

Stuart Warren · Paul Wyatt

ORGANIC SYNTHESIS

The Disconnection Approach
Second Edition

 WILEY

Contents

[*Preface*](#)

[*General References*](#)

[*1 The Disconnection Approach*](#)

[*The Synthesis of Multistriatin*](#)

[*Summary: Routine for Designing a Synthesis*](#)

[*What the Rest of the Book Contains*](#)
[*References*](#)

[*2 Basic Principles: Synthons and Reagents Synthesis of Aromatic Compounds*](#)

[*Synthesis of Aromatic Compounds*](#)

[*Disconnection and FGI*](#)

[*Synthons Illustrated by Friedel-Crafts Acylation*](#)

[*Synthons Illustrated by Friedel-Crafts Alkylation*](#)

[*Functional Group Addition Illustrated by Friedel-Crafts Alkylation*](#)

[*Reliable Reagents for Electrophilic Substitution*](#)

[*Changing the Polarity: Nucleophilic Aromatic Substitution*](#)

[*Thinking Mechanistically*](#)

[Changing the Polarity: Nucleophilic Aromatic Substitution by the SN1 Mechanism](#)
[References](#)

[3 Strategy I: The Order of Events](#) [References](#)

[4 One-Group C-X Disconnections](#) [Carbonyl Derivatives RCO.X](#) [The Synthesis of Ethers](#) [The Synthesis of Sulfides](#) [Summary of Compounds Made from Alcohols](#) [References](#)

[5 Strategy II: Chemoselectivity](#) [A Warning](#) [References](#)

[6 Two-Group C-X Disconnections](#) [One-Group and Two-Group C-X Disconnections](#) [Recognising a Two-Group C-X Disconnection](#) [The 1,3-diX Relationship](#) [The 1,2-diX Relationship](#) [The 1,1-diX Relationship](#) [Two-Group C-X Disconnections as a Preliminary to a Full Analysis](#)

[References](#)

[7 Strategy III: Reversal of Polarity, Cyclisations, Summary of Strategy](#)

[Reversal of Polarity Synthesis of Epoxides and \$\alpha\$ -Halo-Carbonyl Compounds](#)

[The Halogenation of Ketones](#)

[Halogenation of Acids](#)

[Cyclisation Reactions](#)

[Summary of Strategy](#)

[Example: Salbutamol](#)

[References](#)

[8 Amine Synthesis](#)

[Reductive Amination](#)

[Other Ways to Make Amines](#)

[The Synthesis of Monomarine I](#)

[References](#)

[9 Strategy IV: Protecting Groups](#)

[Qualities Needed in a Protecting Group](#)

[Ethers and Amides as Protecting Groups](#)

[The Achilles Heel Strategy](#)

[Protection of Alcohols](#)

[The Literature on Protecting Groups](#)

[Protecting Group Summary](#)

[References](#)

10 One Group C-C Disconnections I: Alcohols

Reagents for Nucleophilic Carbon

'1,1C-C' Disconnections: The Synthesis of Alcohols

Aldehydes and Ketones

Oxidising Agents for the Conversion of Alcohols to Aldehydes

Carboxylic Acids

'1,2C-C' Disconnections: The Synthesis of Alcohols

Example of the Synthesis of Alcohols and Related Compounds

Other One-Group C-C Disconnections

Carbon-Carbon Disconnections to Avoid
References

11 General Strategy A: Choosing a Disconnection

Greatest Simplification

Symmetry

Recognisable Starting Materials

Available Compounds

Summary of Guidelines for Good Disconnections

References

12 Strategy V: Stereoselectivity A

Enantiomerically Pure Compounds

*Stereospecific and Stereoselective
Reactions
References*

13 One Group C-C Disconnections II: Carbonyl Compounds

*Synthesis of Aldehydes and Ketones by
Acylation at Carbon
Carbonyl Compounds by Alkylation of Enols
Carbonyl Compounds by Conjugate Addition
References*

14 Strategy VI: Regioselectivity

*The Regioselective Alkylation of Ketones
Regioselectivity in Nucleophilic Addition to
Enones
References*

15 Alkene Synthesis

*Synthesis of Alkenes by Elimination
Reactions
Alkene Synthesis by the Wittig Reaction
References*

16 Strategy VII: Use of Acetylenes (Alkynes)

*The Reduction of Alkynes to Alkenes
Ketones by Hydration of Acetylenes
An Alkyne-Containing Anti-AIDS Drug*

