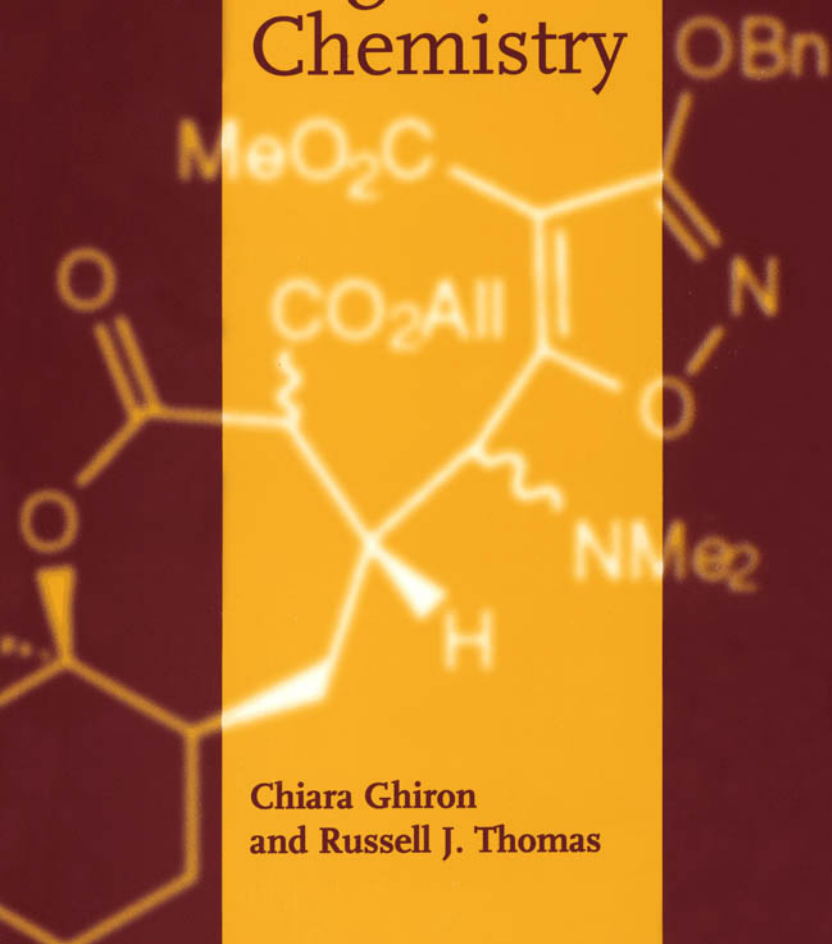


Exercises in
**Synthetic
Organic
Chemistry**



**Chiara Ghiron
and Russell J. Thomas**

Exercises in Synthetic Organic Chemistry

Exercises in Synthetic Organic Chemistry

CHIARA GHIRON and RUSSELL J. THOMAS

*Department of Medicinal Chemistry,
Glaxo Wellcome S.p.A.
Verona,
Italy*

OXFORD NEW YORK TOKYO
OXFORD UNIVERSITY PRESS

1997

*Oxford University Press, Great Clarendon Street, Oxford OX2 6DP
Oxford New York
Athens Auckland Bangkok Bombay Buenos Aires
Calcutta Cape Town Dar es Salaam Delhi Florence Hong Kong
Istanbul Karachi Kuala Lumpur Madras Madrid Melbourne
Mexico City Nairobi Paris Singapore Taipei Tokyo Toronto
and associated companies in
Berlin Ibadan*

Oxford is a trade mark of Oxford University Press

*Published in the United States
by Oxford University Press Inc., New York*

© Chiara Ghiron and Russell J. Thomas, 1997

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, without the prior permission in writing of Oxford University Press. Within the UK, exceptions are allowed in respect of any fair dealing for the purpose of research or private study, or criticism or review, as permitted under the Copyright, Designs and Patents Act, 1988, or in the case of reprographic reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency. Enquiries concerning reproduction outside those terms and in other countries should be sent to the Rights Department, Oxford University Press, at the address above.

