\text{Me}
\end{array}} \xrightarrow{\text{NaH, DMSO}} \text{\begin{array}{c}
\text{\textbf{75}} \\
\text{74\% yield, 9:1 E:Z}
\end{array}}
\]

Birch’s synthesis falls down at the first step, a Diels-Alder reaction between the diene 76 and an enone gives the whole skeleton of juvabione but as a 1:1 mixture of \textit{exo} 77 and \textit{endo} 78 isomers. It is also a long way from these compounds to the final product.\textsuperscript{16}

\[
\text{\begin{array}{c}
\text{\textbf{76}} \\
\text{OMe}
\end{array}} \xrightarrow{180^\circ \text{C}} \text{\begin{array}{c}
\text{\textbf{77}} \\
\text{OMe}
\end{array}} + \text{\begin{array}{c}
\text{\textbf{78}} \\
\text{OMe}
\end{array}}
\]

Stereochemistry is both the most difficult and the most interesting aspect of the design of organic syntheses. In recent years great advances have been made in diastereoselectivity\textsuperscript{17} and enantioselectivity.\textsuperscript{18} These themes are pursued in \textit{Strategy and Control}.\textsuperscript{19}

\textbf{References}

Aromatic Heterocycles

Background Needed for this Chapter Reference to Clayden, Organic Chemistry: Chapters 43 and 44: Aromatic Heterocycles, Structures, Reactions and Synthesis.

Aromatic heterocycles come in many shapes and forms. They may be five-membered rings with one or two heteroatoms such as furan 1, imidazole 2 or thiazole 3. They may be six-membered rings such as pyridine 4 or pyrimidine 5 or even have two rings fused together such as indole 6 or isoquinoline 7. Substituted versions are important in pharmaceuticals, agrochemicals, perfumery, food and colour chemistry. Encyclopaedias and books have been written on this vast subject as more than half of all known organic compounds are aromatic heterocycles. This chapter is a brief introduction to the general strategies available for the synthesis of aromatic heterocycles.

![Chemical structures]

1; furan 2; imidazole 3; thiazole 4; pyridine 5; pyrimidine 6; indole 7; isoquinoline

Carbon–Heteroatom Disconnections

Many heterocyclic rings are made by the formation of a carbon–heteroatom bond and it is important when planning this to get the oxidation level of the carbon electrophile right. If we disconnected either C–N bond of the pyrrole 8, we get back to a ketone and an amine 9. If we disconnected the imine in imidazole 10 we should also get back to a ketone and an amine 11. Both 9 and 11 are unstable and neither is likely to be a real intermediate but the point is worth making. These carbon electrophiles are at the aldehyde or ketone oxidation level.

![Chemical reactions]

By contrast, disconnection of the pyridone 12 gives a similarly unstable amine and a carboxylic acid 13. We are never going to make 8, 10 or 12 from these intermediates but it will
be important to recognise that the marked carbon atoms in 12a, 14 and 15 are at the carboxylic acid oxidation level.

![Chemical structures](http://www.chem4all.vn)

We can put this into practice immediately with the synthesis of pyrroles 16. Disconnection of both C–N bonds gives a very reasonable intermediate, the 1,4-diketone 17. This will need to be made by one of the methods from chapter 25 and treatment with ammonia gives 16. On the other hand, if the furan 18 is needed, no heteroatom needs to be added and treatment with acid cyclises the diketone 17 to the furan 18.

![Chemical structures](http://www.chem4all.vn)

**Synthesis of Pyrroles**

A simple example is the pyrrole 19 required for the synthesis of the anti-inflammatory clopirac. Disconnection of the two C–N bonds reveals the diketone 20, available as ‘acetonylacetone’, and the simple aromatic amine 21. The synthesis is to mix the two together. This synthesis makes N-substituted pyrroles available.

![Chemical structures](http://www.chem4all.vn)

If the 1,4-dicarbonyl compound is unsymmetrical, it will have to be made by methods such as those described in chapter 25. Examples such as 22 appear in papers by Yadav. The 1,4-diketone 23 can be disconnected at a branchpoint with the idea of using a d^1 reagent for BuCHO in conjugate addition to the enone 24.

