Organic Synthesis: Strategy and Control

Paul Wyatt
Senior Lecturer and Director of Undergraduate Studies, School of Chemistry,
University of Bristol, UK

and

Stuart Warren
Reader in Organic Chemistry, Department of Chemistry,
University of Cambridge, UK

John Wiley & Sons, Ltd

Organic Synthesis

Organic Synthesis: Strategy and Control

Paul Wyatt
Senior Lecturer and Director of Undergraduate Studies, School of Chemistry,
University of Bristol, UK

and

Stuart Warren
Reader in Organic Chemistry, Department of Chemistry,
University of Cambridge, UK

John Wiley & Sons, Ltd

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

Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): cs-books@wiley.co.uk
Visit our Home Page on www.wiley.com

Other Wiley Editorial Offices

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 42 McDougall Street, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Canada Ltd, 6045 Freemont Blvd, Mississauga, ONT, L5R 4J3, Canada

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

Anniversary Logo Design: Richard J. Pacifico

Library of Congress Cataloging-in-Publication Data

Wyatt, Paul.
Organic synthesis: strategy and control / Paul Wyatt and Stuart Warren.
p. cm.
Includes bibliographical references.
ISBN: 978-0-470-48940-5
ISBN: 978-0-471-92963-5
1. Organic compounds – Synthesis. 2. Stereochemistry. I. Warren, Stuart G. II. Title.
QD262.W89 2007
547´.2–dc22 2006034932

British Library Cataloguing in Publication Data

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

ISBN: 978-0-471-48940-5 (HB)

ISBN: 978-0-471-92963-5 (PB)

Typeset in 10/12pt Times by Thomson Digital
Printed and bound in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire
This book is printed on acid-free paper responsibly manufactured from sustainable forestry
in which at least two trees are planted for each one used for paper production.

Contents

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.

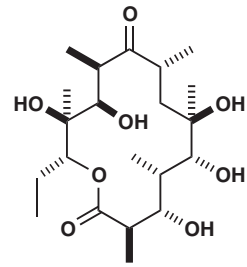
PJW
SGW
July 2006

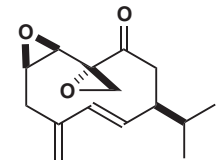
Section A: Introduction: Selectivity

1 Planning Organic Syntheses: Tactics, Strategy and Control

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.

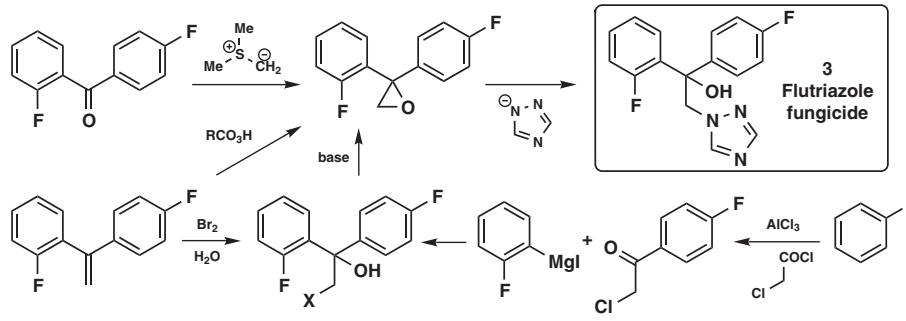
1
erythronolide A



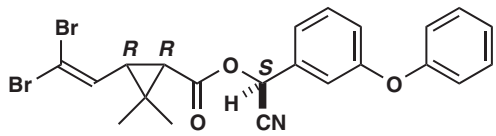


2
periplanone-B

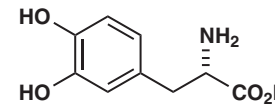
Less applauded, but equally significant, is the general advance in synthetic methods and their industrial applications. AstraZeneca confess that it took them nearly a century to bring Victor Grignard's methods into use, but are proud that Corey's sulfur ylid chemistry made it in a decade. Both are used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

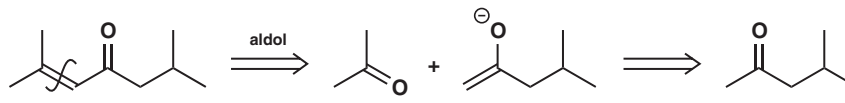


4
deltamethrin



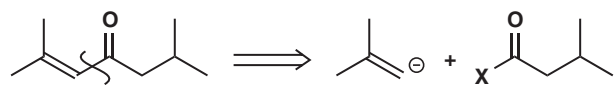
5
(*S*)-L-(–)-DOPA

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.



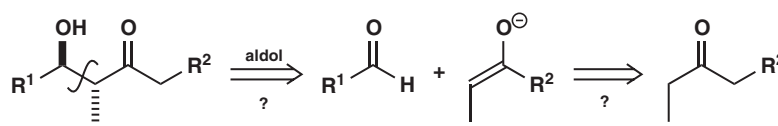
6 **7**

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**

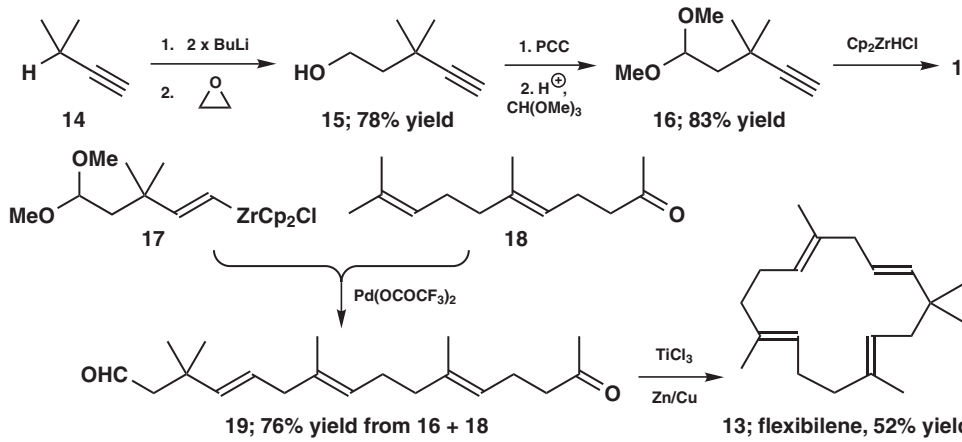
We shall also extend the scope of established reactions. We hope you would recognise the aldol disconnection in TM **10**, but the necessary stereochemical control might defeat you. An early section of this book describes how to control every aspect of the aldol reaction: how to select which partner, 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**