This book is sold subject to the condition that it shall not, by way of trade or otherwise, be lent, re-sold, hired out, or otherwise circulated without the publisher's prior consent in any form of binding or cover other than that in which it is published and without a similar condition including this condition being imposed on the subsequent purchaser.

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

*Library of Congress Cataloging in Publication Data
(Data available)*

*ISBN 0 19 855944 5 (Hbk)
ISBN 0 19 855943 7 (Pbk)*

*Typeset by the authors
Printed in Great Britain by
Butler & Tanner Ltd,
Frome, Somerset*

This book is dedicated to our families

Preface

The advent of ever-more sophisticated methods of information retrieval is revolutionising the way chemists work. The possibility of accessing a database which, in a matter of seconds, is capable of providing hundreds of methods of carrying out a synthetic transformation means that the time in which a synthetic strategy can be planned is reduced enormously.

A subtle, but no less profound effect of this completely new approach is in the way chemists handle the 'vocabulary' of their profession, a knowledge of possible chemical transformations. It could be said that it will become less important to memorise lists of synthetic methods, but this creates a problem. Computer reaction databases are only as good as the questions we ask them, and without a sound knowledge of what is chemically feasible, we cannot construct a query to obtain the exact reaction conditions we need.

Undoubtedly one of the most powerful tools for the design of a synthesis is the elegant concept of retrosynthesis. By looking at the target structure, and having the knowledge of how each of the functional groups, and some of the carbon-carbon bonds, present in the molecule could be introduced, it is possible to dissect the target, taking it back to potential starting materials. This concept again relies on the chemist having a large enough vocabulary of transformations to hand.

One of the best ways of increasing a person's knowledge of the chemical transformations available is to spend time analysing published syntheses. By following a molecule through the various transformations to the final product it is possible to observe, in complex real-life situations, the application of synthetic methods. An even more effective approach is to study an article in the form of a synthetic exercise, either for informal discussion in a group, or private study. This has the benefit of encouraging the chemist or student to reflect for a while on possible mechanisms, reaction conditions, and the stereochemical outcome without having the answer immediately to hand.

An additional benefit, over simply studying an article from the literature, is that in some way it removes the choice of topic. This may be important bearing in mind the natural tendency of many of us to study areas that we already know something about, thus reducing the learning curve. This book has therefore deliberately chosen examples from a wide range of synthetic targets.

The purpose of this book is to provide chemists with a collection of exercises constructed from the recent literature. The exercises are designed to try and provide people at various levels with synthetic challenges, from final year undergraduates to graduate students and more experienced post-doctoral chemists. Thus in a group consisting of final year undergraduate students, post-graduate research students, and more experienced post-doctorate and academic staff members, the less experienced members can learn about the more fundamental organic transformations, protecting group strategies and stereochemical considerations, while the more senior chemists have the possibility to analyse the more detailed mechanistic aspects, while having the opportunity to revise and discuss the basic concepts.

We hope that this text proves useful both in academic and industrial chemistry departments, and may provide the basis for productive group discussions of synthetic problems. We shall always be pleased to receive comments and suggestions from readers as to how we can improve on the concept for future volumes.

Verona
October 1996

C. G.
R. J. T.

The Authors

Chiara Ghiron was born in Genova, Italy in 1965. Having read chemistry at The University of Genova between 1985 and 1990 she joined Glaxo Wellcome in Verona, where she is currently a member of the Medicinal Chemistry Department.

Russell J. Thomas was born in Swansea, Wales in 1966, and read chemistry at the University of Kent at Canterbury between 1984 and 1987. Having completed his Ph.D. with Prof. Stan Roberts at the University of Exeter in 1990, he moved to Verona in Italy to work for Glaxo Wellcome in the Medicinal Chemistry Department.

Acknowledgements

The authors would like to thank Phil Cox, Sylvie Gehanne, Fabrizio Micheli, and Maria Elvira Tranquillini for help in proof-reading the exercises. Thanks also to Daniele Donati, Tino Rossi, and Melissa Levitt for encouragement and helpful suggestions, and to the staff at OUP for their support of the project at its various stages. The authors would also like to acknowledge Glaxo Wellcome S.p.A. for granting permission to undertake the writing of this book.