![Chemical structures](http://www.chem4all.vn)

Any of the d^1 reagents suggested in chapter 25 would do but they preferred a catalytic method using the thiazolium salts 25 devised by Stetter. These are also aromatic heterocyclic compounds
and their mechanism of action is discussed in the workbook. They chose microwaves to assist the first step and the unusual Lewis acid catalyst bismuth triflate for the second in the ‘ionic liquid’ bmim\(^+\) 26, also an aromatic heterocyclic compound. These dialkyl imidazolium salts are easily made by double alkylation of imidazole.\(^6\)

![Chemical structure diagram]

**Thiazoles**

When there are two different heteroatoms in a five-membered aromatic ring, questions of regioselectivity often arise. The unsymmetrical thiazole 27 might be disconnected at the imine to give the unstable primary enamine 28 and then at the thioester to give an acylating agent and the undoubtedly very unstable 30. Note that 30 must have SH and NH\(_2\) on the same side of the alkene for cyclisation to be possible. We want to find a better way.

![Chemical structure diagram]

But the more heteroatoms, the more alternatives. We could disconnect the enamine first 27a and the C–S bond second 31. This suggests a reasonable \(\alpha\)-halo-ketone 33 and an unstable-looking imine 32. Fortunately this is just a tautomer of the thioamide 34. Though thio ketones are unstable, thio-amides are stable thanks to extra conjugation.

![Chemical structure diagram]

This is the strategy followed in most thiazole syntheses. The regioselectivity issue is which way the reagents combine. There are two possibilities: the sulfur could attack either the ketone or the saturated carbon atom as can the nitrogen. But sulfur is excellent at S\(\delta\)2 reactions while nitrogen is better at addition to carbonyls. So 27 and not 35 is the product. No intermediates are isolated: once either the C–S or the C–N bond is formed, cyclisation and aromatisation are fast. This means that aromatic heterocycles are easier to make than the non-aromatic ones.

![Chemical structure diagram]

A simple example is the anti-inflammatory fentiazac\(^7\) 36. Doing both disconnections at once we get available thiobenzamide 37 and the \(\alpha\)-halo-ketone 38. This can be made from the parent ketone 39, available by a Friedel-Crafts reaction using a cyclic anhydride (chapter 25).
The synthesis of the Stetter thiazolium salt 25 uses a different strategy. The first disconnection is obviously of the benzyl group and then we need the α-chloro-ketone 41 for reaction with thio-formamide.

You might think that 41 could easily be made by chlorination of the hydroxy-ketone 43, but how are we to control enolisation? One way would be to add a controlling CO₂Et group 44 as we can then do a C–C disconnection back to ethylene oxide and ethyl acetoacetate 45.

We have already met this sequence in chapter 25: the intermediate is in fact the lactone 46 that is chlorinated in excellent yield and gives the thiazole in a few steps.⁸

The thiazole 40 is available as it is an intermediate in the manufacture of vitamin B₁ and one patented synthesis uses the dichloro-compound 49 to make 41 by rather a different route.⁹

Six-Membered Rings: Pyridines

Disconnection of both C–N bonds of a pyridine 50 gives an ene-dione 51 but the alkene has to be cis for cyclisation to be possible and conjugated cis-enones are rather unstable. It is usually easier to remove the double bond to reveal the saturated 1,5-diketone 52 that can be made by the methods of chapter 21. This usually means conjugate addition of an enolate to an enone.
Treatment of the diketone 52 with ammonia gives the dihydropyridine 53 that is very easily oxidised by a variety of oxidants to the pyridine 50 itself. A hydrogen from C-4 is very easily removed as the product is aromatic. If you know some biological chemistry you will recognise a similarity to NADPH.

If you don’t want to be bothered with the oxidation, you can use hydroxylamine instead of ammonia. The intermediate is now unstable and eliminates water 54 very easily. One of the two marked Hs at C-4 is lost as a proton with cleavage of the weak N–O bond to give the pyridine 50 and water.

A simple example shows just how easy this is. The bicyclic pyridine 55 gives the diketone 56 by disconnection and FGA. Disconnecting 56 at the branchpoint suggests some enolate equivalent of cyclohexanone and the enone 57.

As explained in chapter 21, vinyl ketones such as 57 are unstable and we often prefer to use the Mannich base instead. This example works spectacularly well. Heating the Mannich base 58 with cyclohexanone gives the 1,5-diketone 55 that combines with hydroxylamine to give the pyridine 54 both reactions giving excellent yield.10

Pyrimidones exist as the amide tautomer 60 rather than the enol tautomer 59 unlike the case with phenols 61. The enol tautomer of a phenol 61 is aromatic but the keto tautomer 62 is not.
Both tautomers of pyridones are aromatic as the amide nitrogen in 60 has a delocalised pair of electrons and the extra stabilisation of the carbonyl group carries the day.

