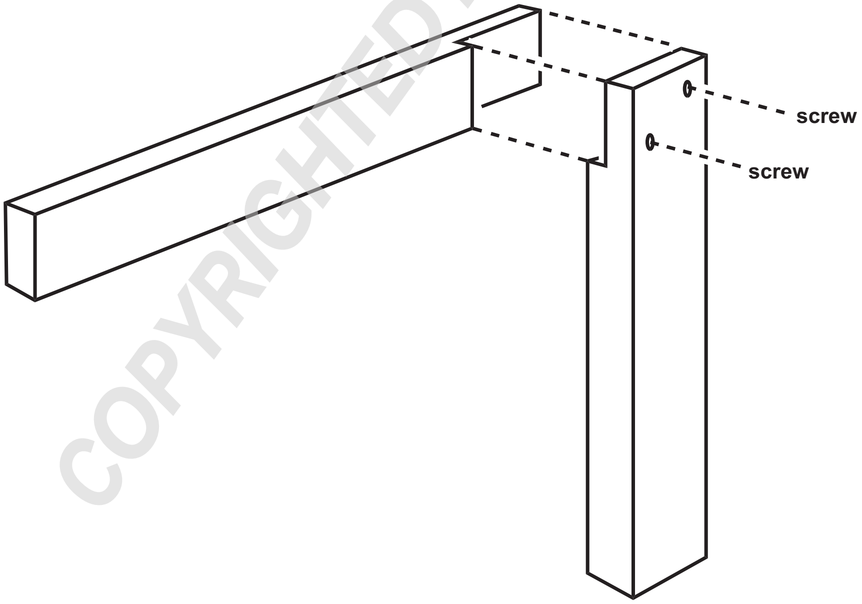
1 The Disconnection Approach

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[1] in 1917. His term was 'imaginary

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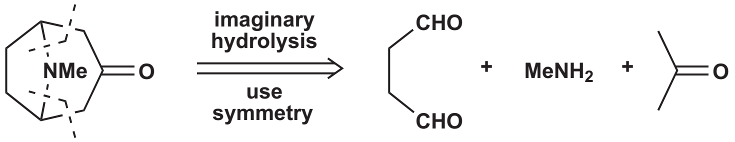
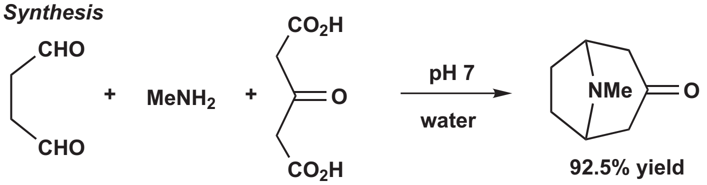
hydrolysis' and he put dashed lines across a tropinone structure.

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[2] in 1935.

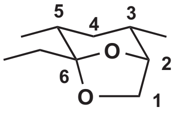
Tropinone: Synthesis



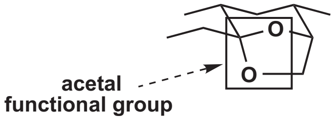
Amazingly, nobody picked up the idea until the 1960s when E. J. Corey at Harvard was considering how to write a computer program to plan organic syntheses.[3] He needed a systematic logic and he chose the disconnection approach, also called retrosynthetic analysis. All that is in this book owes its origin 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

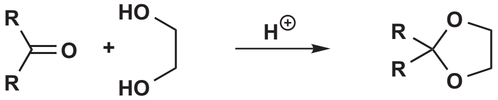
Multistriatin **1** is a pheromone of the elm bark beetle. This beetle distributes the fungus responsible for Dutch elm disease and it was hoped that synthetic multistriatin might trap the beetle and prevent the spread of the disease. It is a cyclic compound with two oxygen atoms both joined to the same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



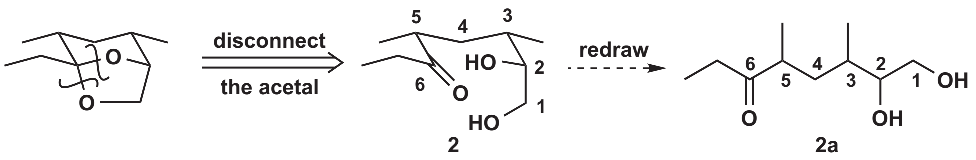
1; multistriatin



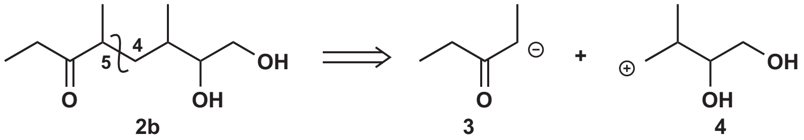
We know one good way to make acetals: the reliable acid-catalysed reaction between two alcohols or one diol and an aldehyde or ketone.



