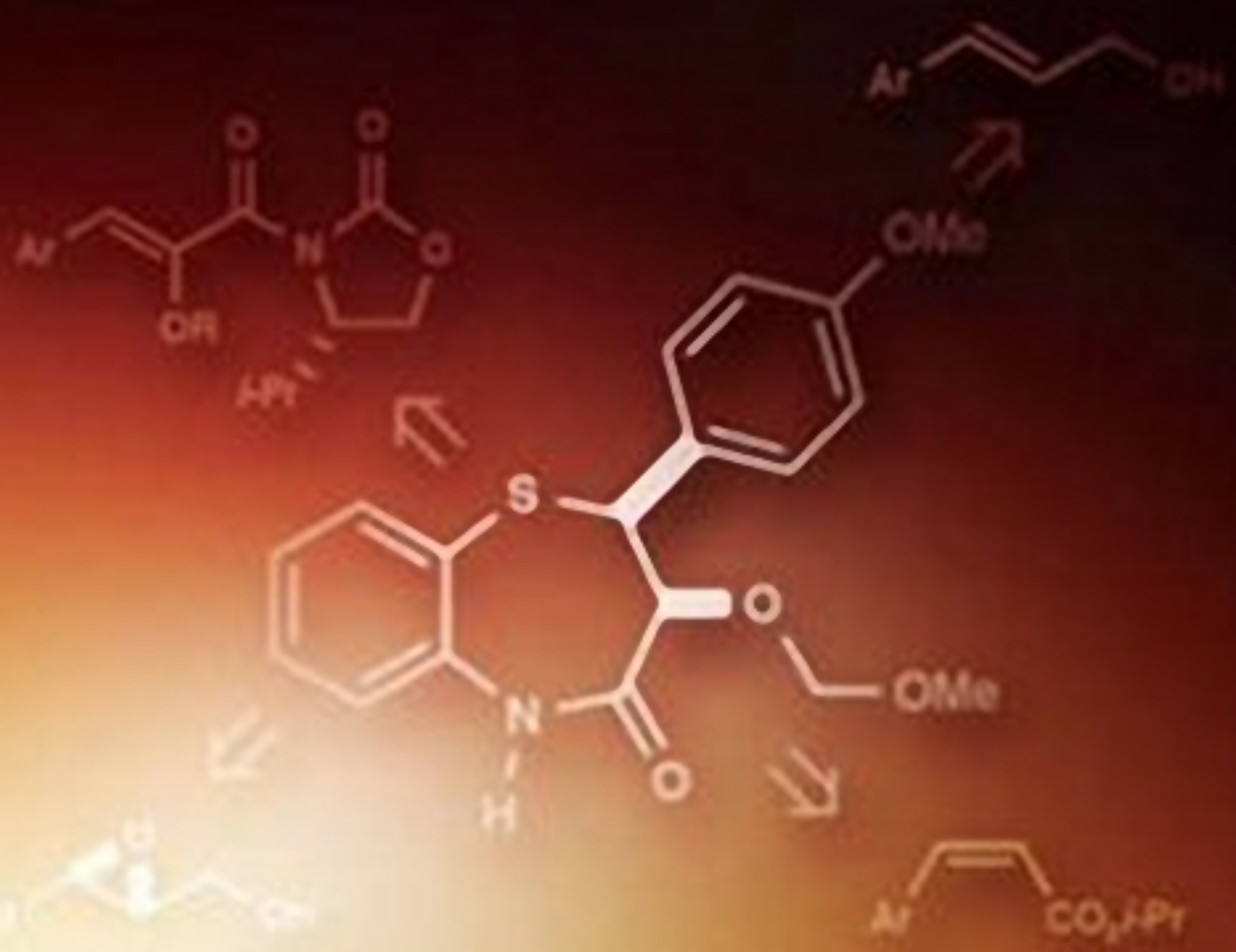

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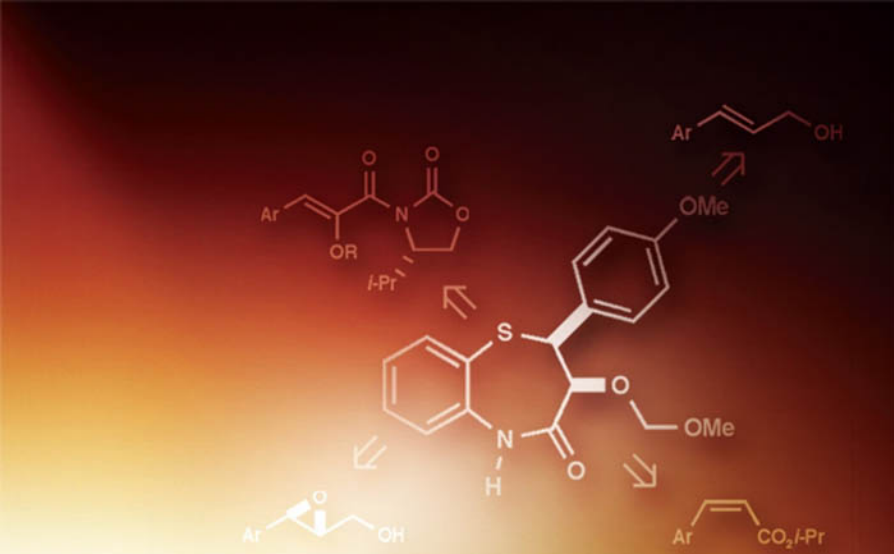

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Organic Synthesis

Organic Synthesis: Strategy and Control

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and

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Preface

We would like to thank those who have had the greatest influence on this book, namely the undergraduates at the Universities of Bristol and Cambridge. But, particularly we would like to thank the organic chemists at Organon (Oss), AstraZeneca (Alderley Park, Avlon Works, Mölndal and Macclesfield), Lilly (Windlesham), Solvay (Weesp) and Novartis (Basel) who contributed to the way the book was written more than they might realise. These chemists will recognise material from our courses on The Disconnection Approach, Advanced Heterocyclic Chemistry, New Synthetic Methods and Asymmetric Synthesis. Additionally we would like to thank the participants at the SCI courses organised by the Young Chemists Panel. All these industrial chemists participated in our courses and allowed us to find the best way to explain concepts that are difficult to grasp. This book has changed greatly over the ten years it was being written as we became more informed over what was really needed. The book is intended for that very audience – final year undergraduates, graduate students and professional chemists in industry.