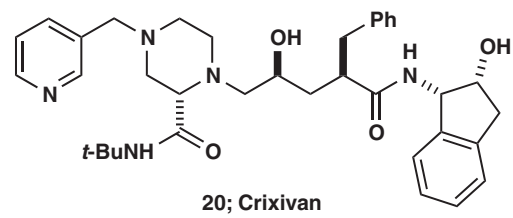
The target molecules we shall tackle in this book are undoubtedly more difficult in several ways than this simple example **10**. They are more complex quantitatively in that they combine functional

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]



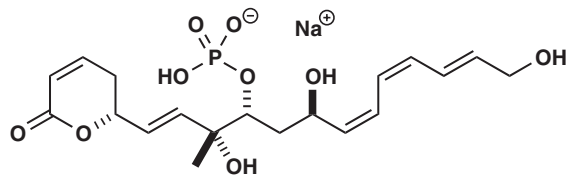
You might think that, say organometallic chemistry using Zr or Pd would never be used in manufacture. This is far from true as many of these methods are catalytic and the development of polymer-supported reagents for flow systems means that organo-metallic reagents or enzymes may be better than conventional 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.

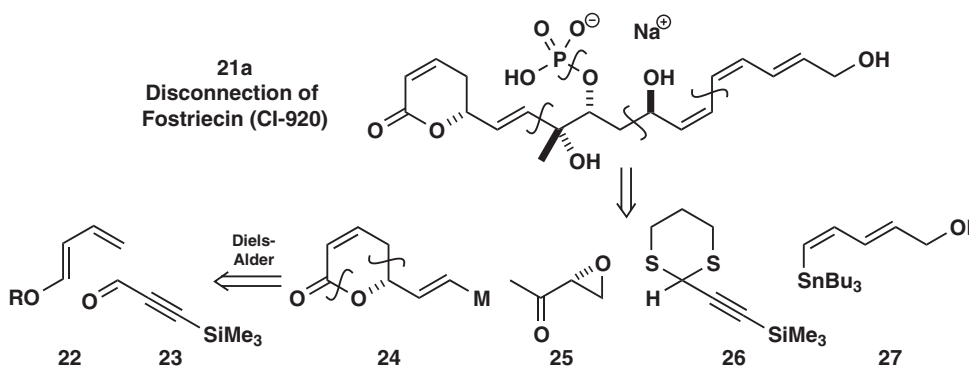
A Modern Synthesis: Fostriecin (CI-920)

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.

References

General references are given on page 893

1. R. B. Woodward, *Pure Appl. Chem.*, 1973, **33**, 145; A. Eschenmoser and C. E. Wintner, *Science*, 1977, **196**, 1410; A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 5.
2. Y. Kishi, *Tetrahedron*, 2002, **58**, 6239.
3. E. J. Corey, K. C. Nicolaou, and L. S. Melvin, *J. Am. Chem. Soc.*, 1975, **97**, 654; G. Stork and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1987, **109**, 1565; *Pure Appl. Chem.*, 1987, **59**, 345; A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky, V. S. Borodkin and N. K. Kochetkov, *Tetrahedron Lett.*, 1987, **28**, 3835, and references therein.
4. W. C. Still, *J. Am. Chem. Soc.*, 1979, **101**, 2493. See also S. L. Schreiber and C. Santini, *J. Am. Chem. Soc.*, 1984, **106**, 4038; T. Takahashi, Y. Kanda, H. Nemoto, K. Kitamura, J. Tsuji and Y. Fukazawa, *J. Org. Chem.*, 1984, **51**, 3393; H. Hauptmann, G. Mühlbauer and N. P. C. Walker, *Tetrahedron Lett.*, 1986, **27**, 1315; T. Kitahara, M. Mori and K. Mori, *Tetrahedron*, 1987, **43**, 2689.

5. P. A. Worthington, ACS Symposium 355, *Synthesis and Chemistry of Agrochemicals*, eds D. R. Baker, J. G. Fenyes, W. K. Moberg, and B. Cross, ACS, Washington, 1987, p 302.
6. M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pullman, *Nature*, 1974, **248**, 710; M. Elliott, *Pestic. Sci*., 1980, **11**, 119.
7. J. Halpern, H. B. Kagan, and K. E. Koenig, *Morrison*, vol 5, pp 1–101.
8. Corey, *Logic*; Nicolaou and Sorensen.
9. *Designing Syntheses, Disconnection Textbook*, and *Disconnection Workbook*.
10. J. McMurry, *Acc. Chem. Res*., 1983, **16**, 405.
11. D. Askin, K. K. Eng, K. Rossen, R. M. Purick, K. M. Wells, R. P. Volante and P. J. Reider, *Tetrahedron Lett*., 1994, **35**, 673; B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. C. Quintero, J. H. Lin, I.-W. Chen, M. K. Holloway, P. M. D. Fitzgerald, M. G. Axel, D. Ostovic, P. S. Anderson and J. R. Huff, *J. Med. Chem*., 1994, **37**, 3443.
12. D. L. Boger, S. Ichikawa and W. Zhong, *J. Am. Chem. Soc*., 2001, **123**, 4161; D. E. Chavez and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2001, **40**, 3667.
13. D. Seebach, *Angew. Chem. Int. Ed*., 1990, **29**, 1320; K. C. Nicolaou, E. J. Sorensen and N. Winssinger, *J. Chem. Ed*., 1998, **75**, 1225.

