Workbook for Organic Synthesis: The Disconnection Approach
Second Edition
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Second Edition

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Contents

Preface vii

General References ix

1. The Disconnection Approach 1
2. Basic Principles: Synthons and Reagents: Synthesis of Aromatic Compounds 5
3. Strategy I: The Order of Events 11
4. One-Group C–X Disconnections 15
5. Strategy II: Chemoselectivity 21
6. Two-Group C–X Disconnections 29
7. Strategy III: Reversal of Polarity, Cyclisations, Summary of Strategy 35
8. Amine Synthesis 41
9. Strategy IV: Protecting Groups 49
10. One-Group C–C Disconnections I: Alcohols 55
11. General Strategy A: Choosing a Disconnection 61
12. Strategy V: Stereoselectivity A 67
13. One-Group C–C Disconnections II: Carbonyl Compounds 75
14. Strategy VI: Regioselectivity 81
15. Alkene Synthesis 87
17. Two-Group C–C Disconnections I: Diels-Alder Reactions 99
18. Strategy VIII: Introduction to Carbonyl Condensations 105
19. Two-Group C–C Disconnections II: 1,3-Difunctionalised Compounds 111
20. Strategy IX: Control in Carbonyl Condensations 115
21. Two-Group C–C Disconnections III: 1,5-Difunctionalised Compounds Conjugate (Michael) Addition and Robinson Annelation 123
23. Two-Group Disconnections IV: 1,2-Difunctionalised Compounds 133
25. Two-Group Disconnections V: 1,4-Difunctionalised Compounds 147
26. Strategy XII: Reconnection 153
27. Two-Group C–C Disconnections VI: 1,6-diCarbonyl Compounds 159
28. General Strategy B: Strategy of Carbonyl Disconnections 165
30. Three-Membered Rings 181
31. Strategy XIV: Rearrangements in Synthesis 189
32. Four-Membered Rings: Photochemistry in Synthesis 195
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>33. Strategy XV: The Use of Ketenes in Synthesis</td>
<td>201</td>
</tr>
<tr>
<td>34. Five-Membered Rings</td>
<td>207</td>
</tr>
<tr>
<td>for Five-Membered Rings</td>
<td></td>
</tr>
<tr>
<td>36. Six-Membered Rings</td>
<td>221</td>
</tr>
<tr>
<td>37. General Strategy C: Strategy of Ring Synthesis</td>
<td>227</td>
</tr>
<tr>
<td>38. Strategy XVII: Stereoselectivity B</td>
<td>235</td>
</tr>
<tr>
<td>39. Aromatic Heterocycles</td>
<td>245</td>
</tr>
<tr>
<td>40. General Strategy D: Advanced Strategy</td>
<td>255</td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td><strong>263</strong></td>
</tr>
</tbody>
</table>
Preface

In the 26 years since Wiley published *Organic Synthesis: The Disconnection Approach* and the accompanying Workbook, this approach to the learning of synthesis has become widespread while the books themselves are now dated in content and appearance. In 2008, Wiley published the second edition of *Organic Synthesis: The Disconnection Approach* by Stuart Warren and Paul Wyatt for which this is the accompanying Workbook.

This workbook contains further examples, problems (and answers) to help you understand the material in each chapter of the textbook. The structure of this second edition of the workbook is the same as that of the textbook. The 40 chapters have the same titles as before but all chapters have undergone a thorough revision with some new material. The emphasis is on helpful examples and problems rather than novelty. Many of the problems are drawn from the courses we have given in industry on ‘The Disconnection Approach’ where they have stimulated discussion leading to deeper understanding. It makes sense for you to have the relevant chapter of the textbook available while you are working on the problems. We have usually devised new problems but some of the problems in the first edition seemed to do such a good job that we have kept them. Usually, the answers are presented in a different and, we hope, more helpful style.

It is not possible to learn how to design organic syntheses just from lectures or from reading a textbook. Only by tackling problems and checking your answers against published material can you develop this skill. We should warn you that there is no single ‘right answer’ to a synthesis problem. Successful published syntheses give some answers that work, but you may well be able to design others that have a good chance of success. The style of this second edition is to give more discussion of alternative routes.

Stuart Warren and Paul Wyatt
2009
General References

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


The Disconnection Approach

We start with a few simple problems to set you at ease with disconnections. **Problem 1.1:** Here is a two-step synthesis of the benzofuran 3. Draw out the retrosynthetic analysis for the synthesis of 2 from 1 showing the disconnections and the synthons.

![Synthesis diagram](image)

**Answer 1.1:** As this is a simple S_N2 reaction, the disconnection is of the C–O bond 2a and the synthons are nucleophilic phenolate anion 4, which happens to be an intermediate in the reaction, and the cation 5, which happens not be an intermediate in the reaction but is represented by the \( \alpha \)-bromoketone 6.

![Diagram of the reaction](image)

**Problem 1.2:** Draw the mechanism of the cyclisation of 2 to 3. This is an unusual reaction and it helps to know what is going on before we analyse the synthesis. **Answer 1.2:** The first step is an acid-catalysed cyclisation of the aromatic ring onto the protonated ketone 7. Loss of a proton 8 completes the electrophilic aromatic substitution giving the alcohol 9.

![Diagram of the cyclisation](image)
Now protonation of the alcohol leads to loss of water 10 to give a stabilised cation that loses a proton 11 to give the new aromatic system 3. **Problem 1.3:** Now you should be in a position to draw the disconnections for this step.

![Chemical structure](image1)

**Answer 1.3:** We hope you might have drawn the intermediate alcohol 9. Changing 3 into 9 is not a disconnection but a Functional Group Interconversion (FGI) – changing one functional group into another. Now we can draw the disconnection revealing the synthons 12 represented in real life by 2.

![Chemical structure](image2)

**A Synthesis of Multistriatin**

In the textbook we gave one synthesis of multistriatin 17 and here is a shorter but inferior synthesis as the yields are lower and there is little control over stereochemistry.\(^1\) **Problem 1.4:** Which atoms in the final product 17 come from which starting material and which bonds are made in the synthesis? **Hint:** Arbitrarily number the atoms in multistriatin and try to trace each atom back through the intermediates. Do not be concerned over mechanistic details, especially of the step at 290 °C.

![Chemical structure](image3)

**Answer 1.4:** However you numbered multistriatin, the ethyl group (7 and 8 in 17a) finds the same atoms in the last intermediate 16a and the rest falls into place. It then follows which atoms come from 14 and which from 15. Finally, you might have said that C-4 in our diagrams comes from formaldehyde.
So the disconnections also fall into place. Just one C–O bond was disconnected at first 17b then one C–O and one C–C 16b and finally the alkene was disconnected 14b in what you may recognise as an aldol reaction with formaldehyde. If you practise analysing published syntheses like this, you will increase your understanding of good bonds to disconnect.

References