References

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

Stereospecificity

Endo-Selectivity

Regioselectivity

FGI on Diels-Alder Products

Intramolecular Diels-Alder Reactions

Diels-Alder Reactions in Water

References

18 Strategy VIII: Introduction to Carbonyl Condensations

Carbon Acids and the Bases Used to Deprotonate Them

Reference

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

β -Hydroxy Carbonyl Compounds: The Aldol Reaction

The Synthesis of α,β -Unsaturated Carbonyl Compounds

1,3-diCarbonyl Compounds

Looking Forward

References

20 Strategy IX: Control in Carbonyl Condensations

The Three Key Questions for Successful Cross-Condensations

Intramolecular Reactions

Cross-Conjugations I: Compounds that Cannot Enolise

Cross-Conjugation II: Specific Enolates

Cross-Condensation III: Removal of a Product from Equilibrium

References

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

Specific Enol Equivalents Good at Michael Addition

Michael Acceptors Good at Conjugate Addition

The Robinson Annellation

Heterocycles Made from 1,5-diCarbonyl Compounds

References

22 Strategy X: Aliphatic Nitro Compounds in Synthesis

Reduction of Nitro Compounds

Diels-Alder Reactions

Summary of Nitro Groups in Synthesis
References

23 Two-Group Disconnections IV:

Acyl Anion Equivalents

Methods from Alkenes

α -Functionalisation of Carbonyl Compounds

Strategy of Available Starting Materials

The Benzoin Condensation

References

24 Strategy XI: Radical Reactions in Synthesis

Functionalisation of Allylic and Benzylic Carbons²

Carbon-Carbon Bond-Forming Reactions

Making 1,2-Difunctionalised Compounds

25 Two-Group Disconnections V:1,4-Difunctionalised Compounds

Reactions of Enol(ate)s with Reagents for α^2 Synthons

Conjugate Addition of Acyl Anion Equivalents

Direct Addition of Homoenolates (α^3 Reagents)

Strategy of Available Starting Materials with a 1,4-diCO Relationship

The FGA Strategy

References

26 Strategy XII: Reconnection

Synthesis of 1,2- and 1,4-diCO Compounds
by Oxidative C=C Cleavage

A Dramatic Example of FGA

References

27 Two-Group C-C Disconnections VI: 1,6-diCarbonyl Compounds

The Diels-Alder Route to 1,6-diCarbonyl
Compounds

Cyclohexenes from Other Sources

Oxidative Cleavage by the Baeyer-Villiger
Reaction

Other Approaches

References

28 General Strategy B: Strategy of Carbonyl Disconnections

The Synthesis of a Lactone

Synthesis of a Symmetrical Cyclic Acetal

Synthesis of a Spiro Enone

The Synthesis of Piquindone

Summary of General Approach to the
Design of Syntheses

References

29 Strategy XIII: Introduction to Ring Synthesis: Saturated Heterocycles

Cyclisation Reactions

Three-Membered Rings

Four-Membered Rings

Five-Membered Rings

Six-Membered Rings

Seven-Membered Rings

References

30 Three-Membered Rings

Cyclopropanes by Alkylation of Enolates

Carbene Insertion into Alkenes

Sulfonium Ylid Chemistry

References

31 Strategy XIV: Rearrangements in Synthesis

Diazoalkanes

Diazoalkanes in Ring Expansion and Contraction

The Pinacol Rearrangement

The Favorskii Rearrangement

References

32 Four-Membered Rings: Photochemistry in Synthesis

Photochemical Cycloadditions

Four-Membered Rings by Ionic Reactions
References

33 Strategy XV: The Use of Ketenes in Synthesis

[2 + 2] Thermal Cycloadditions of Ketenes
References

34 Five-Membered Rings

Five-Membered Rings from 1,4-diCarbonyl Compounds

Cyclopentyl Ketones from 1,6-diCarbonyl Compounds

Cyclopentanes from 1,5-diCarbonyl Compounds

Synthesis of Cyclopentanes by Double Sequential Conjugate Addition

References

35 Strategy XVI: Pericyclic Reaction in Synthesis: Special Methods for Five-Membered Rings

Electrocyclic Reactions

Sigmatropic Rearrangements

36 Six-Membered Rings

Carbonyl Condensations: The Robinson Annelation

The Diels-Alder Reaction

Reduction of Aromatic Compounds
References

37 General Strategy C: Strategy of Ring Synthesis

Cyclisation to Control Selectivity
Early Disconnection of Small Rings
Alternative Disconnections
References