Contents

<i>List of Abbreviations</i>	xiii
Introduction	1
1. Total Synthesis of (–)-Ovatolide	3
2. Total Synthesis of RS-15385	4
3. Total Synthesis of Islandic Acid I Methyl Ester	5
4. Total Synthesis of (+)-Patulolide C	6
5. Asymmetric Synthesis of 1-Deoxy-8,8a-di-epi-castanospermine	8
6. Synthesis of a Structure Related to Hydantocidin	9
7. Total Synthesis of Cryptophycin C	10
8. Total Synthesis of (±)-Leuhistin	12
9. The Asymmetric Synthesis of Bryostatin Fragments	13
10. The Total Synthesis of (–)-Balanol	14
11. Approach to the Synthesis of Pseudopterosins	16
12. Total Synthesis of Neodolabellenol	17
13. Total Synthesis of (–)-Swainsonine	18
14. Total Synthesis of Octalactins A and B	19
15. Asymmetric Synthesis of the Milbemycin β_3 Spiroketal Subunit	20
16. Stereoselective Total Synthesis of (+)-Artemisinin	22
17. The Synthesis of (±)-Prosopinine	24
18. Synthesis of a Protected Fluorocarbocyclic Nucleoside	25
19. Synthesis of Tropane Alkaloid Calystegine A3	26
20. The Synthesis of (±)-Oxerine	28
21. Synthesis of an Enantiopure C-4 Functionalised 2-Iodocyclohexanone Acetal	29
22. Total Synthesis of (–)-Solavetivone	30
23. Total Synthesis of (+)-Himbacine	32
24. Synthesis of 5-Hydroxytiagabine	34
25. An Approach to Zoanthamine Alkaloids	35
26. Total Synthesis of 1233A	36
27. Synthesis of a Key Intermediate of 1 β -Methylcarbapenem Antibiotics	38
28. Total Synthesis of the Enantiomer of Hennoxazole A	40
29. Total Synthesis of (+)-Duocarmycin A	41
30. Studies Towards the Total Synthesis of Rapamycin	42
31. Studies Towards the Total Synthesis of Rapamycin	44
32. Studies Towards the Total Synthesis of Rapamycin	46
33. Synthesis of Isochromanquinones	47
34. The Synthesis of (±)-12a-Deoxytetracycline	48
35. Synthesis of a D- <i>chiro</i> -Inositol 1-Phosphate	50
36. Stereoselective Synthesis of (±)-Aromaticin	51
37. Synthesis of 7-Methoxycyclopropamitosene	52
38. Total Synthesis of (+)- γ -Lycorane	53
39. Enantioselective Total Synthesis of (–)-7-Deacetoxyalcyonin Acetate	54
40. Total Synthesis of (+)-Tetrahydrocerulenin	56