PJW
SGW
July 2006

Section A: Introduction: Selectivity

1. **Planning Organic Syntheses: Tactics, Strategy and Control** **3**

2. **Chemoselectivity** **9**

3. **Regioselectivity: Controlled Aldol Reactions** **27**

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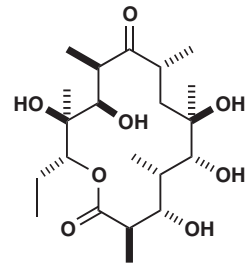
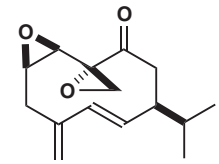
1 Planning Organic Syntheses: Tactics, Strategy and Control

The roll of honour inscribed with successful modern organic syntheses is remarkable for the number, size, and complexity of the molecules made in the last few decades. Woodward and Eschenmoser's vitamin B_{12} synthesis,[1] completed in the 1970s, is rightly regarded as a pinnacle of achievement, but since then Kishi[2] has completed the even more complex palytoxin. The smaller erythromycin and its precursors the erythronolides[3] **1**, and the remarkably economical syntheses of the possible stereoisomers of the cockroach pheromones **2** by Still[4] deal with a greater concentration of problems.

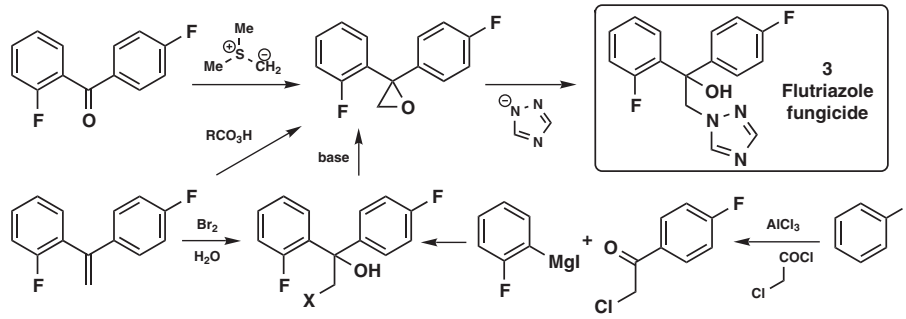
1
erythronolide A





2
periplanone-B

Less applauded, but equally significant, is the general advance in synthetic methods and their industrial applications. AstraZeneca confess that it took them nearly a century to bring Victor Grignard's methods into use, but are proud that Corey's sulfur ylid chemistry made it in a decade. Both are used in the manufacture of the fungicide flutriafol[5] **3**.