38 Strategy XVII: Stereoselectivity B

Synthesis of Molecules with Many Chiral Centres
Stereochemical Control in Folded Molecules
A Synthesis of Copaene
Summary of Stereoselectivity on Folded Molecules
The Synthesis of Juvabione
References

39 Aromatic Heterocycles

Carbon-Heteroatom Disconnections
Thiazoles
Six-Membered Rings: Pyridines
Pyrimidines
Benzene-Fused Heterocycles: Indoles
Example: The Synthesis of Indomethacin
Making Bonds to pre-Formed Heterocycles
References

40 General Strategy D: Advanced Strategy

A Synthesis of Pyrazoles

Convergence

Convergence in a Commercial Synthesis

Key Reaction Strategy

References

Index

Organic Synthesis: The Disconnection Approach 2nd Edition

Stuart Warren

Chemistry Department, Cambridge University, UK

and

Paul Wyatt

School of Chemistry, University of Bristol, UK

 **WILEY**



A John Wiley and Sons, Ltd., Publication

This edition first published 2008

© 2008 John Wiley & Sons, Inc.

Registered office

John Wiley & Sons Ltd, The Atrium, Southern Gate,
Chichester, West Sussex, PO19 8SQ, United Kingdom

For details of our global editorial offices, for customer
services and for information about how to apply for
permission to reuse the copyright material in this book
please see our website at www.wiley.com.

The right of the author to be identified as the author of this
work has been asserted in accordance with the Copyright,
Designs and Patents Act 1988.

All rights reserved. No part of this publication may be
reproduced, stored in a retrieval system, or transmitted, in
any form or by any means, electronic, mechanical,
photocopying, recording or otherwise, except as permitted
by the UK Copyright, Designs and Patents Act 1988, without
the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic
formats. Some content that appears in print may not be
available in electronic books.

Designations used by companies to distinguish their
products are often claimed as trademarks. All brand names
and product names used in this book are trade names,
service marks, trademarks or registered trademarks of their
respective owners. The publisher is not associated with any
product or vendor mentioned in this book. This publication is
designed to provide accurate and authoritative information
in regard to the subject matter covered. It is sold on the
understanding that the publisher is not engaged in
rendering professional services. If professional advice or
other expert assistance is required, the services of a
competent professional should be sought.

The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

Library of Congress Cataloging-in-Publication Data

Warren, Stuart G.

Organic synthesis: the disconnection approach/Stuart Warren and Paul Wyatt.—2nd ed.

p. cm.

Includes bibliographical references and index.

ISBN 978-0-470-71237-5 (cloth)—ISBN 978-0-470-71236-8
(pbk.: alk. paper)

1. Organic compounds-Synthesis. I. Wyatt, Paul. II. Title.

QD262.W284 2008

547'.2-dc22

2008033269

A catalogue record for this book is available from the British
Library.

ISBN 978-0-470-7-12375 (HBK) 978-0-470-7-12368 (PBK)

Typeset in 10/12 Times-Roman by Laserwords Private
Limited, Chennai, India Printed and bound in Great Britain
by Antony Rowe Ltd, Chippenham, Wiltshire

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.

Clayden, *Lithium*: J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, 2002.

Clayden, *Organic Chemistry*: J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, 2000.

Comp. Org. Synth.: eds. Ian Fleming and B. M. Trost, *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, six volumes.

Corey, *Logic*: E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.

Fieser, *Reagents*: L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 20 volumes, 1967-2000, later volumes by T.-L. Ho.

Fleming, *Orbitals*: Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.

Fleming, *Syntheses*: Ian Fleming, *Selected Organic Syntheses*, Wiley, London, 1973.

Houben-Weyl; *Methoden der Organischen Chemie*, ed. E. Müller, and *Methods of Organic Chemistry*, ed. H.-G. Padeken, Thieme, Stuttgart, many volumes 1909-2004.

House: H. O. House, *Modern Synthetic Reactions*, Benjamin, Menlo Park, Second Edition, 1972.

Nicolaou and Sorensen: K. C. Nicolaou and E. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*. VCH, Weinheim, 1996. Second volume now published.

Saunders, *Top Drugs*: J. Saunders, *Top Drugs: Top Synthetic Routes*, Oxford University Press, Oxford, 2000.

Strategy and Control; P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007 and *Workbook*, 2008.