Contents

41. Total Synthesis of (+)-Longifolene	57
42. Studies toward the Total Synthesis of Cerorubenic Acid-III	58
43. Total Synthesis of 10-Decarboxyquinocarcin	60
44. Total Synthesis of (+)-Pyripyropene A	62
45. Total Synthesis of <i>d,l</i> -Isospongiadiol	63
46. Total Synthesis of the Stemona Alkaloid (-)-Stenine	64
47. Total Synthesis of (-)-Papuamine	65
48. Total Synthesis of (+)-Stoechospermol	66
49. Synthesis of the Tricarbonyl Subunit C8–C19 of Rapamycin	68
50. Synthesis of the AB Ring Moiety of Ciguatoxin	70
51. Total Synthesis of (+)-Carbonolide B	72
52. Approach Towards the Asteriscanolide Skeleton	74
53. Total Synthesis of (+)-Dolabellatrienone	75
54. Total Synthesis of Stenine	76
55. Synthesis of 3 β -Acetoxydrimenin	78
56. The Total Synthesis of (+)-Adrenosterone	79
57. Total Synthesis of (-)-Suaveoline	80
58. Total Synthesis of (+)-7-Deoxypancratistatin	82
59. Enantioselective Synthesis of Deoxynojirimycin	84
60. Formal Synthesis of (\pm)-Aphidicolin	85
61. Synthetic Efforts Towards Bruceantin	86
62. Total Synthesis of (+)-FR900482	88
63. Total Synthesis of (3 <i>Z</i>)-Dactomelyne	90
64. Total Synthesis of (\pm)-Acerosolide	92
65. Synthesis of a Vindorosine Precursor	93
66. Synthesis of (-)-PGE ₂ Methyl Ester	94
67. Total Synthesis of (-)-Parviflorin	96
68. Total Synthesis of (-)-Chlorothricolide	98
69. Synthetic Studies on Furanoheliangolides	100
70. Total Synthesis of Staurosporine	102
71. Total Synthesis of (-)-Cephalotaxine	104
72. The Synthesis of Picrotoxinin	106
73. Total Synthesis of (+)-Dactylol	107
74. Synthesis of (\pm)-Ceratopicanol	108
75. Total Synthesis of (\pm)-Myrocin C	110
76. Synthesis of Staurosporine Aglycon	112
77. Synthesis of (20 <i>S</i>)-Camptothecin	113
78. Synthesis of a Fragment of (+)-Codaphniphylline	114
79. The Total Synthesis of Indanomycin	116
80. A Total Synthesis of Taxol	118
81. Total Synthesis of (-)-Grayanotoxin III	120
82. Enantioselective Total Synthesis of (-)-Strychnine	122

Common Abbreviations Used in the Text

AD	Asymmetric dihydroxylation
AE	Asymmetric epoxidation
AIBN	α,α' -Azobisisobutyronitrile
Aldrithiol®	2,2'-Dipyridyldisulphide
All	Allyl
Alloc	Allyloxycarbonyl
9-BBN	9-Borabicyclononane
BMS	Borane-methylsulphide complex
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINAPO	Phosphinous acid, diphenyl-[1,1'-binaphthalene]-2-2'-diyl ester
Boc	<i>tert</i> -Butoxycarbonyl
BOM	Benzyloxymethyl
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Bn	Benzyl
BTAF	Benzyltrimethylammonium fluoride
Bz	Benzoyl
BHT	<i>tert</i> -Butylhydroxytoluene
CAN	Ceric ammonium nitrate
CBS	Corey-Bashki-Shibat
Cbz	Benzyloxycarbonyl
Cp	Cyclopentadienyl
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
CSA	Camphorsulphonic acid
DAST	Diethylaminosulphur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DHQD	Dihydroquinidine
DIBAL	Diisobutylaluminium hydride
DIBAL-H	Diisobutylaluminium hydride
DIC	Diisopropylcarbodiimide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMPM	3,4-Dimethoxybenzyl
DMS	Dimethylsulphide
DMSO	Dimethylsulphoxide
DPPA	Diphenylphosphoryl azide

Common Abbreviations Used in the text

EE	1-Ethoxyethyl
FDPP	Pentafluorophenyl diphenylphosphinate
Fmoc	9-Fluorenylmethoxycarbonyl
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphorous triamide
Ipc	Isopinocampheyl
KDA	Potassium diisopropylamide
KHMDS	Potassium bis(trimethylsilyl)amide (KN(TMS) ₂)
K-Selectride®	Potassium tri- <i>sec</i> -butylborohydride
LDA	Lithium diisopropylamide
LDEA	Lithium diethylamide
LiHMDS	Lithium bis(trimethylsilyl)amide (LiN(TMS) ₂)
MEM	2-Methoxyethoxymethyl
MOM	Methoxymethyl
MPM	<i>p</i> -Methoxybenzyl
MS	Molecular sieves
Ms	Methanesulphonyl
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide (NaN(TMS) ₂)
NBS	<i>N</i> -Bromosuccinimide
NMM	<i>N</i> -Methylmorpholine
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
N-PSP	<i>N</i> -Phenylselenophthalimide
Ns	<i>p</i> -Nitrophenylsulphonyl
PDC	Pyridinium dichlorochromate
PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivaloyl
PMB	<i>p</i> -Methoxybenzyl
PMP	<i>p</i> -Methoxyphenyl
PPA	Polyphosphoric acid
PPL	Porcine pancreatic lipase
PPTS	Pyridinium <i>p</i> -toluenesulphonate
PTSA	<i>p</i> -Toluenesulphonic acid
Pv	Pivaloyl
Py	Pyridine
PyBroP	Bromotripyrrolidinophosphonium hexafluorophosphate
SEM	[2-(Trimethylsilyl)methyl
SEMCl	[2-(Trimethylsilyl)ethoxy]methyl chloride
Red-Al®	Sodium bis(2-methoxyethoxy)aluminium hydride
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TCDI	Thiocarbonyl diimidazole