2 Chemoselectivity

Definitions

Introduction: three types of control

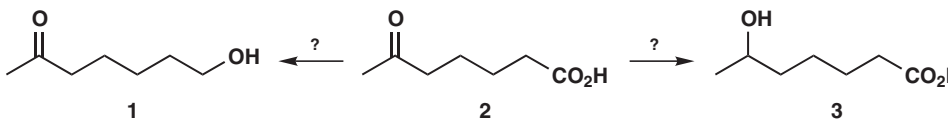
Behind all grand strategic designs in organic synthesis must lie the confidence that molecules can be compelled to combine in the ways that we require. We shall call this *control* and divide it into three sections by mechanistic arguments. These sections are so important that we shall devote the next 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.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Chemoselectivity: simple examples and rules

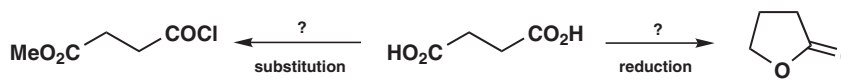
Chemoselectivity is the most straightforward of the three types and might seem too elementary to appear in an advanced textbook. Counting the number of protecting groups in the average synthesis reveals this as a naive view. Selectivity between functional groups might involve:

(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.



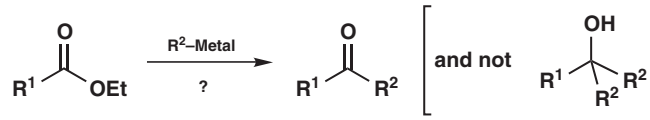
1 **2** **3**

(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.

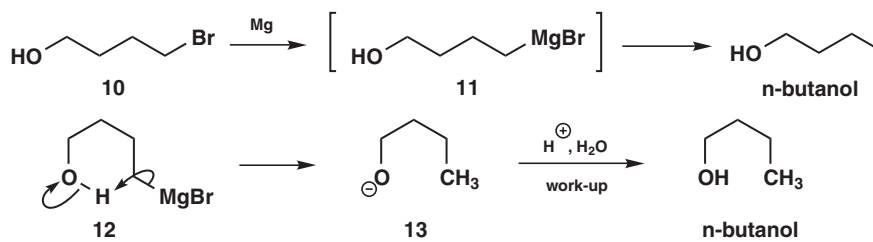


7 **8** **9**

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.

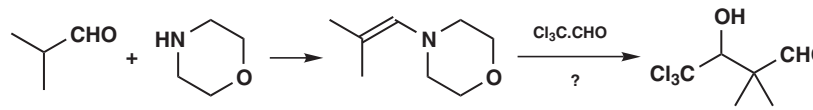
Proviso (ii) is obvious, but (i) and (iii) perhaps need some explanation. It seems hardly worth stating that a reagent should not react with itself, but it is only too easy to suggest using a reagent such as **11** without realising that the organo-metallic reagent will act as a base for its own hydroxyl 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

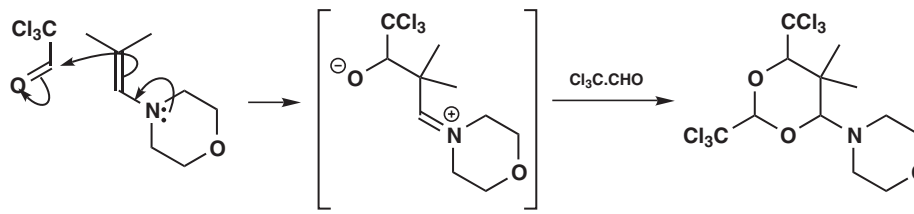
12 **13** n-butanol

Proviso (iii) is more obvious and yet perhaps more often catches people out. It is not always clear in exactly what form the product is produced in the reaction mixture, though a good mechanistic understanding and careful thought should reveal this. The reaction between the simple aldehyde **14** and chloral ($Cl_3C.CHO$) looks like a straightforward route to the aldol **17**, and might reasonably be carried out via the enamine **16**.



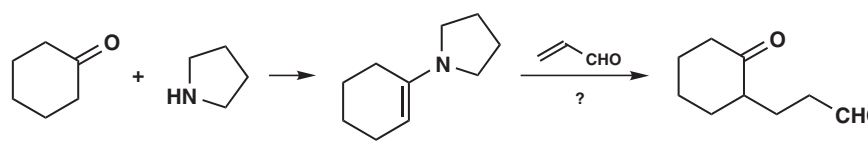
14 **15** **16** **17**

However, mixtures of **16** and chloral, in any proportion, give only the 2:1 adduct **20** which can be isolated in 83% yield.[1] Obviously the immediate product **19** reacts with chloral at least as fast as does **16**. Fortunately the synthesis can be rescued by acid-catalysed cleavage of **20** with HCl which gives a good yield of the target **17**.



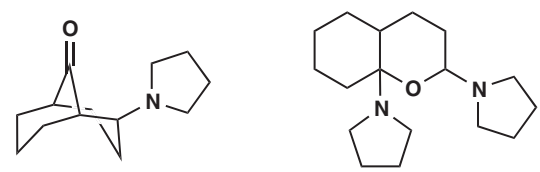
18 **19** **20**

Enamines are excellent at Michael additions and another plausible synthesis which "goes wrong" is the addition of acrolein to cyclohexanone mediated by the enamine **21** formed this time with pyrollidine.



21 **22**

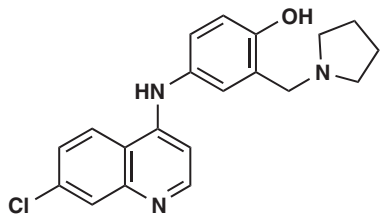
If the product is isolated by distillation, a good yield (75%) of the bicyclic ketone **23** is obtained.[2] A more detailed investigation disclosed that **24** is the immediate product, that **23** is formed from it on distillation, and that the expected Michael adduct **22** can be isolated in good yield simply by the hydrolysis of **24**. In other words, don't distil! If things "go wrong" in a synthesis, this may be a blessing, as here. There are lots of ways to control Michael additions, but few ways to make bicyclic ketones like **23**, and this is now a standard method.[3] The moral is to make sure you know what is happening, and to be prepared to welcome the useful and unexpected result.



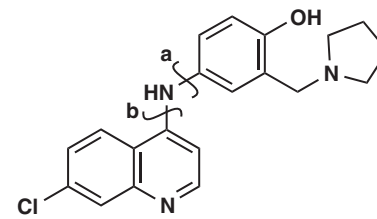
23 **24**

Chemoselectivity by Reactivity and Protection: An anti-Malaria Drug

We need to see some of these principles in action and a proper synthesis is overdue. The anti-malarial drug amopyroquine **25** might have been derived from quinine as it has a quinoline nucleus. It also has five functional groups – three amines (all different - one aromatic, one tertiary, and one secondary), a phenol and an aryl chloride. There are four rings, three aromatic and one saturated heterocyclic.