Optically active and biodegradable deltamethrin[6] **4** has taken a large share of the insecticide market, and asymmetric hydrogenation is used in the commercial synthesis of DOPA **5** used to treat Parkinson's disease.[7] These achievements depend both on the development of new methods and on strategic planning:[8] the twin themes of this book.

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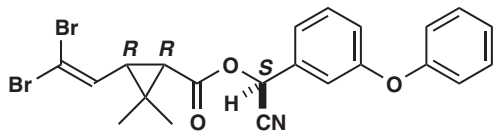
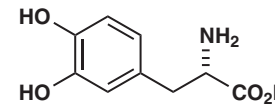
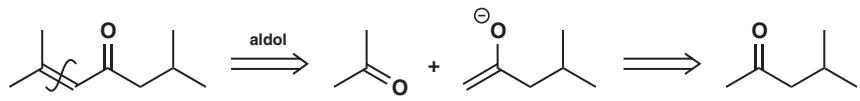


4
deltamethrin



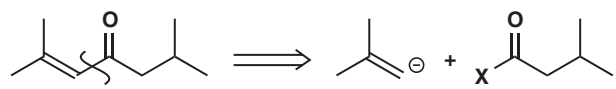
5
(*S*)-L-(–)-DOPA

To make any progress in this advanced area, we have to assume that you have mastered the basics of planning organic synthesis by the disconnection approach, roughly the material covered in our previous books.[9] There, inspecting the target molecule, identifying the functional groups, and counting up the relationships between them usually gave reliable guidelines for a logical synthesis. All enones were tackled by some version of the aldol reaction; thus **6** would require the attack of enolate **7** on acetone. We hope you already have the critical judgement to recognise that this would need *chemoselectivity* in enolising **7** rather than acetone or **6**, and *regioselectivity* in enolising **7** on the correct side.



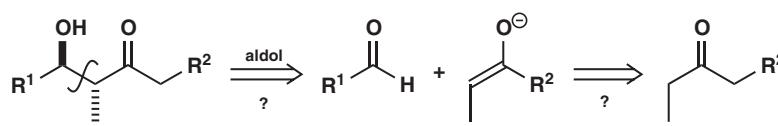
6 **7**

In this book we shall explore two new approaches to such a problem. We shall see how to make specific enol equivalents for just about any enolate you might need, and we shall see that alternative disconnections such as **6a**, the acylation of a vinyl anion **8**, can be put into practice. Another way to express the twin themes of this book is *strategy and control*: we solve problems either by finding an alternative strategy or by controlling any given strategy to make it work. This will require the introduction of many new methods - a whole chapter will be devoted to reagents for vinyl anions such as **8**, and this will mean exploring modern organometallic chemistry.



6a **8** **9**

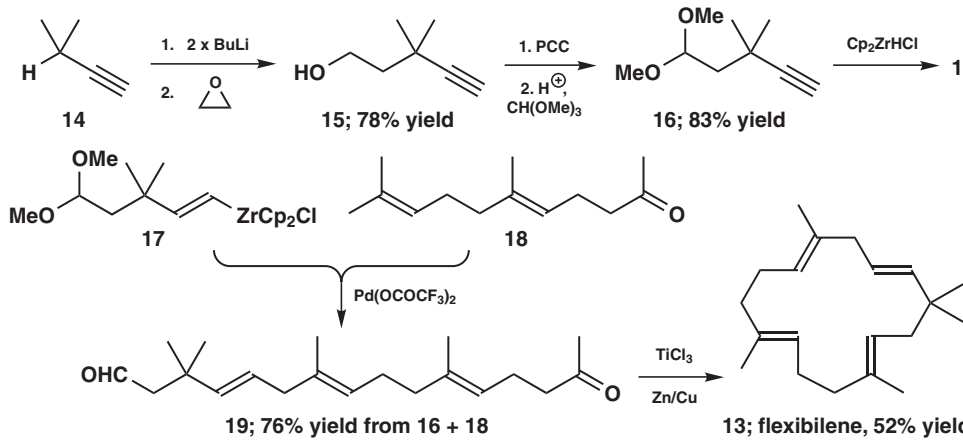
We shall also extend the scope of established reactions. We hope you would recognise the aldol disconnection in TM **10**, but the necessary stereochemical control might defeat you. An early section of this book describes how to control every aspect of the aldol reaction: how to select which partner, i.e. **11** or **12**, becomes an enolate (*chemoselectivity*), how to control which enolate of the ketone **12** is formed (*regioselectivity*), and how to control the stereochemistry of the product **10** (*stereoselectivity*). As we develop strategy, we shall repeatedly examine these three aspects of control.