Common Abbreviations Used in the text

Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
TMSCI	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulphonate
Tol	<i>p</i> -Toluyyl
<i>o</i> -Tolyl	<i>o</i> -Toluyyl
TPAP	Tetra- <i>n</i> -propylammonium perruthenate
Tr	Trityl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	<i>p</i> -Toluenesulphonyl
<i>p</i> -TsOH	<i>p</i> -Toluenesulphonic acid
Vitride®	Sodium bis(2-methoxyethoxy)aluminium hydride
Z	Benzyloxycarbonyl

Introduction

The purpose of the book

The exercises in this book are intended to provide challenges for people with various levels of experience. A final year undergraduate student should obviously not be expected to tackle a problem without the aid of his or her favourite textbooks, and will still undoubtedly have difficulty with the more advanced problems. The advanced aspects of an exercise are intended for a more experienced chemist to analyse and discuss in detail. A student will hopefully find that in studying the exercises, while at first it will be difficult to complete even half of the questions unaided, with time both the size of his or her 'vocabulary' of reactions and the time necessary to study an exercise will change dramatically.

How an exercise is constructed

The problems are taken from recent publications either of total syntheses of natural products, or the syntheses of related systems. The answers to the various questions are not provided in this book, although they can easily be obtained from the original articles. This was done not only to reduce the size of the text, but also to allow study and discussion of a problem in at least a formal situation of not knowing the answer. Seeing a reaction in which an olefin is transformed into a 1,2-diol with osmium tetroxide is a useful way of learning chemistry, but not nearly as effective as having time to think of what the reagent or product could be *before* seeing the solution.

The article, or articles from which the exercise was taken is cited immediately below the title. In the schemes, some of the structures or reaction conditions (in bold letters) are missing. At the end of the scheme there are some additional discussion points, where additional questions regarding mechanism, choice of reagents, stereochemistry, stereoselectivity etc. are listed. Below the discussion points there are usually some additional articles and reviews for further reading on key topics covered in the exercise. These references are usually not cited in the original paper. In order to construct a coherent exercise, it was necessary to change the molecule and reaction numbering used in the original publication.

Although it is a very subjective choice, the exercises are ordered in an approximately ascending order of difficulty. While obviously there can be no absolute guarantees, a final year undergraduate or more junior postgraduate student is advised to start at the front and work through the book from there.

In many cases the target molecules have been synthesised by several research groups around the world with quite differing approaches. Our choice of which article to use in this book should not be considered as a measure of which approach is more valid or innovative, the choice was made simply on the basis of how the syntheses offered

themes to be explored in this book. Similarly, we do not intend that articles chosen for exercises appearing at the start of the book should be considered in any way less innovative than those chosen for more difficult exercises towards the back. Clearly the difficulty of an exercise largely depends on the amount of information provided or omitted.

