Chapter 12: Disconnections And Synthesis

It would be an interesting exercise to try and find a way to use all of the reactions shown so far in this book. One way is to make different individual small molecules and in the process make carbon-carbon bonds and modify functional groups. An important goal in organic chemistry is to string together different reactions to make new and/or larger molecules from smaller ones. Many medicines or other important molecules have many carbon atoms and often several functional groups. If such a molecule is not readily available, it must be made. Normally this means choosing a molecule of fewer carbons as a starting point and building the molecule you want by making the necessary carbon-carbon bonds, and incorporating the functional groups. This process is called synthesis. This chapter will focus on rudimentary techniques for assembling molecules and provide methodology to analyze a molecule and determine what smaller molecule(s) must be used for its synthesis.

12.1. What is Synthesis?

Synthesis is nothing more that taking an available molecule (called the starting material) and transforming it by a series of reactions into a molecule that is required for some purpose (the target). The reactions employed in the synthesis include both carbon-carbon bond forming reactions and functional group transformations. The disconnections and functional group transforms presented at the end of several preceding chapters illustrate individual processes within a synthesis. This chapter will discuss an important strategy for analyzing a target molecule and determine how it can be synthesized.

12.1.A. Disconnections

The place to start a synthesis is with a target molecule. If 1 is the target, we can ask several questions. What is the starting material? What is the first chemical step? What reagents are used? How many chemical steps are required? Answer to these questions are not obvious. Clearly we must have a protocol for analyzing the target that will help us answer these questions. A protocol has been developed that takes the target and simplifies it by a series of mental bond-breaking steps called
**disconnections**, introduced in chapter 10 (section 10.10). An important architect of this strategy is Elias J. Corey (1928-; USA), although many others have contributed to developing this approach. The term **disconnection** implies breaking the bond of a molecule to generate simpler fragments. A disconnection is in fact a mental exercise (we are not actually chemically breaking bonds) and if we disconnect a bond, we must have a chemical process in mind to make that bond. Making a disconnection points towards a bond that must be made.

If we take the relatively simple molecule 1, there are ten bonds (labeled a - j), not counting the bonds within the phenyl group or the C=O bond. The reasons for discounting these bonds will be discussed later in this chapter but the short answer is simply that it is easier to use these as intact units rather than making them. If we disconnect bond e, we generate two smaller fragments 2 and 3 (where "smaller" is defined as having fewer carbon atoms). Both 2 and 3 have a more simple structure than 1, so we can say that the target has been simplified. We will make an assumption that we cannot purchase 1, which means that we have to make it. This means that we must determine how to make it. If we disconnect 1 into fragments 2 and 3, we must be able to make 1 by combining those fragments in a known chemical reaction. We therefore hope that disconnection of bond e will point to a chemical reaction by which we can make 1 from simpler fragments. This is the fundamental principle behind the disconnection process.

Before we can combine our disconnect fragments in a chemical reaction, we must be able to correlate each fragment with a real molecule. Fragments 2 and 3 are not real since each carbon (marked in red) has only
three bonds. Before we can proceed, we must have a method that converts these fragments into real molecules that can be examined for chemical reactivity. In previous chapters we have had some help with this problem. Many of the end-of chapter summaries in chapters 10-14 are, in fact, disconnections. If we can correlate one of these disconnections with one for a given target, we have a real reaction for the synthesis of that bond. In chapter XX, for example, we saw a disconnection that cleaved one bond of an alkyne-alcohol (4) to generate fragments 5 and 6. This simply means that we recognize the fact that we can make 4 by an acyl addition of the anion of 5 to 6. This is the same disconnection we made with 1 to give 2 and 3. There is one problem, however. Fragment 3 has an OH unit whereas 6 has a carbonyl (an aldehyde or ketone). Remember, however, that 3 is only a fragment and the carbon marked in red has only three bonds. Since

![Chemical structure](image)

1. NaNH₂, THF
2. acetone
3. H₃O⁺

...Since oxygen is more electronegative than carbon, it is reasonable to assume that the C-O bond in 3 will be polarized C⁺O⁻. Since the carbon in 3 is electrophilic, it is very reasonable to assume that if we convert 3 into a real molecule, that real molecule will also have an electrophilic carbon. Note that the acyl carbon of 6 is electrophilic and, in fact, we can correlate fragment 3 with a real molecule, acetone. We can similarly assume that we add a hydrogen atom to the red carbon in 2, giving a terminal alkyne (7). If we make these assumptions, then 1 is made by converting 7 into an alkyne anion and reacting it with acetone. The lesson is that we must be able to correlate disconnect fragments with real molecules, and this often means recognizing the chemical relationships of the functional groups involved. 12.1 Show a reasonable disconnection for 3-pentanol; for 3-methylbutanoic acid; for 2-ethyl-3-methylbutanenitrile.