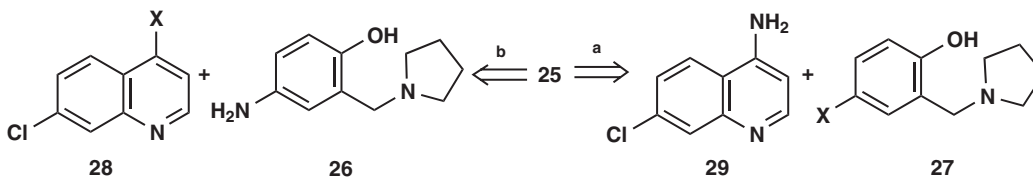


25
Amopyroquine



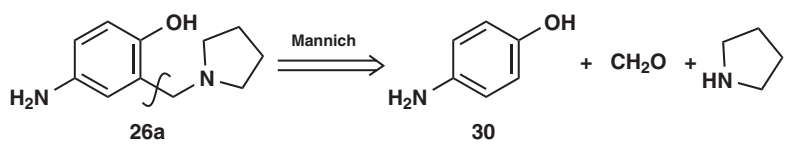
25a, b
Amopyroquine disconnections

There are many possible disconnections, but we should prefer to start in the middle of the molecule to achieve the greatest simplification. Disconnection **25a** would require a nucleophilic displacement (X = a leaving group) on an unactivated benzene ring **27** and looks unpromising. Disconnection **25b** requires nucleophilic displacement at position 4 in a pyridine ring, an acceptable reaction because of the electron-withdrawing effect of the nitrogen atom in the ring, so this is the better route, though we may be apprehensive about controlling the chemoselectivity as there are three potential nucleophiles in **26** and two potential electrophiles in **28**.

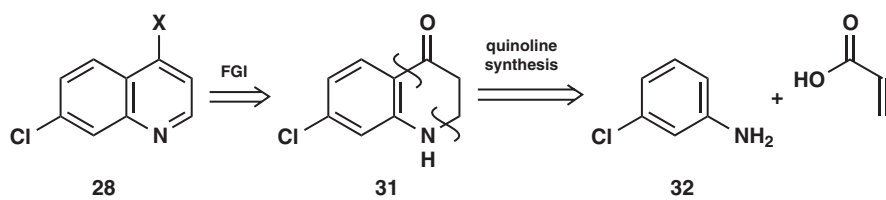


28 **26** **29** **27**

Further disconnections of **26** by the Mannich reaction[4] and of **28** by standard heterocyclic methods give simple starting materials.[5]



26a **30**

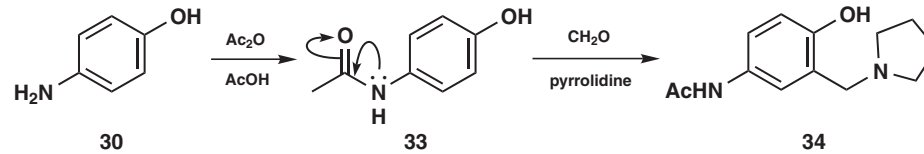


28 **31** **32**

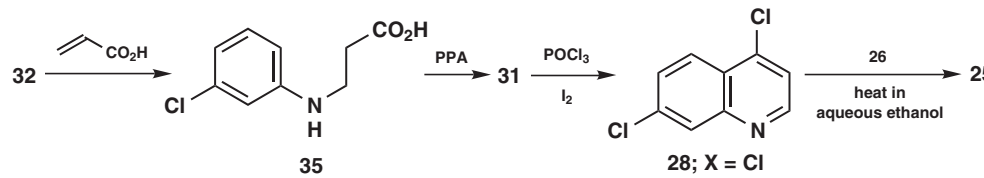
Protection to allow a less reactive group to react

Now the fun begins! Attempted Mannich reaction on the aminophenol **30** would be dominated by the more nucleophilic NH_2 group and is no good. Acylation moderates the NH_2 group by delocalisation

and **33** is a good choice for starting material as it is paracetamol, the common analgesic. Mannich reaction now chemoselectively gives **34** and alkaline hydrolysis of the amide gives **26**.



Michael addition of acrylic acid to the chloroamine **32** is straightforward and Friedel-Crafts cyclisation of **35** gives only **31**, presumably because the position next to the chlorine atom is slightly disfavoured both sterically and electronically. Chlorination and oxidation are conveniently carried out in the same step and the two halves (**26** and **28**) of this convergent synthesis are combined to give amopyroquine **25**.

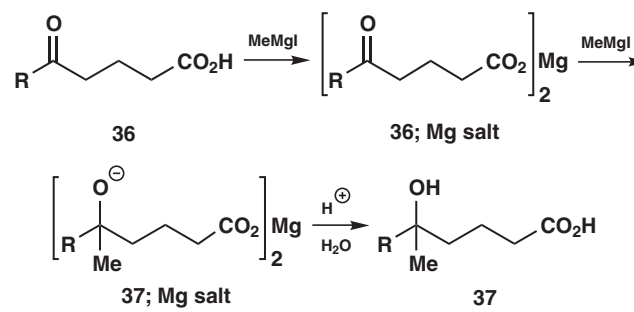


In the last step we return to the original question of chemoselectivity: Only the primary amine in **26** reacts because it is more nucleophilic than OH and because the more nucleophilic tertiary amine adds reversibly – it cannot lose a hydrogen atom as it does not have one. Only the 4-chlorine atom in the pyridine **28** reacts, presumably because addition to the other position would require the disruption of both aromatic rings. Though this compound has been succeeded by better anti-malarials, its synthesis illustrates the all-important principle that predictions of chemoselectivity must be based on sound mechanistic understanding. If doubt remains it is worth trying a model reaction on simpler compounds or, of course, an alternative strategy.