How to approach an exercise

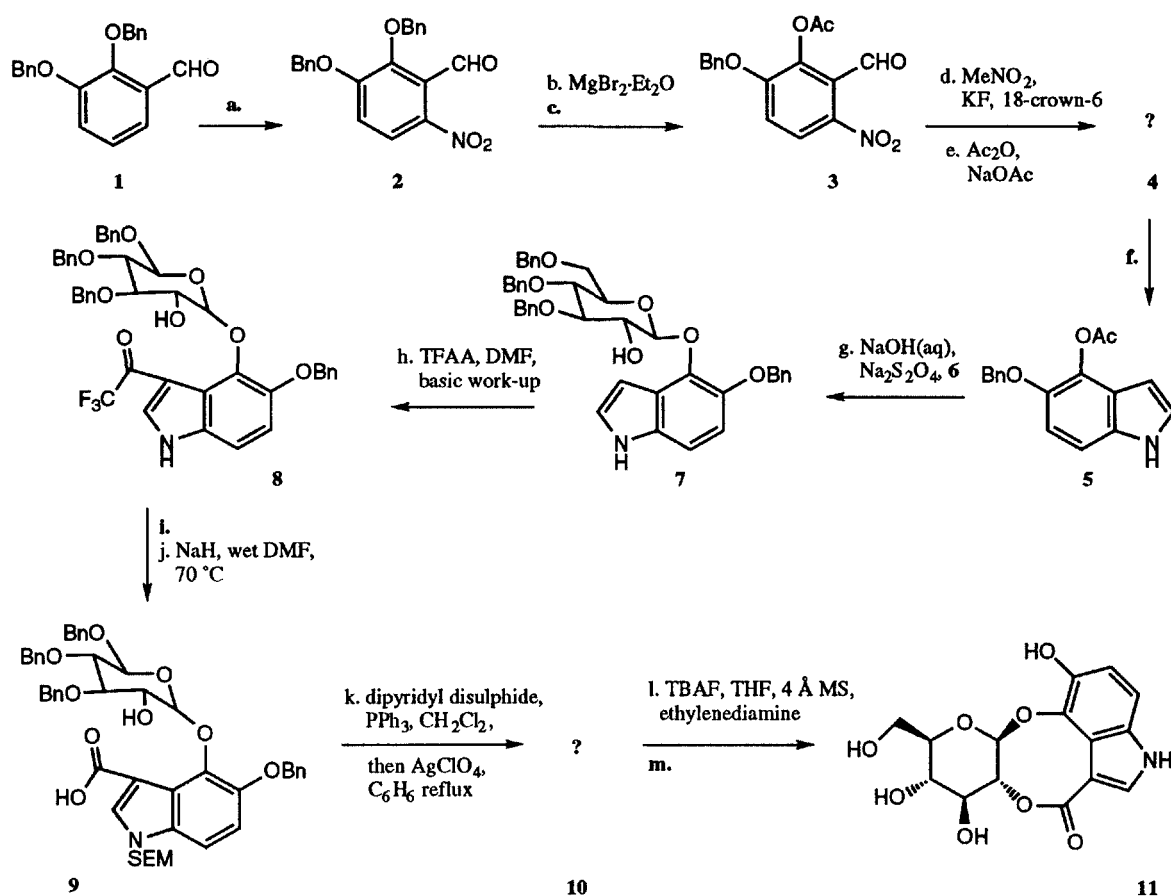
As this book is intended for chemists with a wide range of experience, there is no single best way of approaching an exercise. However, possibly the most effective way for everyone is to first try and complete as much as possible unaided before going back over the more problematic parts with the help of additional textbooks and discussion with colleagues. Having completed these first two passes, a final check of both the answered and unanswered problems can be made with the help of the original article. It is not too surprising how obvious most of the reactions become with the aid of the original text to hand when studying an exercise! An additional benefit of not consulting the original paper until the end is that it gives the possibility of proposing alternative approaches to those used, which can then be discussed with colleagues.

In cases where an unknown structure cannot be deduced from the reagents used to form it, a useful alternative is to look at the next structure in the synthetic sequence and go backwards, using a form of retrosynthetic analysis based on the reagents necessary to arrive at the known structure.

An important concept for the less experienced chemists is that we would be very surprised if someone (other than the authors of the original journal article!) were able to complete all of the questions exactly. With time and experience, the number of unanswered questions will decrease notably, although hopefully it will never arrive at zero.

1. Total Synthesis of (-)-Ovatolide

A. Delgado and J. Clardy, *J. Org. Chem.*, 1993, 58, 2862.



Abstracted with permission from *J. Org. Chem.*, 1993, 58, 2862 ©1993 American Chemical Society

Discussion Points

- What other isomer is formed in the nitration step a?
- Rationalise the regioselectivity of the mono-debenzylation reaction carried out in step b.
- Suggest a structure for compound 6 and give reasons for carrying out the reaction in a reductive environment.
- What is the mechanism of the hydrolysis of compound 8?
- Give an explanation for the use of ethylenediamine in step l.