The first disconnection of 1 leads to a chemical reaction that is actually the last step of the synthesis. The last step is always the one that generates the final target. An important lesson of the disconnection process is that the first disconnection generates the last chemical step in the synthesis. For a complex target, we will repeat this basic disconnection approach until we can construct a synthesis of that molecule based on known reactions. The complete set of disconnections is called a retrosynthesis.
12.1.B. Retrosynthesis

When compound 7 was converted to 1, we called that sequence a synthesis of 1. The sequence proceeded from starting material 7 to target 1. If we work backwards from 1, however, towards 7 (as we did in section 12.1.A) that could logically be called a retrosynthesis (the exact reverse of the synthesis). Clearly, the disconnection method used in section 12.1.A proceeded in a retrosynthetic manner (from target 1 to starting material 7). The retrosynthesis was used to generate key intermediate products and to suggest a chemical reaction that could be used to synthesize 1. The disconnection approach to synthesis is therefore sometimes called a retrosynthetic analysis. A retrosynthetic analysis will lead to a synthetic scheme. The following sections will use a retrosynthetic analysis to show how to devise a synthesis for various targets.

12.2. Specifying a Starting Material for a Given Target

There are many target molecules that must be made from a specific starting material. This can be because there is a large and cheap source of the starting material, or because the starting material contains a chiral center that is necessary to prepare a particular target. There are other reasons, some practical and some esthetic. When we are forced to use a particular starting material, we can use the retrosynthetic analysis approach to disconnect the target. However, the retrosynthesis must be biased towards the given starting material. In essence, this means that we must identify those carbons of the starting material in the target, and then work backwards in a retrosynthetic manner. There are several specific steps that can be used in this process, and they are sufficiently general that we can apply them to many syntheses.

12.2.A. Retrosynthesis Assuming Ionic or Polarized Intermediates

We will begin with a synthetic problem where starting material 8 must be converted to target 9. The first step is to "find" the structure 8 within the structure of target 9. Close inspection shows that the carbon atoms and OH unit highlighted in red in 9 correspond exactly to the carbon atoms and OH of 14. Therefore, when we disconnect bonds in 9, we are going to disconnect bonds around the highlighted carbons, specifically bonds a and b. We must disconnect bonds in 9 to "liberate" the starting material 8. 12.2. "Find" 2-
propanol in 2-ethyl-2-methyl-2-hexanol; in 2-methyl-3-phenyl-2-propanol; in 4-phenyl-2-butaneone.

We must determine the first bond that is to be disconnected in 9. It must be connected to the five carbons of fragment 8, but there are two possibilities; bond a and bond b. Before deciding whether to disconnect bond a or bond b, we must ask a general question about the reactions you have learned in previous chapters. If we look carefully at the reactions in chapters 2-14, all, or almost all reactions discussed in previous chapters involve either formal ionic intermediates (cations or anions), or they involve the reactions of molecules with a dipole (positive or negative polarized atoms). The reactions where new carbon-carbon bonds were formed involved carbocation intermediates, carbanion intermediates, compounds containing a nucleophilic (negative dipole) carbon, or those with an electrophilic (positive dipole) carbon atom. It can therefore be said that most of the organic chemistry we know so far involves ionic chemistry of one sort or another.

12.3. Draw the structure of three molecules that react with a negative dipole or a carbanion; three molecules that react with a positive dipole or a carbocation.

If most reactions involve ionic chemistry, as a first step, we should disconnect those bonds that lend themselves to formation of ionic intermediates! In all reactions studied so far, the dipole of a polarized bond resulted from the presence of a heteroatom. It is fair to assume that many reactive intermediates arise from a functional group. Therefore, when we are ready to make a disconnection, we should look to the functional group. Disconnection of a polarized bond in a retrosynthesis should lead to a polarized or ionic fragment, which is required if a chemical reaction is to be found that will make that bond in a synthesis.

In the case of 9, we "found" 8 as part of the structure (highlighted in red). Since the red atoms include the heteroatom O, the bonds connecting O to carbon will be polarized. These include bonds a (in blue) and b (in green). We should therefore disconnect these polarized bonds preferentially to any other. If we disconnect bond a, we obtain disconnect fragments 10 and 11. Disconnection of bond b leads to fragments 12 and 13.
This leaves us with several problems. Fragments 10-13 are not real molecules since they are missing at least one bond (the atoms marked with green dots or blue dots have only three bonds connected to them). They are only pieces of a molecule (we will call them disconnect products; sometimes they are called retrons). Since they are not real molecules, we have no reaction to use that will regenerate the bond in a synthesis. To determine what reaction we should use, we must first convert these disconnect fragments into real molecules. The second problem is that we have two possible retrosynthetic sequences, fragmentation of 9 to 10 and 11 or fragmentation of 9 to 12 and 13. To determine if one disconnection is better than the other, we must focus on translating the fragments into real molecules so we can evaluate them based on our chemical knowledge. This translation of disconnect fragments to real molecules involves the use of a synthetic equivalent.