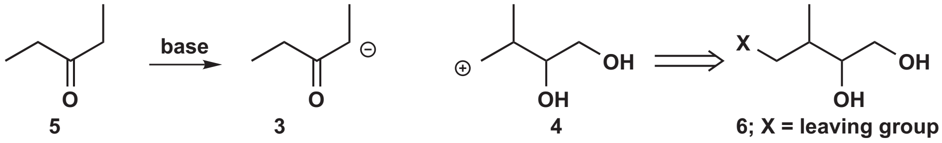
Intending to use this reliable reaction for our acetal we must disconnect the two C–O bonds to C–6 and reveal the starting material **2**, drawn first in a similar way to **1**, and then straightened out to look more natural **2a**. Numbering the carbon atoms helps to make sure **2** and **2a** are the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



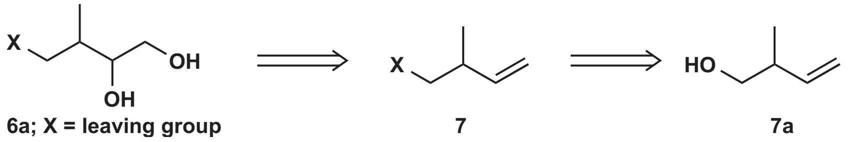
We now have a continuous piece of carbon skeleton with two OH groups and a ketone. No doubt we shall make this by forming a C–C bond. But which one? We know that ketones can form nucleophilic enolates so disconnecting the bond between C–4 and C–5 is a good choice because one starting material **3** is 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.



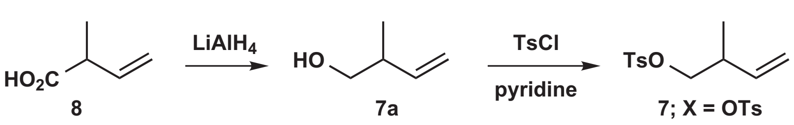
Anion **3** can be made from the available ketone **5** but the only sensible way to make **4** electrophilic is to add a leaving group X, such as a halogen, deciding later exactly what to use.



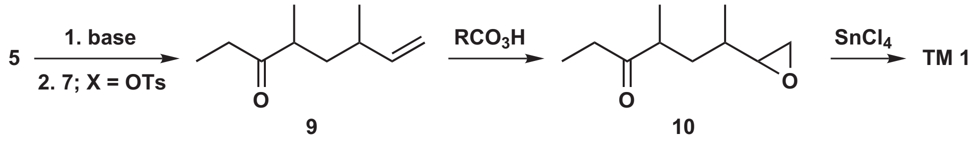
Compound **6** has three functional groups. One is undefined but the other two must be alcohols and must be on adjacent carbon atoms. There is an excellent reaction to make such a combination: the dihydroxylation of an alkene with a hydroxylating agent such as OsO_4. A good starting material becomes the unsaturated alcohol **7a** as that is known.



In one synthesis[4] 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 peroxyacid 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.

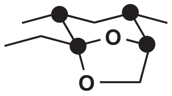
Summary: Routine for Designing a Synthesis

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.



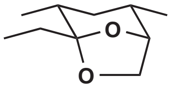
11; chiral centres in multistriatin

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

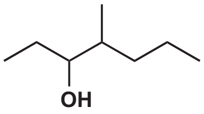
1. An understanding of reaction mechanisms.
2. A working knowledge of reliable reactions.
3. An appreciation that some compounds are readily available.
4. An understanding of stereochemistry.

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 α-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.



1; multistriatin



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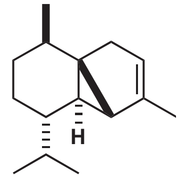

13; α-cubebene

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

1. R. Robinson, *J. Chem. Soc.*, 1917, **111**, 762.
2. C. Schöpf and G. Lehmann, *Liebig's Annalen*, 1935, **518**, 1.
3. E. J. Corey, *Quart. Rev.*, 1971, **25**, 455; E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.
4. G. T. Pearce, W. E. Gore and R. M. Silverstein, *J. Org. Chem.*, 1976, **41**, 2797.