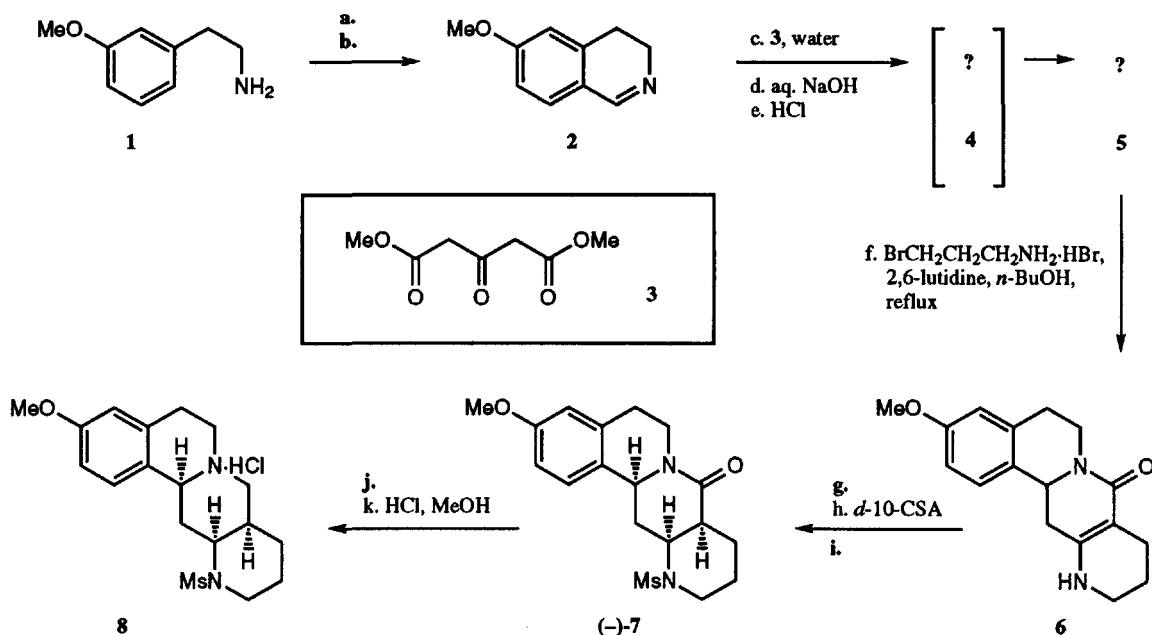
Further Reading

- For a review on diastereoselective nitroaldol reaction, see: D. Seebach, A. K. Beck, T. Mukhopadhyay and E. Thomas, *Helv. Chim. Acta*, 1982, 65, 1101. For a modification of the nitroaldol reaction using alumina, see: G. Rosini, E. Marotta, P. Righi and J. P. Seerden, *J. Org. Chem.*, 1991, 56, 6258.

2. Total Synthesis of RS-15385

J. C. Rohloff, N. H. Dyson, J. O. Gardner, T. V. Alfredson, M. L. Sparacino and J. Robinson III,

J. Org. Chem., **1993**, *58*, 1935.



Abstracted with permission from *J. Org. Chem.*, **1993**, *58*, 1935 ©1993 American Chemical Society

