

Stuart Warren · Paul Wyatt

ORGANIC SYNTHESIS

The Disconnection Approach
Second Edition

 WILEY

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Organic Synthesis: The Disconnection Approach 2nd Edition

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and

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Organic Synthesis: The Disconnection Approach

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.

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.

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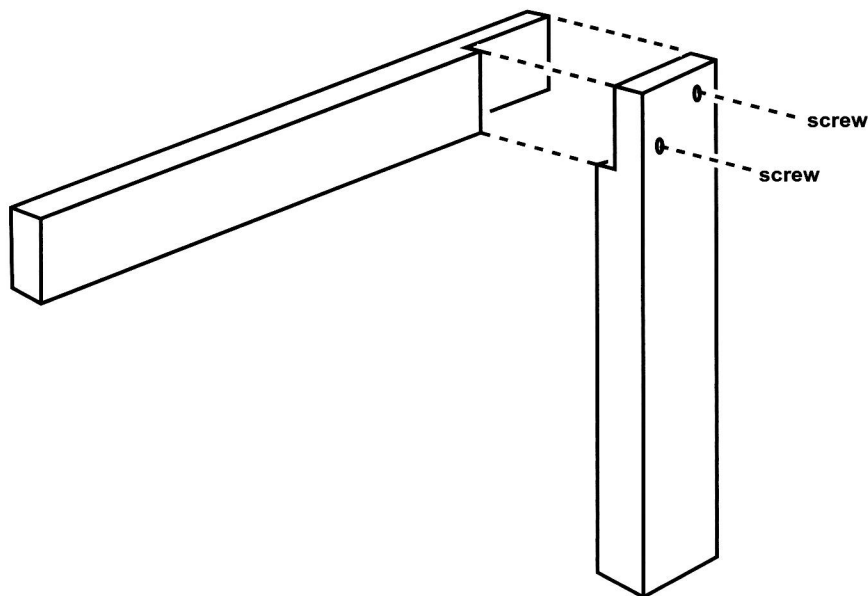
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1 The Disconnection Approach

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.

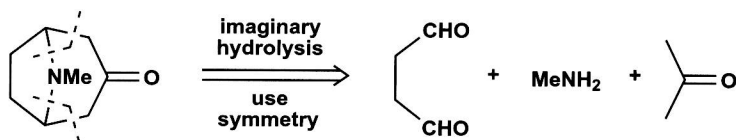
When you plan the synthesis of a molecule, all you know for certain is the structure of the molecule you are trying to make. It is made of atoms but we don't make molecules from atoms: we make them from smaller molecules. But how to choose which ones? If you wanted to make, say, a wooden joint, you would 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 synthesis¹ in 1917. His term was 'imaginary

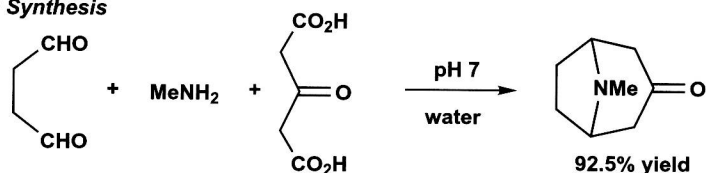
hydrolysis' and he put dashed lines across a tropinone structure.

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 Schöpf² in 1935.

Tropinone: Synthesis



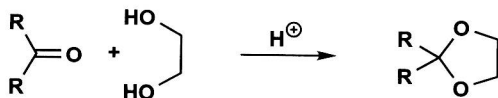
Amazingly, nobody picked up the idea until the 1960s when E. J. Corey at Harvard was considering how to write a computer program to plan organic syntheses.³ He needed a systematic logic and he chose the disconnection approach, also called retrosynthetic analysis. All that is in this book owes its origin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

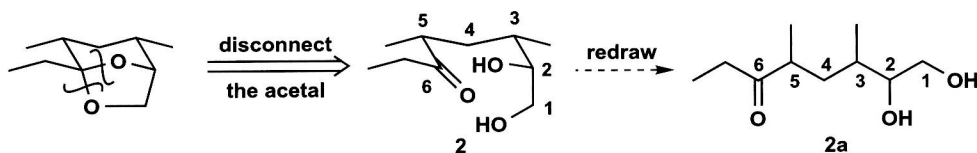


We know one good way to make acetals: the reliable acid-catalysed reaction between two alcohols or one diol and an aldehyde or ketone.

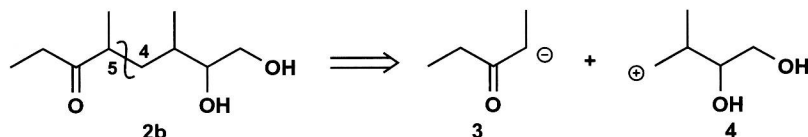


Intending to use this reliable reaction for our acetal we must disconnect the two C–O bonds to C-6 and reveal the starting material **2**, drawn first in a similar way to **1**, and then straightened

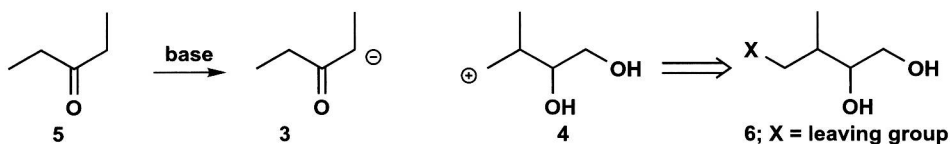
out to look more natural **2a**. Numbering the carbon atoms helps to make sure **2** and **2a** are the same.