12.2.B. Making Real Molecules and Evaluating Reactions

To translate disconnect fragments to real molecules, we first evaluate each fragment in terms of its functionality. We will begin with fragments 12 and 13. Since we disconnected a bond that was polarized, we can polarize each fragment as positive or negative. Rather than making cations and anions, we will instead use the idea that a negatively polarized carbon will donate electrons (a nucleophile) and a positively polarized
carbon will accept electrons (an electrophile). Therefore, we can use the symbol "d" for a nucleophilic carbon (a donor carbon) and "a" for an electrophilic carbon (an acceptor carbon). When we try to do this with 13, we have another problem. The disconnect carbon (the carbon that was part of the disconnected bond) can be either a donor (d) or an acceptor (a). If we assign that carbon to be a donor in 13, however, then the disconnect carbon in 12 must be an acceptor. Conversely, if the carbon in 13 is made an acceptor, then the analogous carbon in 12 must be a donor. We will look at both possibilities. In Figure 12.1, 12 and 13 are drawn as both donors and acceptors. Logically, we should take advantage of the natural bond polarization for each key bond and let that guide us. Since O is more electronegative than C, the fragment with O<sup>d</sup> and Ca is probably more useful (fragment 12<sup>a</sup>).

12.4. Draw the disconnect fragments for disconnection of 2-(N,N-dimethylamino)-3-methylbutane at C<sub>2</sub>-C<sub>3</sub> and label each as its most logical donor or acceptor. These are not real fragments that can now be evaluated as suggested in section 12.2.A. We must do something else before they become real molecules. We must invoke the concept of a synthetic equivalent - a fragment that represents a real molecule. We determine the identity of a synthetic fragment based on its potential reactivity. If 13 has a donor carbon, C<sup>d</sup>, that carbon is a nucleophilic carbon (an electron donor). A real molecule with a carbon that acts as an electron donors is a carbanion. 12.5. Make a list of four common carbanions, all from different functional groups. There are many types of functional groups and molecules that have donor carbons. These include Grignard reagents, organolithium reagents, enolate anions, cyanide, and alkyne anions. Of these, only Grignard reagents and organolithium reagents do not have another functional group or a heteroatom. Therefore, a simple carbon marked as C<sup>d</sup> has the synthetic equivalent of C-MgX or C-Li. In Table 1, we see a correlation of various real carbanions with an appropriate synthetic equivalent. In addition to the simple cases represented by Grignard reagents and
organolithium reagents, we see that $O=\cdot C-C^d$ correlates with an enolate anion, $N\equiv C^d$ can correlate with cyanide, and $C\equiv C^d$ correlates with an alkyne anion. We can take this a step further by recognizing the functional group

Table 1. Disconnect fragments and their synthetic equivalents

<table>
<thead>
<tr>
<th>Disconnect Fragment</th>
<th>Synthetic Equivalent</th>
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<tbody>
<tr>
<td>$C^d$</td>
<td>$C$-MgX, X-Li</td>
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<tr>
<td>$O-\cdot C-C^d$</td>
<td>$O=\cdot C=\cdot C^d$</td>
</tr>
<tr>
<td>$N\equiv C^d$</td>
<td>$N\equiv C^\ominus$</td>
</tr>
<tr>
<td>$R-C\equiv C^d$</td>
<td>$R-C=\cdot C=\cdot C^d$</td>
</tr>
<tr>
<td></td>
<td>$R-C\equiv C^\ominus$</td>
</tr>
<tr>
<td>$C^a$</td>
<td>$C-X$</td>
</tr>
<tr>
<td>$O=\cdot C^a$</td>
<td>$O=\cdot C$</td>
</tr>
<tr>
<td>$O-C-C^a$</td>
<td>$\backslash\backslash\cdot C-O$</td>
</tr>
</tbody>
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relationships of these molecules. Since a carbonyl can be reduced to an alcohol and an alcohol oxidized to a carbonyl (chapter 14), the enolate equivalent can also include $RO-C-C^d$. Since nitriles can be reduced to amines (chapter 14), we can include $N-C^d$ as an equivalent. Finally, an alkyne can be reduced to an alkene (chapter 14) or even to an alkane fragment, so we can include $C=C^d$ and $C-C^d$ as synthetic equivalents.

Drawing on our knowledge of the important reactions discussed in previous chapters, we have many possibilities that will allow us to make $C^d$ for $13^d$ (Figure 12.1) into a real molecule. In this particular case, there is no oxygen, nitrogen, double or triple bond, so this is a "simple" donor carbon. Either the Grignard or the organolithium reagent is reasonable, so we will make $13^d$ the Grignard reagent (PhCH$_2$MgBr, 14; see Figure 12.2). What happens if we try to make $12^d$ a donor? We have a serious problem. The natural bond polarization of $O-C$ is $\delta-\cdot O-C^\delta^+$. This means that the carbon wants to be polarized positive. To attempt to make that carbon negative (a donor) is contrary to the normal bond polarization. Therefore, we will not use fragment $12^d$ because there it does not represent a reasonable
synthetic equivalent based on chemistry that we know. This of course also rules out 13a. If 13d is a Grignard reagent, we must identify 12a.