10 **11** **12**

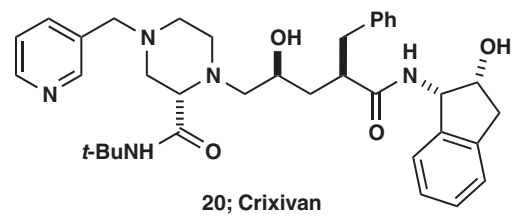
The target molecules we shall tackle in this book are undoubtedly more difficult in several ways than this simple example **10**. They are more complex quantitatively in that they combine functional

groups, rings, double bonds, and chiral centres in the same target, and qualitatively in that they may have features like large rings, double bonds of fixed configuration, or relationships between functional groups or chiral centres which no standard chemistry seems to produce. Molecules **1** to **5** are examples: a quite different one is flexibilene **13**, a compound from Indonesian soft coral. It has a fifteen-membered ring, one di- and three tri-substituted double bonds, all *E* but none conjugated, and a quaternary centre. Mercifully there are no functional groups or chiral centres. How on earth would you tackle its synthesis? One published synthesis is by McMurry.[10]



This short synthesis uses seven metals (Li, Cr, Zr, Pd, Ti, Zn, and Cu), only one protecting group, achieves total control over double bond geometry, remarkable regioselectivity in the Zr-Pd coupling reaction, and a very satisfactory large ring synthesis. The yield in the final step (52%) may not look very good, but this is a price worth paying for such a short synthesis. Only the first two steps use chemistry from the previous books: all the other methods were unknown only ten years before this synthesis was carried out but we shall meet them all in this book.

An important reason for studying alternative strategies (other than just making the compound!) is the need to find short cheap large scale routes in the development of research lab methods into production. All possible routes must be explored, at least on paper, to find the best production method and for patent coverage. Many molecules suffer this exhaustive process each year, and some sophisticated molecules, such as Merck's HIV protease inhibitor **20**, a vital drug in the fight against AIDS, are in current production on a large scale because a good synthesis was found by this process.[11]



20; Crixivan

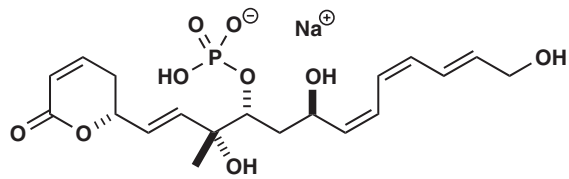
You might think that, say organometallic chemistry using Zr or Pd would never be used in manufacture. This is far from true as many of these methods are catalytic and the development of polymer-supported reagents for flow systems means that organo-metallic reagents or enzymes may be better than conventional organic reagents in solution with all the problems of by-product disposal and solvent recovery. We shall explore the chemistry of B, Si, P, S, and Se, and of metals

such as Fe, Co, Ni, Pd, Cu, Ti, Sn, Ru and Zr because of the unique contribution each makes to synthetic methods.

In the twenty years since McMurry's flexibilene synthesis major developments have changed the face of organic synthesis. Chiral drugs must now be used as optically pure compounds and catalytic asymmetric reactions (chapters 25 and 26) have come to dominate this area, an achievement crowned by the award of the 2001 Nobel prize for Chemistry to Sharpless, Noyori and Knowles. Olefin metathesis (chapter 15) is superseding the Wittig reaction. Palladium-catalysed coupling of aromatic rings to other aromatic rings, to alkenes, and to heteroatoms (chapter 18) makes previously impossible disconnections highly favourable. These and many more important new methods make a profound impact on the strategic planning of a modern synthesis and find their place in this book.