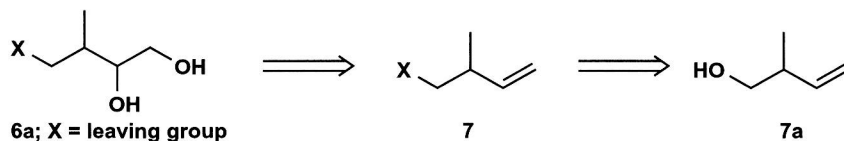
We now have a continuous piece of carbon skeleton with two OH groups and a ketone. No doubt we shall make this by forming a C–C bond. But which one? We know that ketones can form nucleophilic enolates so disconnecting the bond between C–4 and C–5 is a good choice because one starting material **3** is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



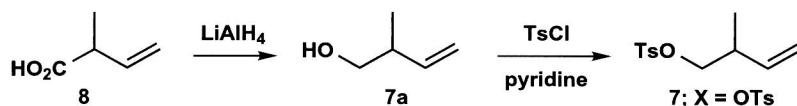
Anion **3** can be made from the available ketone **5** but the only sensible way to make **4** electrophilic is to add a leaving group X, such as a halogen, deciding later exactly what to use.



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.

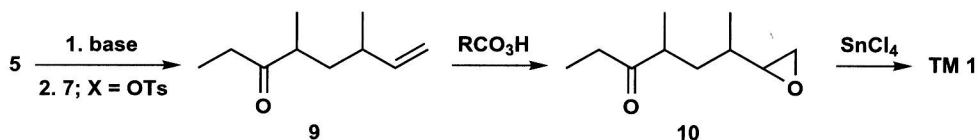


In one synthesis⁴ the alcohol **7a** was made from the available acid **8** and the leaving group (X in **6**) was chosen as tosylate (OTs; toluene-*p*-sulfonate).



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

- Recognise the functional groups in the target molecule.
- Disconnect with known reliable reactions in mind.
- Repeat as necessary to find available starting materials.

2. Synthesis

- Write out the plan adding reagents and conditions.
- 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.

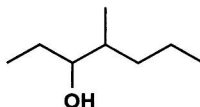
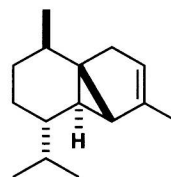


We must add stereochemistry to the list of essential background knowledge an organic chemist must have to design syntheses effectively. That list is now:

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****12****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.

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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.

2 Basic Principles: Synthons and Reagents

Synthesis of Aromatic Compounds

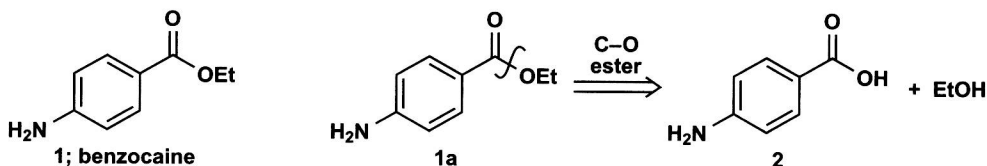
Background Needed for this Chapter References to Clayden, *Organic Chemistry*:
Electrophilic aromatic substitution; chapter 22. (Electrophilic Aromatic Substitution)
Nucleophilic aromatic substitution: chapter 23 (Electrophilic Alkenes).
Reduction: chapter 24 (Chemoselectivity: Selective Reactions and Protection).

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.

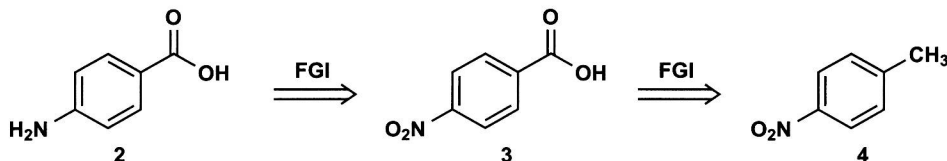
Disconnection and FGI

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.

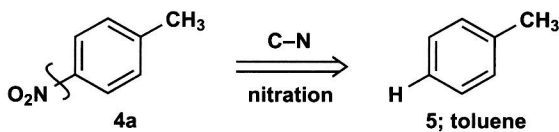


The sign for a disconnection on a molecule is some sort of wiggly line across the bond being disconnected. You can draw this line in any way you like within reason. The 'reaction arrow' is the 'implies' arrow from logic. The argument is that the existence of any ester *implies* that it can be made from an acid and an alcohol.

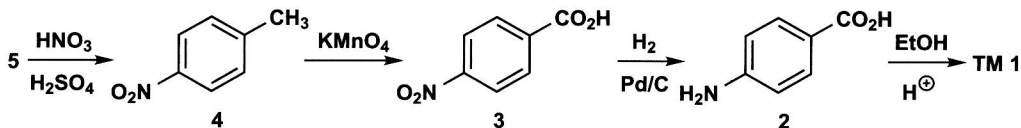
We should now like to disconnect either the NH_2 or the CO_2H group but we know of no good reactions corresponding to those disconnections. We need to change both groups into some other groups that can be added to a benzene ring by a known reliable reaction. This process is called *functional group interconversion* 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.



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.



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



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 AlCl_3 gives **6** in 94–96% yield—a good reaction indeed.