![Figure 12.2. Donor/acceptor possibilities for fragments 12 and 13.](image)

Since Ca is an electrophilic carbon (an acceptor) a synthetic equivalent must have a positive dipole. There are several molecules we know about that have this type of polarization. A common class of molecules polarized in this manner are alkyl halides and sulfonate esters which have a $\delta^+X-C\delta^-$ unit. Since these molecules undergo $S_N2$ reactions with loss of $X^-$, it is clear that the carbon can accept electrons from a donor atom. We also know that the polarized carbon group ($\delta^-O=C\delta^+$) has the necessary bond polarization, and acyl addition reactions clearly support the idea of carbon accepting electrons from a donor. Another molecule with this type of polarization with a carbon that accepts electrons from a donor is an epoxide with a $\delta^+C\delta^-O-C\delta^+$ unit. Armed with this knowledge, Table 1 includes these synthetic equivalents for Ca. A "simple" Ca with no heteroatoms is best represented by an alkyl halide or a sulfonate ester. If an oxygen is connected directly to the acceptor carbon (O-Ca or O=Ca), the synthetic equivalent is the carbonyl, but if the oxygen is on the adjacent carbon (O-C-Ca), then the equivalent is the epoxide. If we now return to 12a, we find that Ca has an oxygen directly attached, so the synthetic equivalent is a carbonyl. This means that the real molecule for 12a is the ketone, 15 (see Figure 12.2). Our first disconnection is now 9 to Grignard 14 and ketone 15. 12.6. Draw at least one actual molecule for each synthetic equivalent in Table 1.

Before evaluating disconnect fragments 10 and 11, we will complete the retrosynthesis based on the disconnection to 15. Once we have done this, we will return to the other fragments and perform the same analysis. This then allows us to make a determination as to which, if either, is better. We must continue the retrosynthesis in order to "reach" 8 as a starting material. This means that we must disconnect ketone 15 (see Figure 12.3). Analysis of 15 shows that the requisite carbon atoms of 8 are still there (in red). Once again, we disconnect the polarized bonds connected to the carbonyl group and we obtain two possible fragmentations. Cleavage of bond "a" leads to 10 and 16 whereas cleavage of bond "c" leads to 17 and 18. Since the goal is to "find" 8, we immediately rule out 17 and 18 because 17 contains four of the carbons.
found in \( \textbf{8} \) but the fifth carbon is part of \( \textbf{18} \). Only \( \textbf{16} \) contains all five carbons of \( \textbf{8} \) so that is the important

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synthesis. The reaction of 19 and 20 gives alcohol 21, and this must be oxidized (see chapter 14) to give ketone, 15. We have almost completed the synthesis because there is a relationship between aldehyde 20 and alcohol 8. All we must do is reduce 20 to generate 8 in the retrosynthesis so the synthesis requires that we oxidize 8 to give 20. We now have all the pieces. If we take 8 and oxidize it with PCC to 20, treatment with 19 gives 21. Oxidation 21 with PCC gives 15, which then reacts with Grignard reagent 14 to give the final target, 9. This is the synthesis based on the retrosynthesis inspired by disconnection of bond a in 9 (see Figure 12.5). 12.8. Show a retrosynthesis and a real synthesis for preparing 2-methyl-3-hexanone from 1-propanol.

**Retrosynthesis**

Before we go on, we should return to the original disconnection of 9 (see Figure 12.1) since there was another possible disconnection, to 10 and 11. If we do the same analysis as above (shown in Figure 12.6), we find that 11 has Cα connected to an oxygen, so the equivalent is the carbonyl. This leads to ketone 22. Fragment 10 must therefore be a donor, and it correlates with Grignard reagent 19 (the same one used above
in Figure 12.4). With the first disconnection established we turn to ketone 22, which has all five carbon
found

Figure 12.6. Disconnection of bond \( b \) in 9.

in 8. Therefore, ketone 22 is the next site for disconnection. The only reasonable disconnection is of bond \( b \)

Figure 12.7. Disconnect fragments for bond \( a \) in 22.

to give fragment 16 (which has all five carbons of 8), and fragment is 13, as seen in Figure 12.7. Fragment
16 is identical to that seen previously and it has the O-C\(^a\) unit. The synthetic equivalent is the aldehyde 20, as
before. The means that 13 is a donor fragment and it will correlate with the Grignard reagent, 14 (this is identical to the synthetic equivalent used previously). Factoring in the functional group transformation as we did before, we arrive at an alternative synthesis based on a retrosynthesis beginning with disconnecting bond $b$ (see Figure 12.8). The oxidation of 8 with PCC leads to 20 (as in the first synthesis - see Figure 12.5), and 20 reacts with 19 to give alcohol 23. Oxidation of this alcohol product with PCC leads to ketone 22, and this reacts with 14 to give the target, 8.