When drawing disconnections it doesn’t matter which tautomer you use. If we disconnect both C–N bonds 63 we get a keto-acid 64 and removal of the alkene gives a simple 1,5-dicarbonyl compound 65. Reaction with ammonia followed by oxidation gives the pyrimidone.

**Pyrimidines**

Pyrimidines are pyridines with two nitrogen atoms having a 1,3-relationship 66. They occur in nucleic acids as pyrimidine bases such as cytosine 67 and thymine 68 and you will notice that these are pyrimidones. An important new type of anti-cancer drug Glivec 69 has a pyrimidine core with a linked pyridine ring.

The compound Aphox, that kills greenfly without harming ladybirds, is a pyrimidinone 70. Disconnection of the ester side chain reveals a pyrimidine 71 that we should rather draw as a pyrimidone 72. Disconnection of two C–N bonds gives simple starting materials: available dimethyl guanidine 73 and the acetoacetate derivative 74.

The synthesis used ethyl acetoacetate which was methylated and cyclised with the guanidine 73 to give the pyrimidine 72: acylation on oxygen gives Aphox directly.
Benzene-Fused Heterocycles: Indoles

The most important of the heterocycles fused to benzene rings are the indoles 75. The obvious enamine disconnection gives 76 which would certainly cyclise to the indole, but how are we to make 76? As a result of this difficulty, many special reactions have been invented to make indoles and the most important is the Fischer indole synthesis. A phenylhydrazone 77 of a ketone or aldehyde is treated with acid or Lewis acid and the product is an indole.

\[
\begin{align*}
\text{R} & \quad \text{C-N} \quad \text{enamine} \quad \rightarrow \quad \text{R} \\
\text{75} & \quad \text{76} & \quad \text{?} & \quad \text{75} \\
\text{HOAc} & \quad \text{or ZnCl}_2 \\
\end{align*}
\]

In essence, the phenylhydrazone 77, formed from the ketone 78 and PhNHNH₂, tautomerises to an enamine that can undergo a [3,3]-sigmatropic rearrangement, with cleavage of the weak N-N bond 79, to give an unstable intermediate 80 that aromatises to 81. Cyclisation of the NH₂ group onto the imine and loss of ammonia gives the indole.

\[
\begin{align*}
\text{R} & \quad \text{C=O} \quad \text{PhNHNH}_2 \quad \rightarrow \quad \text{R} \\
\text{78} & \quad \text{77} & \quad \text{HOAc} & \quad \text{or ZnCl}_2 \quad \rightarrow \quad \text{R} & \quad \text{[3,3]} & \quad \text{R} & \quad \text{R} & \quad \text{NH}_2 & \quad \text{NH}_2 \\
\text{79} & \quad \text{80} & \quad \text{81} \\
\end{align*}
\]

The easiest way to work out how to make an indole is to disconnect the only two bonds formed in the reaction: the C-C and C-N bonds in 82 and write the hydrazine 83 and ketone 78 required. There are two questions of selectivity: here we ask which of the two ortho positions (black blobs in 84) will react? Answer: it doesn’t matter—they are the same.

\[
\begin{align*}
\text{MeO} & \quad \text{R} \quad \rightarrow \quad \text{MeO} \\
\text{R} & \quad \text{82} & \quad \text{R} & \quad \text{83} & \quad \text{R} & \quad \text{78} \\
\text{MeO} & \quad \text{84} & \quad \text{86} \\
\end{align*}
\]

The other question is: which side of the ketone will ‘enolise’ or more accurately form the enamine 79? Here it may be easy as they may again both be the same as in 86. In diagrams 84 and 86, the dotted line shows the symmetry.

\[
\begin{align*}
\text{NR} & \quad \text{85} \quad \rightarrow \quad \text{phenylhydrazone} \\
\text{85} & \quad \text{86} \\
\end{align*}
\]

Example: The Synthesis of Indomethacin

Indomethacin 87 is a Merck non-steroidal anti-inflammatory. Amide disconnection reveals a simpler indole 88 and the Fischer disconnection gives the two starting materials 89 and 90.
It should be obvious that the hydrazine has the ideal symmetry—both ortho-positions are the same—but the ketone does not.