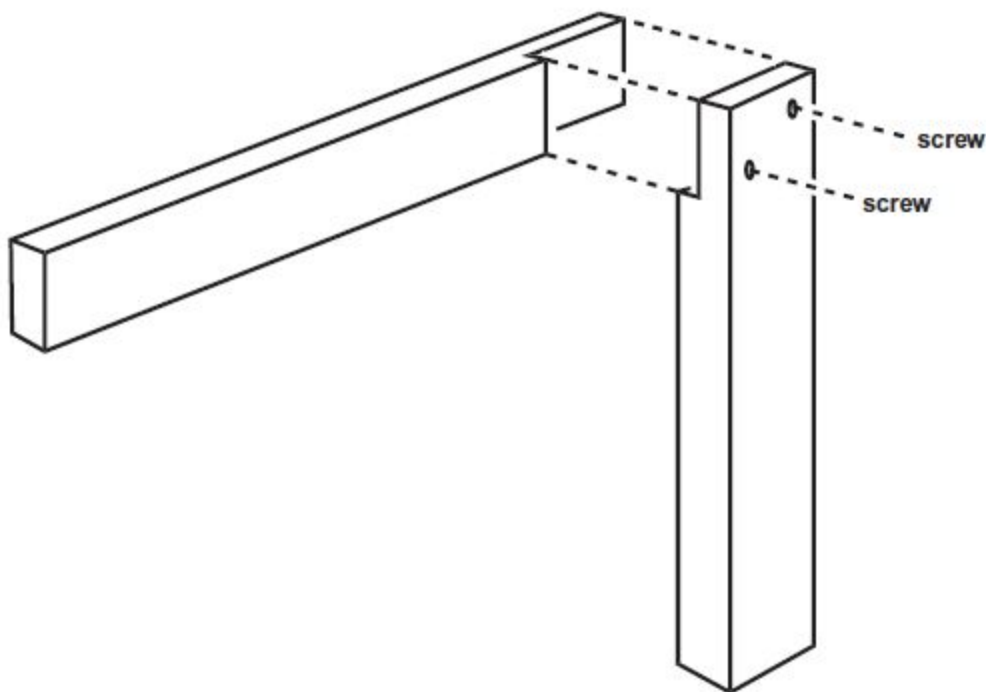
Vogel: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Longman, Harlow, 1989.

1

The Disconnection Approach

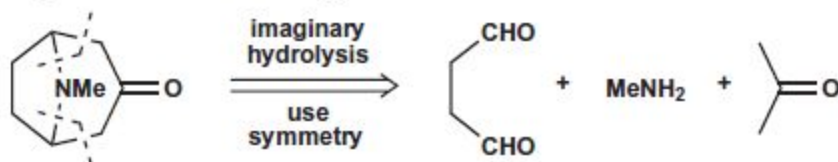
This book is about making molecules. Or rather it is to help you design your own syntheses by logical and sensible thinking. This is not a matter of guesswork but requires a way of thinking backwards that we call the disconnection approach.

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.

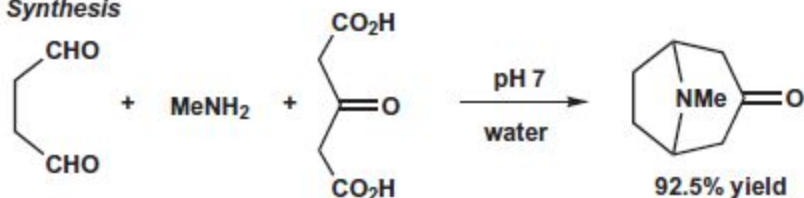
Tropinone: Robinson's Analysis



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.

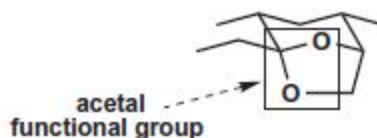
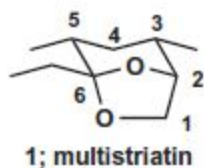
Tropinone: Synthesis



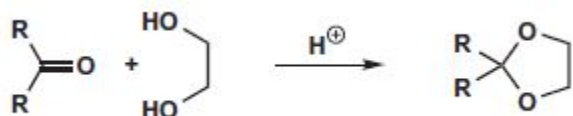
Amazingly, nobody picked up the idea until the 1960s when E. J. Corey at Harvard was considering how to write a computer program to plan organic syntheses.³ He needed a systematic logic and he chose the disconnection approach, also called retrosynthetic analysis. All that is in this book owes its origin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