![Figure 12.8. Synthesis of 9 from 8 based on the disconnection of bond $b$.](image)

It is possible that one of these two routes is better than the other. In fact, both are reasonable, reliable and straightforward. There is no best answer and, therefore, there is no "best" disconnection. The only difference is in the order in which the bonds are formed and which intermediate ketone is formed. The reagents are the same. If it turns out that the yield is better in one sequence, then that is better. If it is easier to isolate products from one sequence, that is better. If one of the intermediate ketones (15 or 22) is more reactive than the other, then that is better. Best is determined by which route gives the best yield of product in the shortest and most facile manner. This is a very important lesson. Always look for several disconnections and evaluate all possible routes to see which is the shortest (fewest chemical steps), which requires less expensive reagents,
and which is amenable to easy isolation of the products. Another factor to consider is the number of functional
group transformations. In the case at hand, they are identical. In some cases, however, it is possible that two
disconnections have the same number of steps to form carbon-carbon bonds, but one disconnection requires
five functional group reactions whereas the other requires only three. Clearly, the disconnection with only
three functional group changes will be shorter and probably preferred. 12.9. **Show the retrosynthesis
and the corresponding synthesis of 1,2-diphenyl-2-pentanol from benzaldehyde.**

**12.2.C. Functional Group Manipulation**

In the synthetic example shown above, we had to manipulate an alcohol to a give a ketone as part of the
synthesis. There are many functional group transformations in this book. In order to decide what functional
group you will incorporate we must recognize that there is a chemical relationship between many functional
groups. Once this general relationship is known, it is easy to transform one group into another that might be
useful. Figure 12.9 is provided to show the chemical relationship of common functional groups.

![Chemical relationship of various functional groups](image)

Figure 12.9. Chemical relationship of various functional groups

A carbonyl can be reduced to an alcohol (chapter 14) and an alcohol can be oxidized to a carbonyl (chapter
14). The OH unit of an alcohol can be converted to an X group, where X is a halide (or a sulfonate ester) by
standard means (chapter 12, section 12.12) and hydrolysis of a halide or a sulfonate ester can give an alcohol (chapter 12, section 12.3). Elimination of a halide leads to an alkene (chapter 12, section 12.6) and addition of HX to an alkene gives C-X molecules (chapter 13). Addition of two equivalents of a halogen to an alkene, followed by elimination leads to an alkyne (chapter 13) whereas reduction of the alkyne can give the alkene again (chapter 14). An alkyne can be hydrolyzed to an enol, which tautomerizes to a carbonyl and halogenation of a carbonyl followed by elimination gives an alkyne.

To use Figure 12.9, imagine that your target or a disconnect fragment contains a carbonyl. We could change the carbonyl into an alcohol or even a C-X unit by functional group exchange reactions, and retain the essence of the disconnection. Similarly, an alcohol could be changed into an alkene unit and retain the essence of a disconnection. It is important to recognize the fact that these groups are related by relatively few chemical transforms. Understanding these relationships makes those functional group manipulations important to synthesis easier to understand.

12.10. Write full reactions that show starting materials, products, and reagents for conversion of 1-butanol to (a) butanal (b) 2-hexyne (c) 1-phenyl-2E-hexene (d) 3-hexanol.

As seen in Figures 12.5 and 12.8, a functional group can be manipulated to give a more logical disconnection that may be needed to complete the synthesis. Another example where we identify the starting material is a synthesis of 24 from the one-carbon unit iodomethane. The one-carbon fragment in 24 could, in
principle, be anywhere. Since the methyl group attached to a position \( \beta \)- to the OH leads to a known reaction (methylmagnesium iodide and an epoxide), that is the likely position of the methyl (in green). As for the other methyl group, we do not know of a reaction that attaches methyl to a C=C unit. Therefore, we have chosen the other methyl group. The first disconnection will be of the red bond in 24 since that is a polarized bond and it is connected to both functional groups (see Figure 12.10). This disconnection gives 25 and 26. Note that 25 is an aldehyde equivalent (propanal, 27), which makes 26 a donor alkene fragment. This leads to vinyl Grignard reagent 28. Disconnection of the C=C unit from the methyl group leads to iodomethane. We can generate a vinyl Grignard from a vinyl halide such as 2-bromo-1-propene (29), but we make a vinyl bromide first. Using Figure 12.9, an alkene is related to an alkyne and we know that reaction of an alkyne with HBr gives a vinyl bromide (see chapter 13, section 13.5.A). **12.11. Draw the product of a reaction between 1-pentyne and HCl.** All we must do is treat commercially available 1-propyne with HBr and we obtain 29. Disconnection of the bond adjacent to the carbonyl in 27 (the functional group) leads to 30 and 31. Since 30 is the one-carbon fragment, it becomes the acceptor and the equivalent of iodomethane. This makes 31 the donor, which means it is the enolate anion of acetaldehyde, 32. This leads to the overall synthesis shown, based on the retrosynthesis described (see Figure 12.11). The ability to see the relationship between an alkene and an alkyne allowed us to complete the logical disconnection and make it successful.