The hydrazine 89 is made from the amine by nitrosation and reduction and the keto-acid 90 is available as levulinic acid. Now comes the big question: when the Fischer indole synthesis is carried out on the hydrazone 91: which enamine is formed, the one we want 92, or the one we don’t want 93? Since the Fischer indole is an acid- (or Lewis acid-) catalysed reaction we expect the more substituted enamine 92 to be favoured.

And it is. The t-butyl ester of 90 was used and a good yield of the indole 96 was obtained just by heating in ethanol with HCl as catalyst. The acylation required the acid chloride 97 and the t-butyl ester was ‘hydrolysed’ by heating.\(^ {13} \)

Making Bonds to pre-Formed Heterocycles

So far we have concentrated on making complete heterocycles with substituents. So indomethacin 87 was made with one substituent (OMe) on the benzene ring and two on the pyrrole ring. Only the substituent on nitrogen was added after the indole was formed. Now we shall consider what reactions can be used to add substituents to heterocycles after they are formed. This will usually be by electrophilic or nucleophilic aromatic substitution. The most important distinction between
Electrophilic Substitution on Pyroles, Indoles and Furans

These five-membered rings have lone pair(s) delocalised from the heteroatom round the ring and are 'electron-rich'. They react all too easily with electrophiles and are unstable in acid whether protic or Lewis. We have to find reactions that can be used in neutral or only very weakly acidic solution. The synthesis of tolmetin 99 illustrates the two most important reactions. The disconnection of the ketone would lead naturally to an AlCl₃-catalysed Friedel-Crafts reaction between the acid chloride 100 and the pyrrole 101.

But this mixture would decompose the pyrrole 101. We use instead the Vilsmeier acylation, replacing the acid chloride by the tertiary amide and AlCl₃ by POCl₃. The amide is very unreactive but combines with POCl₃ 102 to give a reactive species that does attack the pyrrole 104 in the right position to give, after rearomatisation 105, the iminium salt 106 that is hydrolysed to the ketone 101. You will notice the similarities to electrophilic substitution on benzene.

We still have to make the pyrrole with the alkyl side chain for this acylation reaction. Friedel-Crafts alkylation is not an option but pyroles are reactive enough to do the Mannich reaction. Formaldehyde and an amine combine to give another iminium salt 107 that reacts with N-methyl pyrrole to give, after rearomatisation 109 the substituted pyrrole 110.

You will also notice a problem: the amine 110 is not what we want. However, the tertiary amino group in Mannich products is often replaced by other functionalities: in chapter 20 we
saw alkylation and elimination used to make enones. Here alkylation and substitution is used to make a nitrile 111 and it was this compound that was used in the acylation sequence. At the end, hydrolysis of the nitrile 112 gave tolmetin 99.

Notice that both substitutions 104 and 108 occurred next to nitrogen. Indoles on the other hand react very selectively at C-3 113 with electrophiles such as Vilsmeier and Mannich salts. This is probably because reaction at C-2 116 would disrupt the benzene ring as well as the pyrole ring. As you have seen, substituents at C-2 are easy to put in during indole synthesis, so this is no great handicap.

**Nucleophilic Substitution on Pyridines and Pyrimidines**

Pyridines on the other hand are very bad at electrophilic substitution, so much so that it is hardly attempted, but they are excellent at nucleophilic substitution. A most important example is the transformation of pyridine into 2-chloro pyridine 119 and hence into any derivative needed, such as the amines 120. The reagent is again POCl₃ which attacks oxygen 117 to give a very reactive intermediate with a good leaving group that is attacked by chloride ion 118. All these reactions occur by the addition–elimination mechanism like 118. It is essential to have at least one nitrogen in the ring for this to work but two nitrogens, as in a pyrimidine, are better.

**The Synthesis of an Anti-Cancer Compound**

We conclude this chapter with the synthesis of Novartis PKI 166 121, a new anti-cancer drug of great promise. It has fused pyrole and pyrimidine rings and the reaction we have just discussed allows disconnection of the amine from the pyrimidine ring 121. Now we can use standard C–N disconnections on the two rings in turn 122 and 123 to reveal a much simpler starting material 124.
The keto-acid has a 1,4-diCO relationship 124a and the most promising disconnection 124b gives an α-halo-ketone 125 and a curious double enamine 126. The reaction will require selectivity as the nucleophilic carbon must displace bromide by an S_N2 reaction while the nitrogen must attack the carbonyl group. This is the ‘right’ way round mechanistically too.