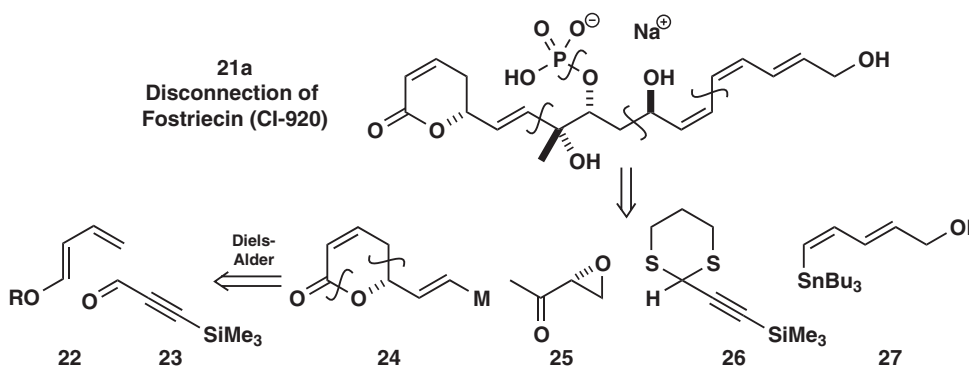
A Modern Synthesis: Fostriecin (CI-920)

The anti-cancer compound Fostriecin **21** was discovered in 1983 and its stereochemistry elucidated in 1997. Not until 2001 was it synthesised and then by two separate groups.[12] Fostriecin is very different from flexibilene. It still has alkene geometry but it has the more challenging three-dimensional chirality as well. It has plenty of functionality including a delicate monophosphate salt. A successful synthesis must get the structure right, the geometry of the alkenes right, the relative stereochemistry right, and it must be made as a single enantiomer.



21; Fostriecin (CI-920)

The brief report of Jacobsen's total synthesis starts with a detailed retrosynthetic analysis. The compound was broken into four pieces **21a** after removal of the phosphate. The unsaturated lactone **24** (M is a metal) could be made by an asymmetric oxo-Diels-Alder reaction from diene **22** and ynal **23**. The epoxide **25** provides a second source of asymmetry. One *cis* alkene comes from an alkyne **26** and the rest from a dienyl tin derivative **27**.



The synthesis is a catalogue of modern asymmetric catalytic methods. The epoxide **25** was resolved by a hydrolytic kinetic resolution (chapter 28) using a synthetic asymmetric cobalt complex. The asymmetric Diels-Alder reaction (chapter 26) was catalysed by a synthetic chromium

complex. The vinyl metal derivative **24** was made by hydrozirconation of an alkyne (this at least is similar to the flexibilene synthesis) and the secondary alcohol chiral centre was derived from the dithian **26** by hydrolysis to a ketone and asymmetric reduction with a synthetic ruthenium complex (chapter 24). The dienyl tin unit **27** was coupled to the rest of the molecule using catalytic palladium chemistry (chapter 18). Almost none of these catalytic methods was available in 1983 when flexibilene was made and such methods are a prominent feature of this book. Organic synthesis nowadays can tackle almost any problem.[13]

Please do not imagine that we are abandoning the systematic approach or the simpler reagents of the previous books. They are more essential than ever as new strategy can be seen for what it is only in the context of what it replaces. Anyway, no-one in his or her right mind would use an expensive, toxic, or unstable reagent unless a friendlier one fails. Who would use pyrophoric tertiary butyl-lithium in strictly dry conditions when aqueous sodium hydroxide works just as well? In most cases we shall consider the simple strategy first to see how it must be modified. The McMurry flexibilene synthesis is unusual in deploying exotic reagents in almost every step. A more common situation is a synthesis with one exotic reagent and six familiar ones. The logic of the previous books is always our point of departure.

The organisation of the book

The book has five sections:

A: Introduction, selectivity, and strategy
B: Making Carbon-Carbon bonds
C: Carbon-Carbon double bonds
D: Stereochemistry
E: Functional Group Strategy

The introductory section uses aldol chemistry to present the main themes in more detail and gives an account of the three types of selectivity: *chemo-*, *regio-*, and *stereo-selectivity.* We shall explore alternative strategies using enones as our targets, and discuss how to choose a good route using cyclopentenones as a special case among enones. Each chapter develops strategy, new reagents, and control side-by-side. To keep the book as short as possible (like a good synthesis), each chapter in the book has a corresponding chapter in the workbook with further examples, problems, and answers. You may find that you learn more efficiently if you solve some problems as you go along.