**12.3. I Was Not Given a Starting Material!**

In preceding sections, a starting material was specified for a given target, and we had to "find" the starting
material in the target. The retrosynthesis was then biased towards that starting material such that the only
disconnections we looked at were those involving the carbon atoms of the starting material. If we are given a
target, but there is no obvious or given starting material we still use the disconnection approach and develop a
retrosynthetic analysis. Determining the starting material is a problem, however. Normally, we disconnect the
target until we see a molecule that we can purchase commercially, or one that is readily available in our
laboratory. For the purposes of this book, we will assume that any compound of six or fewer
carbons with no more than two functional groups is commercially available and can be used
as a starting material. This is obviously an arbitrary choice, but it makes life simpler, and we can illustrate
the methodology used for such a problem.

![Retrosynthesis and synthesis of target 24.](image)

**Figure 12.11. Retrosynthesis and synthesis of target 24.**

**12.3.A. Looking for the Best Disconnection**

Although we do not have a designated starting material, the retrosynthetic analysis is done essentially the
same as described in section 12.1. We examine the carbon-carbon bonds connected to the functional group
and look for disconnections that will simplify the target in such away that we can make the bond via synthesis.
Since we are disconnecting carbon-carbon bonds, we must focus on reactions that make carbon-carbon bonds
as a guide to the disconnection. Table 2 shows the reactions discussed in previous chapters that form carbon-carbon bonds. The reactions in this table were used to assemble a list of synthetic equivalents for $C^d$ and $C^a$

<table>
<thead>
<tr>
<th>Table 2. Carbon-carbon bond forming reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. $S_N^2$: halides or sulfonate esters + cyanide; alkyne anions; enolate anions; organocuprates</td>
</tr>
<tr>
<td>2. Acyl addition to aldehydes and ketones: + Grignard reagents; organolithium reagents; enolate anions; alkyne anions</td>
</tr>
<tr>
<td>3. Epoxide substitution: + cyanide; alkyne anions; Grignard reagents; organolithium reagents; enolate anions</td>
</tr>
<tr>
<td>4. Acyl substitution of esters, acid chlorides, anhydrides: alkyne anions; Grignard reagents; organolithium reagents; enolate anions</td>
</tr>
</tbody>
</table>

that correlated to each disconnection in Table 1 (see section 12.2.B). **12.12. Give one real example for each category in Table 2.** The equivalents for $C^d$ are Grignard reagents, organolithium reagents and organocuprates. The equivalent for $C≡C^d$ or $C≡C^d$ is an alkyne anion and that for $NC^d$ is cyanide. The equivalent for $O-C-C^d$ is an enolate anion. For simple $C^a$ the synthetic equivalent is an alkyl halide or a sulfonate ester. The equivalent for $O-C^a$ is an aldehyde or a ketone and that for $O-C-C^a$ is an epoxide. Given these synthetic equivalents and the need to disconnect carbon-carbon bonds near the functional group, we can look at an example.

![Image of molecular structures]

Compound 33 is the target, and we have labeled the bonds $a-h$. Notice that the $\pi$-bond of the carbonyl ($C=O$) is not labeled, nor are the $\pi$-bonds of the benzene ring. *We will not disconnect carbon-carbon $\pi$-*
bonds, including those in benzene rings. In general, we will take the benzene ring as a single entity (a unique functional group). Disconnection of the $\pi$-bonds leads to a problem, since there are few ways to take two carbon atoms and directly form a C=C or C=O bond. One is the Wittig reaction, discussed in chapter 10 (section 10.9), but for now we will ignore this disconnection. Of the labeled bonds, we will subdivide them into two categories: the $\alpha$-bond that is connected directly to the functional groups and/or heteroatom, and the $\beta$-bond that is one removed from the functional group or heteroatom. In 33A, the $\alpha$-bonds to the carbonyl (C=O is one functional group and the phenyl ring is a second functional group) are labeled in red. In 33B, the $\beta$-bonds to those two functional groups are labeled in blue. The purpose of identifying these special bonds is to choose one of them for the first disconnection. In principle, any of them are suitable, but there are clues in the structure of the molecule that suggests that some bonds may be more important than others. 12.13. Label all $\alpha$ and $\beta$ bonds for each functional group in (a) 4-hydroxy-5-methyl-2-hexanone (b) 2-cyano-1-phenyl-1-propanol (c) 2-methyl-6-phenyl-3-hexanone.