It turns out that we must protect the phenol as its methyl ether 127 and that 126 is best used as an amidine-ester rather than the double enamine. The synthesis is then quite short. We have barely scratched the surface of aromatic heterocyclic synthesis in this chapter but the encouraging message is that cyclisation is easy and that cyclisations to form aromatic compounds are the easiest of all. Disconnect with confidence!

References

General Strategy D: Advanced Strategy

Some guidelines on strategy are collected in this final chapter and applied to a range of the types of molecules we have been discussing.

A Synthesis of Pyrazoles

The disconnection of pyrazoles 1 by the methods of the last chapter is straightforward and leads to hydrazine 2 in combination with a 1,3-dicarboxyl compound 3. This is simply disconnected by the methods of chapter 19 to an enol(ate) of 4 and an acylating agent 5.

So what is new here? We can save time, materials and effort if we combine two reactions in one operation. These tandem processes, as they are called, avoid the isolation of potentially difficult intermediates and may avoid the need for control over reactions: in chapter 19 we discussed the need for control in the acylation of enolates. Workers at Merck\(^1\) combined the difficult acylation of enolates 7 by acid chlorides with the capture of the intermediates 9 by hydrazine to give stable pyrroles 10. This is a summary of their method:
When compounds such as pyrazoles are being made to develop new drugs, a number of related compounds can be prepared at once by diversity-oriented synthesis, that is, methods designed to be general for a wide range of compounds. An example where both components are aliphatic 13 and a tri-substituted example 15 make the point. In this work, the synthesis of 25 different di- or tri-substituted pyrazoles was attempted by the same method: only one example failed.

Convergence

Long linear sequences of reactions give low yields; a linear 10-step sequence (i) with each step giving 90% yield gives only just under 35% overall. And how often does each step give 90% yield? Convergent or branching strategies make things better by reducing the longest linear sequence. Even one branch reduces the loss: sequence (ii) has only eight steps in the longest linear sequence and the yield rises to 43%.

\[ A \rightarrow B \rightarrow C \rightarrow D \rightarrow E \rightarrow F \rightarrow G \rightarrow H \rightarrow I \rightarrow J \rightarrow TM \]  

(i)

\[ A \rightarrow B \rightarrow C \]
\[ D \rightarrow E \rightarrow F \]
\[ G \rightarrow H \rightarrow I \rightarrow J \rightarrow K \rightarrow TM \]  

(ii)

But we can do much better: branching later (iii) means only five steps in the longest linear sequence and a yield of 59% while more branches (iv) and (v) give different levels of improvement. There is no magic about this: we are just ‘thwarting the arithmetical demon’ by our strategy and the bigger the molecule, the easier it is to devise a convergent strategy. In fact, this is what we have been doing by choosing disconnections in the middle of the molecule and at branchpoints.

\[ A \rightarrow B \rightarrow C \rightarrow D \rightarrow E \rightarrow F \rightarrow G \rightarrow K \rightarrow TM \]  

(iii)

\[ A \rightarrow B \rightarrow C \]
\[ D \rightarrow E \rightarrow F \rightarrow G \]
\[ H \rightarrow I \rightarrow J \rightarrow K \rightarrow L \rightarrow M \rightarrow TM \]  

(iv)

\[ A \rightarrow B \rightarrow C \]
\[ D \rightarrow E \rightarrow F \]
\[ H \rightarrow I \rightarrow J \rightarrow K \rightarrow L \rightarrow M \rightarrow TM \]  

(v)
Synthesis of Methoxatin

Methoxatin 16 is a coenzyme that allows some bacteria to use methanol as their source of carbon. It oxidises methanol by using the ortho-quinone on the middle ring and so it seemed reasonable to synthesise it from the much more stable benzene 17 as biological reagents must be reversible. Disconnecting either the pyrrole or the pyridine ring would lead to a linear strategy so Hendrickson decided to disconnect the central benzene ring. This sounds tricky but they realised that the alkene 18 would cyclise easily to 17.

A Wittig disconnection 18a split the molecule into two and the decision to put the aldehyde on the pyrrole was influenced by a known synthesis from available starting materials and the hope that the phosphonium salt 20 could be made from the known pyridine 21.