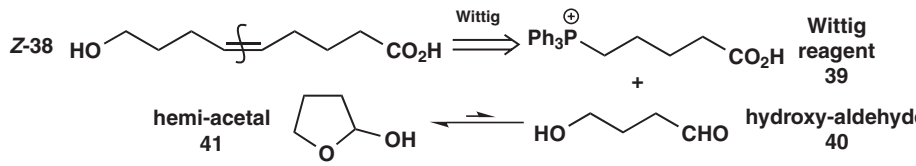
When Protection is not Needed

Dianions: wasting reagent to achieve selectivity

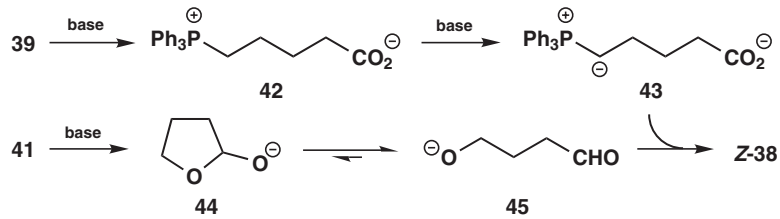
In that synthesis we moderated an over-reactive amino group by protection. Sometimes, protection is not necessary if we are prepared to squander some of our reagents. A trivial example is the addition of methyl Grignard to the ketoacid **36**. We have already seen how acidic protons destroy Grignard reagents, but if we are prepared to waste one molecule of the Grignard, we get automatic protection of the carboxylic acid by deprotonation. Nucleophilic MeMgI will not add to the anion of a carboxylic acid but adds cleanly to the ketone to give, after workup, the alcohol **37**.



At first sight, the synthesis of *Z*-**38** by the Wittig reaction seems too risky. The phosphonium salt **39** has a more acidic proton (CO_2H) than the one we want to remove to make the ylid, and the aldehyde **40** not only also has an acidic proton (OH), but it prefers to remain as the cyclic hemiacetal **41** so that there is no carbonyl group at all.

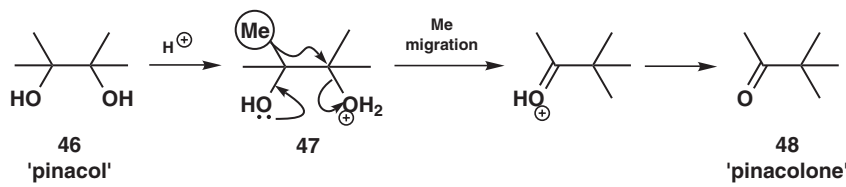


However, simply using a large excess of base makes the reaction work without any protection. The phosphonium salt **39** does indeed lose its first proton from the CO_2H group **42**, but the second molecule of base forms the ylid **43** as the two anions are far enough apart not to influence each other.[6] Base also catalyses the equilibrium between the anions **44** and **45** so that **43** and **45** can react to give the target molecule. The transition state for this reaction has three partial negative charges, but they are well apart from each other and there is obviously not too much electrostatic repulsion as the reaction goes well. This case is opposite to the previous ones: careful mechanistic analysis shows that expected chemoselectivity problems do not materialise.



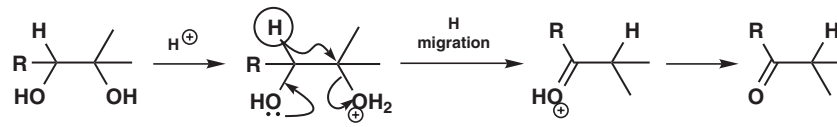
Chemoselectivity by Reagent: The Pinacol Rearrangement

So far we have discussed chemoselectivity between different functional groups. The situation gets more complicated if the functional groups are similar, or even the same. The pinacol rearrangement is a useful route to carbonyl compounds from diols, the classical example being the rearrangement of **46** in acid solution to give the *t*-alkyl ketone **48**. There are no chemoselectivity problems here: the two hydroxyl groups in **46** are the same so it does not matter which gets protonated and, in the rearrangement step **47**, all four potential migrating groups are methyl.

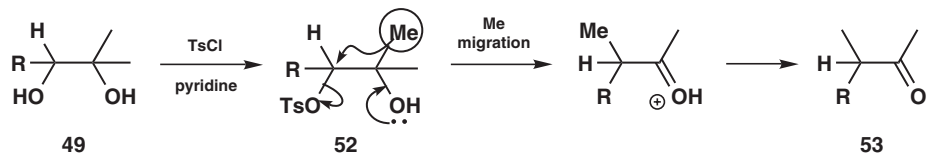


Selectivity between secondary and tertiary alcohols by reagent

Unsymmetrical diols provide a serious problem of chemoselectivity with an ingenious solution.[7] Treatment of the diol **49** with acid leads to loss of OH from what would be the more stable *t*-alkyl cation and hence, by hydrogen shift, to the ketone **51**.

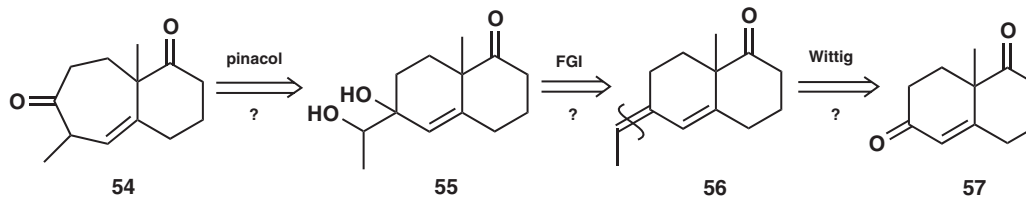


The alternative, more interesting rearrangement to give **53** can be initiated by tosylation of the diol **49** in weak base. It is impossible to tosylate tertiary alcohols under these conditions, as both the *t*-alcohol and TsCl are large, so only the secondary alcohol becomes sulfonylated and so leaves, and the rearranged ketone **53** is the only product.