One of the first things to look for in a disconnection is for it to simplify the target to the greatest extent possible. If we disconnect either bond $b$ or bond $d$ in 33, we obtain one very large fragment and one very small fragment. Disconnection of bond $d$, for example, gives 34 and a one-carbon fragment (35) and
disconnection of bond $b$ leads to 36 and a two-carbon fragment (37). Compare these fragments with disconnection of bond $c$, which gives 38 and 39, or disconnection of bond $e$, which gives fragments 40 and 41. In each case, the fragments are close to the same size and these disconnections give a great deal of simplification. There is a second important characteristic to look for in a target; chiral centers. Target 33 there has two chiral centers. We can begin by focusing on the carbonyl functional group, which is more suitable for making bonds $a$-$h$ than is the benzene ring. We arrive at this conclusion by simply knowing that there are many reactions involving a carbonyl that make a carbon-carbon bond, but few if any reactions involving benzene that do the same thing. The carbonyl is the more important group. Note that connected to the chiral center adjacent to the carbonyl is one bond $\alpha$-to C=O and two bonds $\beta$-to C=O. These three bonds connected to a chiral carbon are $c$, $d$, and $e$. **When possible, disconnect a bond that is connected to a chiral center.** 12.14. Give one reasonable disconnection for (a) 3-methyl-1-phenyl-1-pentanone and (b) 3-cyclohexyl-2-methyl-3-hexanol. The rationale for this statement is that if we can form the carbon center during a reaction we have the potential to control the stereochemistry of that center. If we form a bond with a fragment that has a chiral center that is remote to the bond being formed, that fragment becomes more difficult to obtain. Bonds $f$, $g$, and $h$ are also connected to a chiral center. These bonds are less important than the others because less simplification occurs by disconnecting these bonds and, as noted above, that we have not yet studied many reactions that can make these bonds with a phenyl group in the position shown. ’
12.3.B. Retrosynthetic Analysis

Based on discussion in the preceding section, it appears that bonds $c$ and $e$ in target 33 are the best candidates for a disconnection. We showed above that disconnection of bond $e$ led to 40 and 41. When we disconnected bond $c$, we obtained fragments, 38 and 39. As we noted in section 12.2, these are disconnect fragments and not real molecules. Therefore, we cannot yet evaluate if this is a reasonable disconnection.

Using the method described in section 12.2, we categorize each fragment as a donor or an acceptor. Since fragment 39 is a O=C-C fragment, it is logically an acceptor (see Table 1), O=Ca-C. This correlates well with a carbonyl, specifically an aldehyde (propanal, 43). This assignment means that 38 is the donor fragment, the Grignard reagent derived from halide 42. Propanal fits our criteria for a starting material, but 42 does not and we must do another disconnection. Since the halide is not obviously amenable to a disconnection, we change to functional group to an alcohol (see Figure 12.9), so our new target becomes 43.

There are several possible disconnections, but cleavage of bond $f$ leads to 44 and 45. This was chosen because Table 1 contains the $\text{C=C-O}$ fragment that correlates with an epoxide, and this correlates with acceptor fragment 45, which has epoxide 47 as an equivalent. 12.15. Write a reaction that prepares 47 from propanol. If 45 is the acceptor fragment, then 44 is the donor, which correlates with the Grignard reagent
derived from halide 46. Although 47 fits the criteria for a starting material, halide 46 does not (it has too many carbon atoms). As above, we exchange the halide for an alcohol (Table 1), making alcohol 48 the new target. If we disconnect bond g, we obtain the phenyl fragment 49 and the C-C-OH fragment, 50. If we make this latter fragment the acceptor, it correlates with C-C<sup>α</sup>-OH which has a carbonyl as an equivalent, specifically acetaldehyde, 52. This means that 49 is the donor and its equivalent is the Grignard reagent.
derived from bromobenzene (51). Since 51 has six carbons, it fits the criteria for the starting material. This means that bromobenzene (51) is the starting material for the entire synthesis, which is based on the retrosynthetic scheme shown in Figure 12.12. **12.16. Write a retrosynthesis for 1-cyclohexyl-2-methyl-1-butanone.**

![Figure 12.12. Retrosynthesis of 33 based on disconnection of bond c.](image)

It should be emphasized that there no "correct" disconnection for this molecule. There are choices that must be made by evaluating the actual reactions used in each synthesis. We must look at each choice to see which might be easier and better suited to our needs.

![Figure 12.14. Synthesis of 33 based on disconnection of bond c.](image)
12.3.C. The Synthesis

The synthesis based on the retrosynthesis in Figure 12.12 is shown in Figure 12.14. 12.18. Devise an alternative to the reaction sequence in Figure 12.14 that converts 43 to 33. Note that there are a total of 9 steps (not counting the hydrolysis steps) but all reactions are straightforward and there should be no major problems.

**Concepts**

- The target is the molecule to be synthesized.
- The starting material is the molecule used to begin the synthesis.
- Disconnection is the process of mentally breaking bonds in a target to generate simpler fragments as new targets to be used in the synthesis.
- The disconnection approach to synthesis is sometimes called retrosynthetic analysis.
- Assume that ionic reactions are used, and convert each disconnect fragment into a donor (nucleophilic) or acceptor (electrophilic) site, if possible based on the natural bond polarity of any heteroatoms that are present.
- A synthetic equivalent is the molecular fragment that correlates with the disconnect fragment in terms of the desired reactivity.
- If a starting material is designated, try to identify the carbon atoms of the starting material in the target. The disconnections will occur at bonds connecting that fragment to the rest of the molecule.
- If no starting material is designated, use retrosynthetic analysis to find a commercially available or readily prepared starting material.
- Identify the relationship of functional groups and manipulate the functional group as required to complete the synthesis.
- In most retrosynthetic analyses, the bond α- to the functional group and that β- to the functional group are the most important for disconnection.