The synthesis of 23 was known to be amazingly simple: pyruvic acid 22 is mixed with ammonia! The yield is low, but who minds? If you must have a low-yielding step, it is a good idea to have it at the start of the synthesis to avoid the waste of materials and energy. In this case, so much is achieved that a low yield is acceptable. Esterification gave the diester 21; R = Me which could be brominated with NBS (chapter 24) and combined with Ph₃P to give the phosphonium salt. This is the first branch complete.

The pyrrole 19 was made by a Friedel-Crafts reaction on the known and deactivated pyrrole 25. The CO₂Et group deactivates C-3 and C-5 so reaction occurs at the only unaffected position. The electron-withdrawing CO₂Et group also makes the pyrrole less susceptible to Lewis acid degradation (chapter 39). The Wittig reaction with the ylid from 20 went in excellent yield but
the product was >95% *trans* and this compound cannot cyclise.

\[
\begin{align*}
\text{F} & \quad \text{CO}_2\text{Et} \quad \text{Cl} \\
\text{H} & \quad \text{CO}_2\text{Et} \\
\text{N} & \quad \text{Cl} \quad \text{OMe}
\end{align*}
\]

1. \text{AlCl}_3 \\
\text{CH}_2\text{Cl}_2, 0^\circ \text{C} \\
2. \text{H}^+, \text{H}_2\text{O}

\[
\begin{align*}
\text{OHC} & \quad \text{CO}_2\text{Et} \\
\text{N} & \quad \text{R} \quad \text{Me}
\end{align*}
\]

19; \text{R} = \text{Et}, 82%

20; \text{R} = \text{Me}

\[
\begin{align*}
\text{NaH} & \quad \text{esters of} \\
\text{E-18} & \quad \text{84\% yield}
\end{align*}
\]

The ingenious solution was to isomerise the alkene and cyclise it in a single operation using light to catalyse both reactions. Cyclisation of \textit{Z}-18 should give \textit{trans}-27 by a conrotatory electrocyclic reaction but the reaction was conducted with diphenyldiselenide PhSe−SePh which oxidised it to the benzene 28 in the reaction mixture. So three steps were combined in one.

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{EtO}_2\text{C} \\
\text{H} & \quad \text{C}_\text{H} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
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\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
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\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Two linear syntheses appeared about the same time: both start with the central benzene ring and work outwards, first in one direction and then in the other. Both mark the positions on the benzene ring where oxidation will be needed. The Corey synthesis\(^3\) puts one OMe group on the ring 29 and disconnects the pyridine ring to an indole 30 and an unsaturated ketoester 31 that might be made from available ketoglutarate 32.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Fischer disconnection of the indole 30\(a\) (chapter 39) gives methyl pyruvate and an aryl hydrazine that would have to be made from the corresponding diazonium salt that would have to be protected on the other amino group 36. They decided to take a short cut by using the Japp–Klingemann reaction on the same diazonium salt with the easily made acetoacetate 35.
The enol of 35 adds to the diazonium salt 36 and is deacylated in KOH to give the hydrazone 38 that isomerises to the enamine 39 for the Fischer indole to give the indole \((N\text{-formyl} \; 30)\) that is finally hydrolysed to 30 in aqueous HCl. The remarkably high regioselectivity in the cyclisation may be due to steric hindrance: it is difficult to insert a substituent between two others.

The ketodiester 31 was made from 32 by bromination and elimination. Reaction with 30 gave first the heterocycle 40 that was dehydrated and aromatised in dry HCl. Oxidation of this methoxy-compound with Ce(IV) was quite easy and methoxatin was synthesised.

Weinreb’s synthesis has two OMe groups where the ortho-quinone will be and puts in the pyrrole last. The idea was to use a Reissert indole synthesis where reduction of the nitro group in 42 would lead to condensation with the ketone.

The Reissert depends on using the nitro group to stabilise an anion on the methyl group of 43 suggesting the C–C disconnection shown on 42. Direct nitration of 44 is expected to put the nitro group in the right place as it is the only free position on the activated (two OMe groups) benzene ring. Nitration is not expected on the pyridine ring (chapter 39) particularly as it has two CO\(_2\)Me groups. The disconnections on the pyridine ring 44 are the same as those in Corey’s synthesis 29 but the chemistry used was quite different. Even the same strategy (same disconnections) need not restrict the chemist to one particular reaction.
So now we start the synthesis. Available 46 was converted in two steps into 45 and an interesting reaction with chloral hydrate and hydroxylamine gave the amido-oxime 47, cyclised to 48 with polyphosphoric acid.5

This reaction makes the wrong ring size! But another interesting reaction with pyruvic acid makes the required quinoline 50, esterified without isolation.6

The Reissert reaction would now require a base-catalysed acylation of the methyl group with dimethyl oxalate to give 42. They say ‘All attempts ... in the presence of various bases to produce intermediate [42] failed.’ So they used the radical bromination of 43 with NBS (chapter 24) to give 51, alkylated with the anion of methyl acetoacetate to give 52.