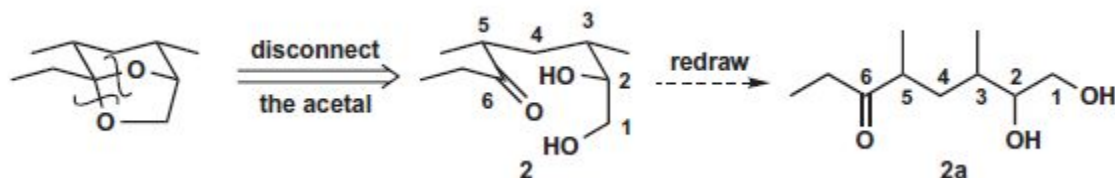
Multistriatin **1** is a pheromone of the elm bark beetle. This beetle distributes the fungus responsible for Dutch elm disease and it was hoped that synthetic multistriatin might trap the beetle and prevent the spread of the disease. It is a cyclic compound with two oxygen atoms both joined to the same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



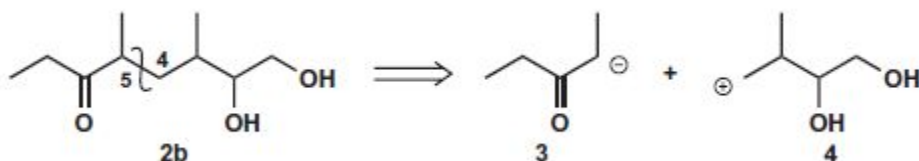
We know one good way to make acetals: the reliable acid-catalysed reaction between two alcohols or one diol and an aldehyde or ketone.



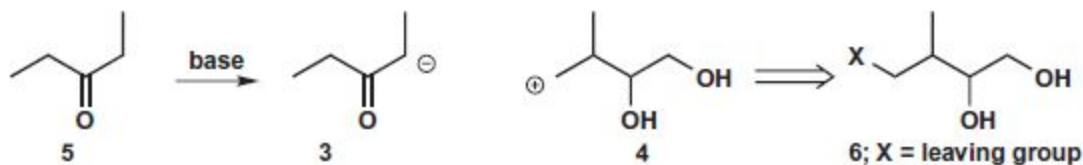
Intending to use this reliable reaction for our acetal we must disconnect the two C-O bonds to C-6 and reveal the starting material **2**, drawn first in a similar way to **1**, and then straightened out to look more natural **2a**. Numbering the carbon atoms helps to make sure **2** and **2a** are the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



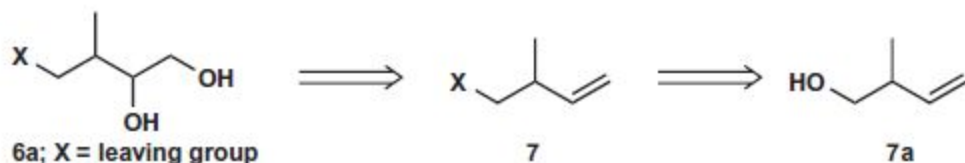
We now have a continuous piece of carbon skeleton with two OH groups and a ketone. No doubt we shall make this by forming a C-C bond. But which one? We know that ketones can form nucleophilic enolates so disconnecting the bond between C-4 and C-5 is a good choice because one starting material **3** is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



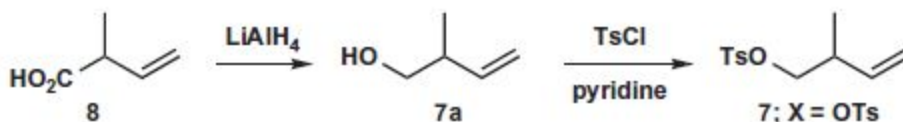
Anion **3** can be made from the available ketone **5** but the only sensible way to make **4** electrophilic is to add a leaving group X, such as a halogen, deciding later exactly what to use.



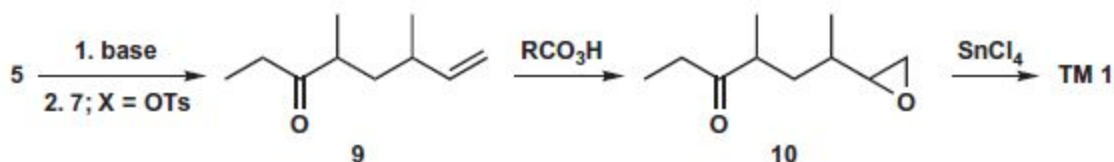
Compound **6** has three functional groups. One is undefined but the other two must be alcohols and must be on adjacent carbon atoms. There is an excellent reaction to make such a combination: the dihydroxylation of an alkene with a hydroxylating agent such as OsO_4 . A good starting material becomes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

- (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.