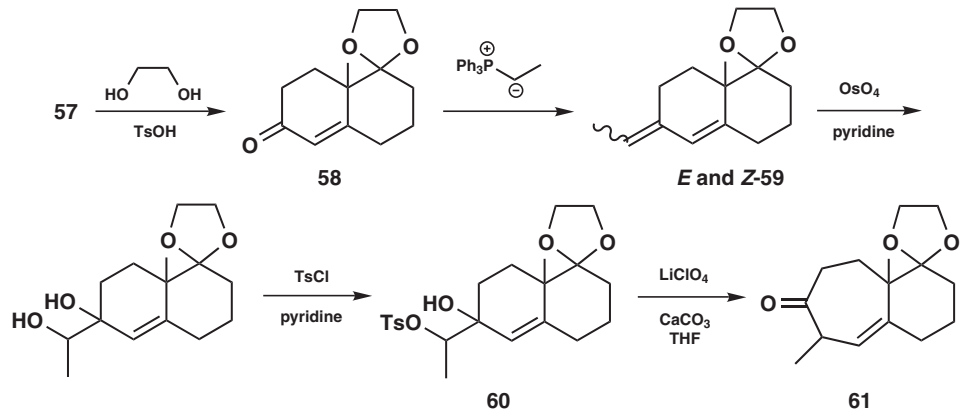


Corey's longifolene synthesis

The question of which group migrates in a pinacol rearrangement is also a question of chemoselectivity, and usually groups that can participate because they have lone pair or π-electrons migrate best. In Corey's longifolene synthesis,[8] the 6/7 fused enone **54** was an important intermediate. Synthesis from the readily available Robinson annelation product **57** is very attractive, but this demands a ring expansion step such as the pinacol rearrangement of **55** of unknown selectivity. 1,2-Diols such as **55** normally come from the hydroxylation of an alkene, in this case the diene **56** which might be made by a Wittig reaction on the dione **57**. Every step in this sequence raises a question of chemoselectivity. Which of the two ketones in **57** is more reactive? Which of the two double bonds in **56** is more easily hydroxylated? Which side of the ring migrates in the pinacol rearrangement on **55**?



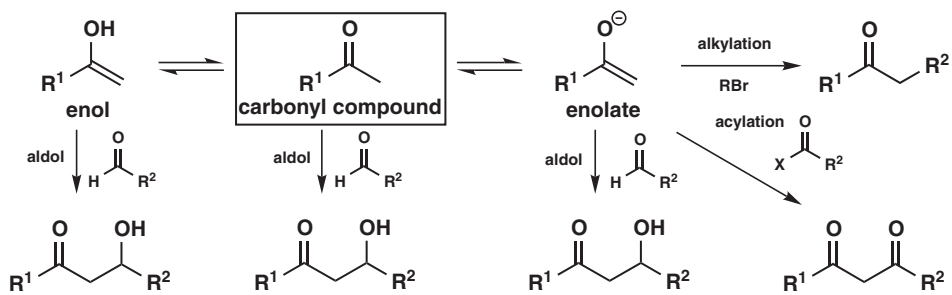
One of the ketones in **57** is conjugated, and one is not. The unconjugated one is less stable and we can therefore use *thermodynamic control* if we protect as an acetal, a reversible process. The unconjugated ketone would also be more *kinetically* reactive towards the Wittig reagent. Of the two double bonds in **59**, the one outside the ring is more reactive towards electrophilic reagents, again for both kinetic and thermodynamic reasons. The tosylation route ensures that the right OH group leaves in the pinacol rearrangement and because the remaining π-bond migrates better than the simple alkyl group when **60** rearranges with a weak Lewis acid, all is well. The synthesis therefore follows the route below, with all questions of chemoselectivity neatly solved. The acetal protecting group was also useful later in the synthesis.



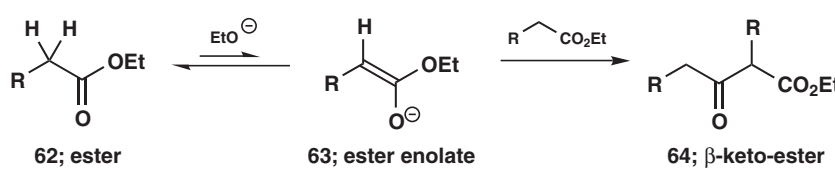
Chemoselectivity in Enol and Enolate Formation

General discussion of enols and enolates

We have concentrated so far on two functional groups within the same molecule. The chemoselectivity problem is just as important when we want two molecules to react together in a certain way, but, because both molecules have similar functional groups, the reaction can occur the other way round, or one of the molecules may react with itself and ignore the other. This problem is particularly acute in reactions involving enolisation. The alkylation or acylation of enols or enolates and the reaction of one carbonyl compound with another, the aldol reaction, are classical and important examples summarised in the general scheme below. We shall concentrate in this chapter on the chemoselectivity of these processes, that is we shall look at the enolisation of esters, aldehydes, and the like.

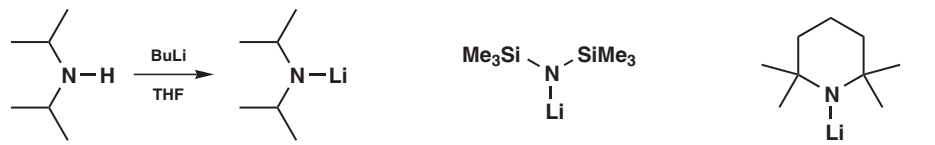


Reaction of an ester **62** with its own alkoxide ion produces a small amount of enolate **63** that reacts with unenolised ester to give the ketoester **64**. This reaction, though useful in its own right, precludes the direct alkylation of esters under these conditions.



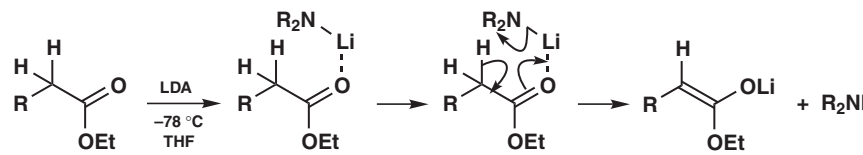
Formation of specific enol equivalents

What is needed for the alkylation is rapid conversion of the ester into a reasonably stable enolate, so rapid in fact that there is no unenolised ester left. In other words *the rate of proton removal must be faster than the rate of combination of enolate and ester.* These conditions are met when lithium enolates are made from esters with lithium amide bases at low temperature, often −78 °C. Hindered bases must be used as otherwise nucleophilic displacement will occur at the ester carbonyl group to give an amide. Popular bases are LDA (Lithium Di-isopropyl Amide, **66**), lithium hexamethyldisilazide **67**, and lithium tetramethylpiperidide **68**, the most hindered of all. These bases are conveniently prepared from the amine, e.g. **65** for LDA, and BuLi in dry THF solution.