The same kind of reaction as we saw in Corey’s synthesis to give 39 now gave the hydrazone 53 and reduction finally produced the tricyclic compound 41. As expected, oxidation was now easier, but still needed AgO and HNO3. This is a linear sequence of 11 steps, but it was the first.
Convergence in a Commercial Synthesis

Convergence is even more important in commercial syntheses. The Merck anti-HIV drug MIV-150 54 was synthesised in the laboratory in a 14-step linear sequence from meta-fluorophenol and 55 in 1% overall yield.1

The fluorophenol could be converted into 56 in four good steps but the insertion of the vinyl group to give 57 by formylation and a Wittig reaction went in only 18% and the cyclopropanation with a diazoester and Cu(I) (chapter 30) gave poor selectivity in favour of the cis isomer of 57. Worse still, it was necessary to protect the phenol as a methyl ether and the removal of the methyl group, the last step, went in only 52% yield, wasting nearly half of all the material.

One branch of the convergent route made the ketone 59 while the other made enantiomerically pure cis cyclopropane 60. These were combined to give the isocyanate 61 in two steps which was coupled to the amine 55 to give the urea 54. Though protection was still needed and the last step was still poor, the overall yield was 27%—a considerable improvement on 1%. The details of the chemistry are too advanced for this book but appear in Strategy and Control.
Key Reaction Strategy

The Diels-Alder Reaction

We have already discussed strategies dominated by the availability of a starting material or the need to control stereochemistry. Another similar strategy revolves around one key reaction that achieves so much that it is worth basing our synthesis on it. The Diels-Alder is pre-eminent among such reactions. Some Diels-Alder disconnections are barely concealed by the structure of the target molecule: the sex pheromone 62 of the southern green stink bug *Nezara viridula* for instance. Getting back to the known Diels-Alder product 64 looks obvious.

It turns out that it is difficult to use the ketone to control the stereochemistry of the epoxidation. If acrylic acid is used as the dienophile, bromolactonisation of the product 67 gives a mixture of five- 68 and six-membered 69 lactones in 86% yield and a 1:1.5 ratio. Fortunately, treatment of both with an alkyl-lithium makes the same epoxide 70 by ring opening and *SN2* closure of the epoxide. The reaction works well only with an electron-withdrawing group X such as SPh that must be removed later. Addition of MeLi to the ketone and elimination gives 62.

The lycorine alkaloids come from plants such as daffodils. Among the simplest are the lycoranes 71–73 differing only in stereochemistry. They contain a saturated six-membered carbocyclic ring and that might make you think immediately of the Diels-Alder reaction.

Writing a general structure 74 for the lycoranes, we can remove the unique carbon atom between N and the benzene ring, with a Mannich reaction in mind, and disconnect the remaining C–N bond that does not go to a chiral centre to give 76. For a Diels-Alder we need an electron-withdrawing group such as nitro 77 and an alkene in the ring such as 78. Now Diels-Alder disconnection gives a simple diene 79 and a conjugated nitro-alkene 80.
The regiochemistry 81 is fine: the nucleophilic end of the diene attacks the electrophilic end of 80. But stereochemistry is all important. Undoubtedly the \textit{trans} isomers \textit{E}-79 and \textit{E}-80 will be easiest to make so we should explore the result of the Diels-Alder with these two. We expect a \textit{endo} transition state 82 and this gives 83. Unfortunately this stereochemistry is wrong for all the lycoranes.

An alternative is to put the alkene in another place 84 and discover a different pair of diene 86 and dienophile 85. Again the \textit{E}-isomers will be easier to make and this time we get the right stereochemistry 88 for \(\alpha\)-lycorane 71. This strategy was followed in an early synthesis by Hill.\textsuperscript{9} Another synthesis using the Diels-Alder reaction is by Irie.\textsuperscript{10} More details appear in the workbook.