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2 Chemoselectivity

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Chemoselectivity: simple examples and rules
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When Protection is not Needed
Dianions: wasting reagent to achieve selectivity
Chemoselectivity by Reagent: The Pinacol Rearrangement
Selectivity between secondary and tertiary alcohols by reagent
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General discussion of enols and enolates
Formation of specific enol equivalents
Lithium enolates, enamines and silyl enol ethers
Enamines
Silyl enol ethers
Synthesis of the ant alarm pheromone mannicone
Examples of Chemoselectivity in Synthesis
Synthesis of lipstatin, rubrynolide and hirsutene

Definitions

Introduction: three types of control

Behind all grand strategic designs in organic synthesis must lie the confidence that molecules can be compelled to combine in the ways that we require. We shall call this *control* and divide it into three sections by mechanistic arguments. These sections are so important that we shall devote the next three chapters to the more detailed explanation of just what the divisions mean. If you can recognise what might go wrong you are in a better position to anticipate the problem and perhaps avoid it altogether. Our three types of control are over chemoselectivity (selectivity between different functional groups), regioselectivity (control between different aspects of the same functional group), and stereoselectivity (control over stereochemistry). Examples of selectivity of all three kinds are given in *The Disconnection Approach*: Chemoselectivity in chapter 5, Regioselectivity in chapter 14, and Stereoselectivity in chapters 12 and 38. These aspects will not be addressed again in the present book.

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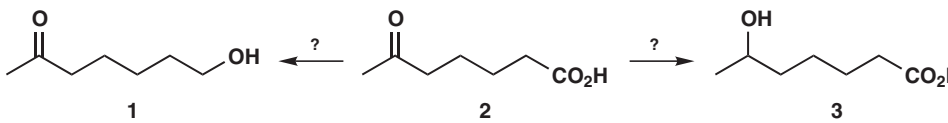
Chemoselectivity: simple examples and rules

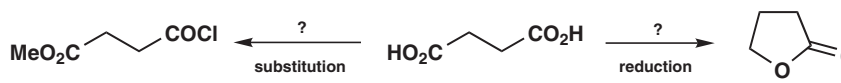
Chemoselectivity is the most straightforward of the three types and might seem too elementary to appear in an advanced textbook. Counting the number of protecting groups in the average synthesis reveals this as a naive view. Selectivity between functional groups might involve:

(a) Selective reaction of one among several functional groups of different reactivity, as in the reduction of the keto-acid **2** to give either product **1** or **3** at will.



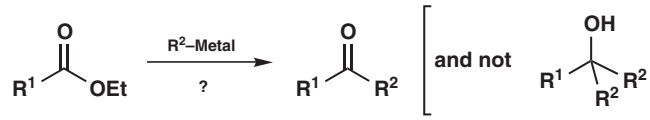
1 **2** **3**

(b) Selective reaction of one of several identical functional groups, as in the conversion of the symmetrical diacid **5** to the half ester, half acid chloride **4**, or the lactone **6** in which one of the two acids has been reduced. There is a more subtle example of this at the end of the chapter.



4 **5** **6**

(c) Selective reaction of a functional group to give a product which could itself react with the same reagent, as in the classical problem of making a ketone **8** from an acid derivative **7** without getting the alcohol **9** instead.

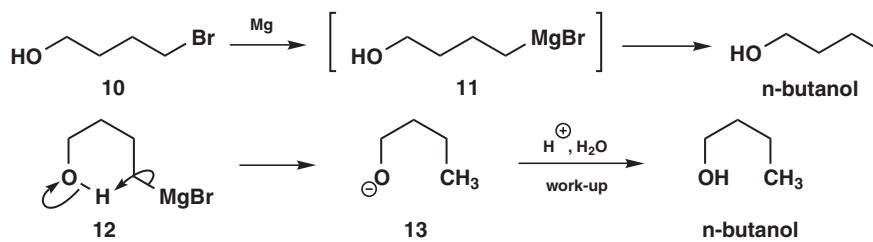


7 **8** **9**

Organic chemists are developing ever more specific reagents to do these jobs. These reagents must carry out the reaction they are designed for and must *not*:

(i) react with themselves.
(ii) react with functional groups other than the one they are aimed at.
(iii) react with the product.

Proviso (ii) is obvious, but (i) and (iii) perhaps need some explanation. It seems hardly worth stating that a reagent should not react with itself, but it is only too easy to suggest using a reagent such as **11** without realising that the organo-metallic reagent will act as a base for its own hydroxyl group **12** and destroy itself. The traditional solution to this problem is protection of the OH group in **10** but ideally we should like to avoid protection altogether though this is not yet possible.



10 **11** n-butanol

12 **13** n-butanol