65 Di-isopropylamine | **66; LDA** Li Di-isopropyl Amide | **67; LHMDS** Li HexaMethylDiSilyazide | **68; LTMP** Li TetraMethylPiperidide

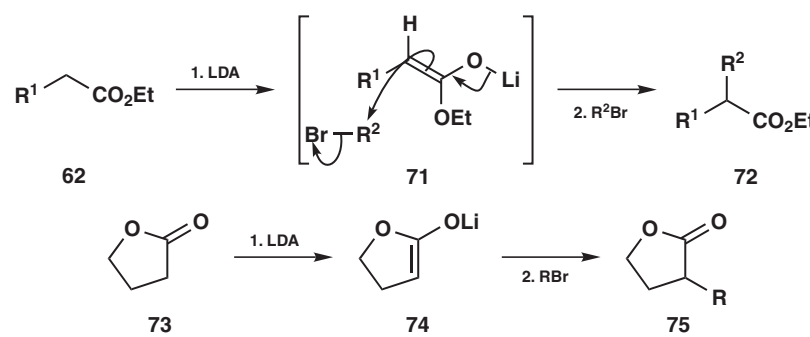
Treatment of a simple ester **62** with one of these bases at −78 °C leads to a stable lithium enolate **70** by initial coordination of lithium to the carbonyl group **69** and proton removal via a six-membered cyclic transition state **69a**.



62; ester | **69** | **69a** | **70**

Lithium enolates, enamines and silyl enol ethers

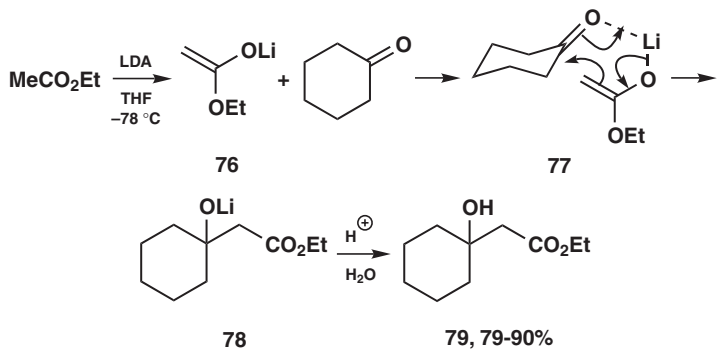
Direct alkylation of lithium enolates of esters[9] **62** and lactones **73**, *via* the lithium enolates **71** and **74**, with alkyl halides is usually successful.



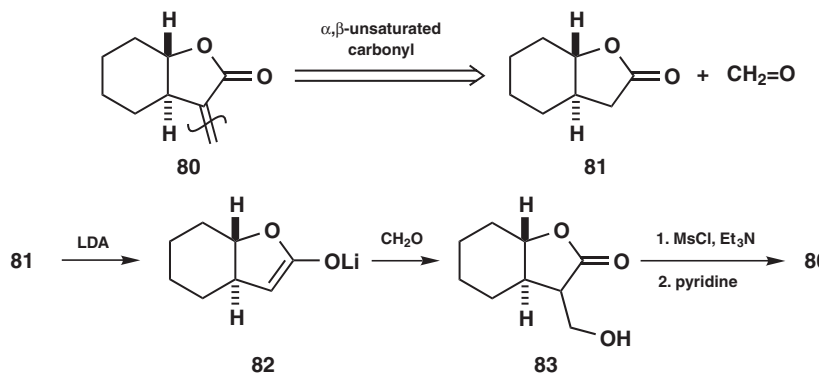
62 | **71** | **72**

73 | **74** | **75**

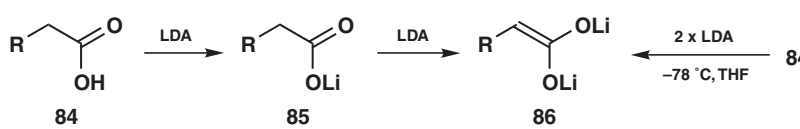
More impressive and more important is the performance of these lithium enolates in aldol reactions. Ester enolates are awkward things to use in reactions with enolisable aldehydes and ketones because of the very efficient self-condensation of the aldehydes and ketones. The traditional solutions involve such devices as Knoevenagel-style reactions with malonates.[11] Lithium enolates of esters, e.g. **76**, react cleanly with enolisable aldehydes and ketones to give high yields of aldols,[12] e.g. **79** in a single step also involving a six-membered cyclic transition state **77**.



They even react cleanly with formaldehyde, thus solving the problem that the Mannich reaction is not applicable to esters. The synthesis of the *exo*-methylene lactone **80** can be accomplished this way. Enone disconnection[13] reveals formaldehyde as the electrophilic component in a crossed aldol reaction, realised with a lithium enolate **82**.[14] The mono-adduct **83** of formaldehyde and the lactone **81** can be isolated and the cautious dehydration step is to avoid migration of the double bond into the ring.

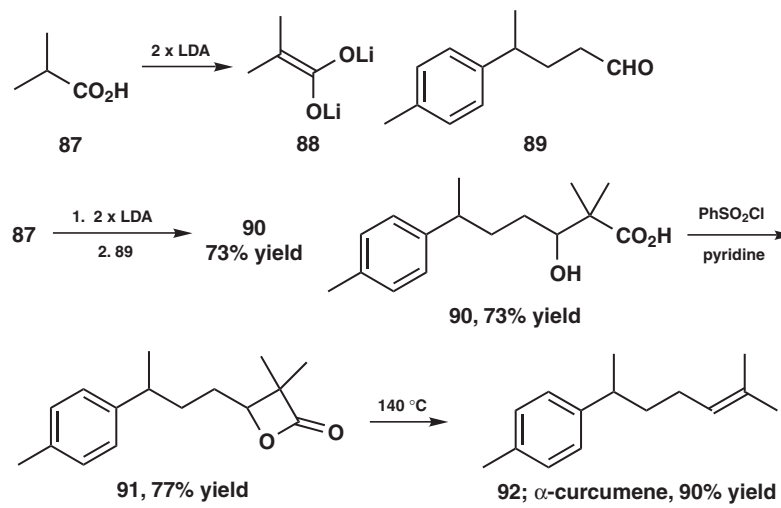


The same technique can even be applied to carboxylic acids themselves **84** providing two molecules of base are used. The first removes the acid proton to give the lithium salt **85** and the second forms the lithium enolate **86**.