\textbf{Aldol and Conjugate Addition Reactions}

Among other important reactions that build up a molecule rapidly are aldol and conjugate addition. Together with Diels-Alder and Wittig reactions they are major players in organic synthesis. Another synthesis of lycoranes uses these reactions.\textsuperscript{11} Similar preliminary disconnections with the addition of a carbonyl group 89 lead to the amino acid 90.
Now the first conjugate addition, an intramolecular reaction between the nitroalkane and unsaturated ester in 92 is followed by conjugate addition of some aryl metal derivative to the unsaturated nitro-compound 93. Both the unsaturated nitro-compound and ester could be made by aldol or Wittig reactions but there is clearly a potential selectivity problem.

The stable hemiacetal tetrahydropyranol 94 was used in a Wittig reaction to give the unsaturated ester 95 mostly as the E-isomer. Oxidation, nitroaldol and elimination gave the unsaturated nitro-compound 98. It turns out that the aryl-lithium does conjugate addition without any copper and that it reacts exclusively with the nitroalkene to give 99.

Now comes the key step: intramolecular conjugate addition of the nitroalkane anion to the unsaturated ester. When catalysed by CsF and a tetra-alkyl ammonium salt, this is selective (1.5:1) for the all equatorial products 100. Reduction and cyclisation give the lactam 102 having the right stereochemistry for β-lycorane 72.

Reductive removal of the amide carbonyl with borane and Mannich closure of the middle ring give β-lycorane 72. A feature of this synthesis is that by changing the order of events and by adding ArLi with chelation control, all three lycoranes can be made selectively.
A Stereochemically Dominated Synthesis of γ-Lycorane

Stereochemistry has been a serious issue in all the syntheses of lycoranes but it dominates in one synthesis\textsuperscript{12} of γ-lycorane 73. All three hydrogens at the chiral centres are on the same face so the idea is that two of them could be put in by catalytic hydrogenation of a pyrrole such as 104 or 105 from the less hindered side of the alkene.

Another advantage of this approach is that we can now use electrophilic substitution on the pyrrole to add the rest of the molecule. So the secondary benzylic alcohol 106 might well cyclise to 105 with Lewis acid catalysis as the cation will be reasonably stable and the reaction is intramolecular. But the Friedel-Crafts alkylation to give 107 will not succeed as the cation would be primary.

So the decision was taken to use succinic anhydride as the electrophile (chapter 5). Pyroles prefer to react next to nitrogen with electrophiles (chapter 39), but with a large group on nitrogen 108 (\textit{i}-Pr\textsubscript{3}Si), Friedel-Crafts reaction occurred at the other position to give the keto-acid 109. Reduction to the ‘benzylic’ alcohol and catalytic hydrogenation gave 110 in excellent yield.

After exchange of the protecting group, the Weinreb amide 111 (an alternative to nitriles for the formation of ketones discussed in detail in Strategy and Control) reacted with the aryl Grignard reagent to give, after reduction, 112—the protected version of the alcohol 106 required for cyclisation.

Tin (II) triflate gave a quantitative yield of the Friedel-Crafts product 113, emphasising the efficiency of cyclisation, and this compound was hydrogenated over platinum oxide to give
only the required all-cis compound 114. As there is an acyl group already on nitrogen, the original idea of using a Mannich reaction was replaced by intramolecular acylation with \( \text{POCl}_3 \) (Vilsmeier—chapter 39) and the amide could be reduced away with borane.

\[ \text{Sn(OTf)}_2 \rightarrow 112 \xrightarrow{\text{Sn(OTf)}_2} \text{Ar} \xrightarrow{\text{H}_2} \text{Ar} \xrightarrow{\text{H}_2 \text{PtO}_2} \text{RO}_2\text{C} \xrightarrow{\text{POCl}_3} \text{O} \xrightarrow{\text{RO}_2\text{C}} 115; 71\% \text{ yield} \]

Notice that the three key reactions work brilliantly in this synthesis: the hydrogenation of 113 is totally stereoselective and very high yielding while the two electrophilic substitutions on the pyrrole are perfectly regioselective: acylation of 108 controlled by steric hindrance and alkylation of 112 controlled by electronic preference and because it is intramolecular.

We hope you will gather from these varied syntheses of one small group of natural products that even such relatively simple compounds can be made by a variety of strategies. There is no ‘right’ answer to a synthesis problem: workers in universities and industrial laboratories all over the world may devise routes to the same compound based on totally different reactions. In addition, solving the problems associated with a synthesis often brings into being new synthetic methods of lasting value.

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