**Answers to In-Chapter Questions**

12.1.
12.2.  
3 molecules that react with a δ- C or with a carbanion

CH₃I  H₂O

3 molecules that react with a δ+ C or with a carbocation

CH₃MgBr  O⁻  CN⁻

12.3.  
N has a δ- dipole, so the adjacent C should be a

12.4.  

12.5. Four common carbanions are: Grignard reagents, enolate anions, alkyne anions, and cyanide.
12.6. Ph

CH₃CH₂MgBr

O has a δ⁻-dipole, so the adjacent C should be a

12.7.
1. PhCH₂MgBr
2. aq. NH₄Cl

12.9.
(a) \( \text{OH} \) \( \text{CHO} \) 
\( \text{PCC} \) 

(b) \( \text{OH} \) \( \text{Br} \) 
\( \text{PBr}_3 \) 
\( \text{Br}_2 \) 
\( \text{NaNH}_2 \) 
heat

(c) \( \text{OH} \) \( \text{Br} \) 
\( \text{PBr}_3 \) 

(d) \( \text{OH} \) \( \text{CHO} \) 
\( \text{PCC} \) 

12.10. 

12.11. 

1. Ph \( \text{CHO} \)
2. aq, \( \text{NH}_4\text{Cl} \)
3. PhCH\(_2\)CHO 

1. PPh\(_3\)
2. BuLi 
3. CH\(_3\)CHO 

1. EtMgBr
2. aq, NH\(_4\)Cl
1. \[ \text{BrCN, DMF} \rightarrow \text{CN} \]

2. \[ \text{EtMgBr, aq. NH}_\text{4}Cl \rightarrow \text{Et} \]

3. \[ \text{PhMgBr, aq. NH}_\text{4}Cl \rightarrow \text{Ph} \]

4. \[ \text{2 eq. PhMgBr, aq. NH}_\text{4}Cl \rightarrow \text{Ph} \]

12.12.

12.13.

1. CS$_2$
2. MeI
3. 200°C

12.15. Chugaev reaction
12.16.

12.17. To convert 54 to the enolate requires treatment with lithium diisopropylamide [LiN(iPr)₂] in THF at 
-78°C. These are typical kinetic control conditions.

12.18.

**HOMEWORK**

1. Show the first two disconnections for the following molecules. Label each disconnect product as d/a and 
convert it to a real molecule for both disconnections. Remember that your starting material cannot have more 
than 5 carbon atoms.
2. Give the structure of a real molecule that is the synthetic equivalent for each of the following.

(a) \[ \text{Cyclic structure with OH} \]
(b) \[ \text{Linear structure with OH} \]
(c) \[ \text{Linear structure with OH} \]
(d) \[ \text{Linear structure with CO}_2\text{Et} \]

3. Give a retrosynthetic analysis and then a complete synthesis for each of the following.

(a) 3-heptanone from 1-propanol
(b) 2-aminohexane from 1-butene
(c) 2-methylcyclopentanol from cyclopentene
(d) 2-methylcyclopentanol from cyclohexene
(e) 3-methyl-1,2-hexanediol from 3-methyl-2-hexanol
(f) cis-2-hexene from 1-bromopropane

4. Give a retrosynthetic analysis and then a complete synthesis for each of the following.
5. Show a synthesis of 3-methyl-4-heptanone (a) from 1-butanol  (b) from 1-butanenitrile  (c) from 1-butene  
(d) from 2-methyl-2-hexene  (e) from 3-hexanol  (f) from 2-methylbutanal

6. Show three different syntheses of 4-methyl-2-octene oxide from *three different* starting materials that have 5 carbon atoms or less.

7. Show four different syntheses of 2-methylhexanoic acid from (a) 1-hexanol  (b) ethyl propanoate  
(c) 2-bromohexane  (d) 1-heptene.
8. Show a retrosynthetic analysis and a complete synthesis for N,N-diethyl-2-benzylhexanamide, from a starting material of your choice that has 5 carbons or less.

9. Describe in detail why I can make the statement that cyclohexanol is a synthetic equivalent for cyclopentanone.

10. Show reactions that support the premise that the alkyne unit in 1-pentyne is synthetically linked to 5 other different functional groups.

11. Show reactions that support the premise that the cyano unit in 1-pentanenitrile is synthetically linked to 3 other functional groups.

12. Show reactions to show that a ketone unit can be prepared from 3 different functional groups.

13. Show reactions to show that an alkene unit can be prepared from 3 different functional groups.

14. Show reaction to show that an alcohol unit can be prepared from 4 different functional groups.

15. Show a complete retrosynthetic analysis and then the complete synthesis for each of the following. Choose any starting material that has 5 carbons or less.