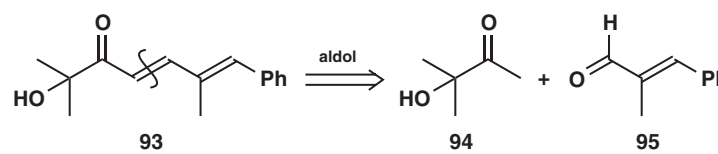


These lithium derivatives are also well behaved in alkylations and aldol reactions. Krapcho's synthesis[15] of the sesquiterpene α-curcumene **92** starts with the chemoselective condensation of

the dilithium derivative of the acid **87** with the enolisable aldehyde **89**. The aldol product **90** is converted into the β-lactone **91** and hence by heating and loss of CO_2 into α-curcumene **92**.

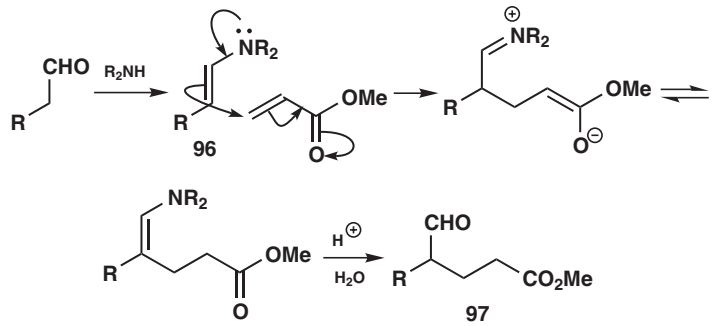


You might be forgiven for thinking that lithium enolates solve all problems of enolate chemoselectivity at a stroke and wonder why they are not always used. They are very widely used, but they require strictly anhydrous conditions at low temperatures (usually −78 °C, the temperature of a dry ice/acetone bath) and no-one in their right mind would use these conditions if mixing the reagents in ethanol at room temperature with a catalytic amount of NaOH did nearly as well. These are the conditions of many simple aldol reactions and are preferred where practical, particularly in industrial practice. The intermediate **93** was needed in a synthesis of geiparvirin. The best aldol disconnection in the middle of the molecule gives a ketone **94**, that must be enolised in the only possible position, and then react with an unenolisable and more electrophilic aldehyde **95**. No selectivity problems arise and an equilibrating aldol reaction between **94** and **95** catalysed by NaOEt in EtOH gives **93** in 89% yield.[16]

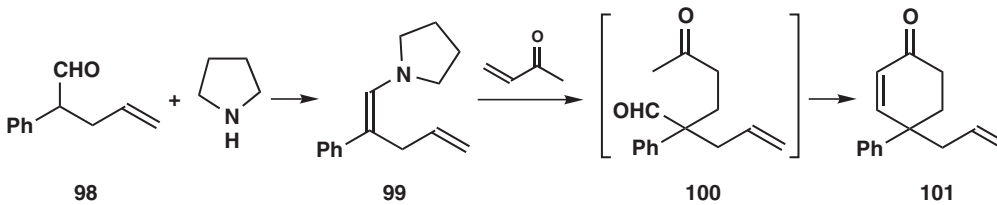


Enamines

Lithium enolates do not even solve all problems of chemoselectivity: most notoriously, they fail when the specific enolates of aldehydes are needed. The problem is that aldehydes self-condense so readily that the rate of the aldol reaction can be comparable with the rate of enolate formation by proton removal. Fortunately there are good alternatives. Earlier in this chapter we showed examples of what can go wrong with enamines. Now we can set the record straight by extolling the virtues of the enamines **96** of aldehydes.[17] They are easily made without excessive aldol reaction as they are much less reactive than lithium enolates, they take part well in reactions such as Michael additions, a standard route to 1,5-dicarbonyl compounds, e.g. **97**.[18]

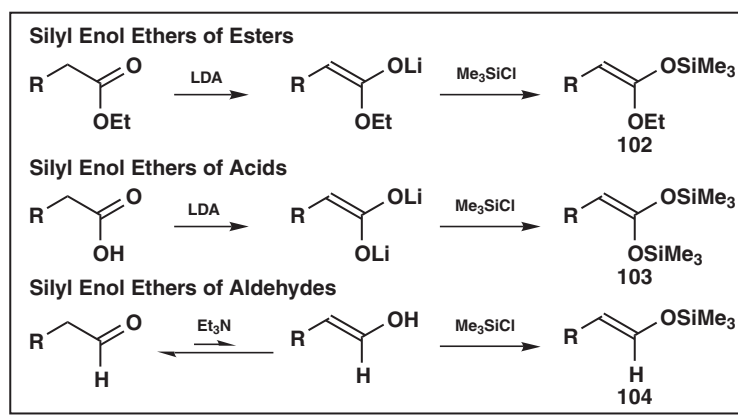


An impressive example[19] is the Robinson annelation of the unsaturated aldehyde **98** where neither aldol reaction nor double bond migration in the enamine **99** interferes. The 1,5-dicarbonyl compound **100** cyclises spontaneously to the enone **101**.



Silyl enol ethers

For all their usefulness, enamines have now largely been superseded by silyl enol ethers. These (**102**-**104**) can be made directly with Me_3SiCl from the lithium enolates of esters or acids or from aldehydes under milder conditions with a tertiary amine. The silicon atom is an excellent electrophile with a strong preference for more electronegative partners and it combines with the oxygen atom of an enolate so rapidly that no self condensation occurs even with aldehydes.



The silyl enol ethers **102** and **104** are shown as single geometrical isomers for convenience: in fact they are normally formed as mixtures, though this does not usually affect their reactions. They are thermodynamically stable compounds but are easily hydrolysed with water or methanol and are usually prepared when they are needed. They are much less reactive than lithium enolates, or even enamines, and their reactions with electrophiles are best catalysed by Lewis acids, often