Discussion Points

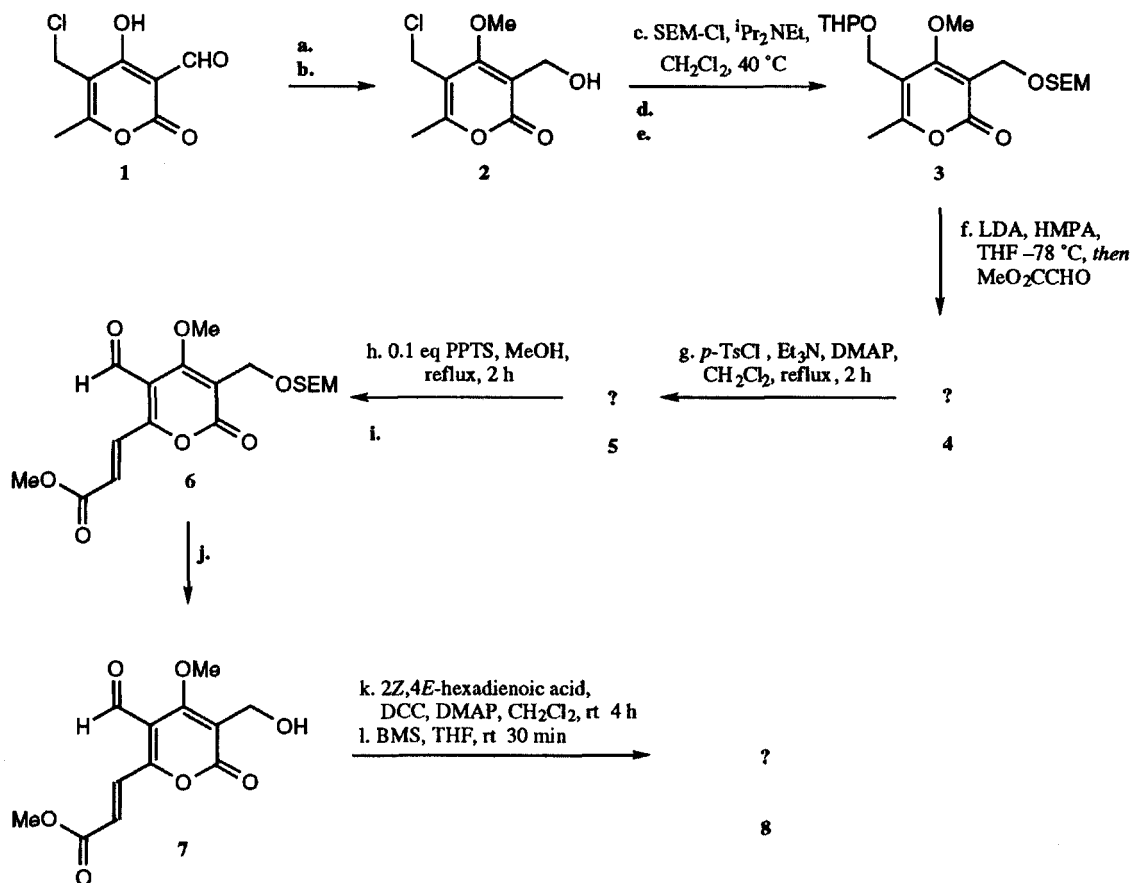
- What is the mechanism of the Bischler–Napieralski reaction of step b?
- Suggest a reason why less hindered bases could not be used in step f.
- Propose structures for the minor diastereomers obtained during the hydrogenation step g.
- Suggest a derivatising agent for the HPLC analysis of the optical purity of the 10-camphorsulphonic acid salt obtained in step h.

Further Reading

- For reviews on isoquinoline alkaloids synthesis, see: M. D. Rozwadowska, *Heterocycles*, **1994**, *39*, 903; E. D. Cox and J. M. Cook, *Chem. Rev.*, **1995**, *95*, 1797.
- For a review on chiral derivatising agents, see: Y. Zhou, P. Luan, L. Liu and Z.-P. Sun, *J. Chromatogr. B: Biomed. Appl.*, **1994**, *659*, 109.

3. Total Synthesis of Islandic Acid I Methyl Ester

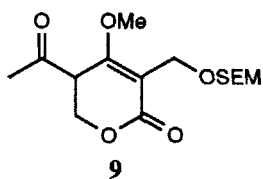
T. Shimizu, S. Hiranuma, T. Watanabe and M. Kirihara, *Heterocycles*, 1994, 38, 243.



Abstracted with permission from *Heterocycles*, 1994, 38, 243 ©1994 The Japan Institute of Heterocyclic Chemistry

Discussion Points

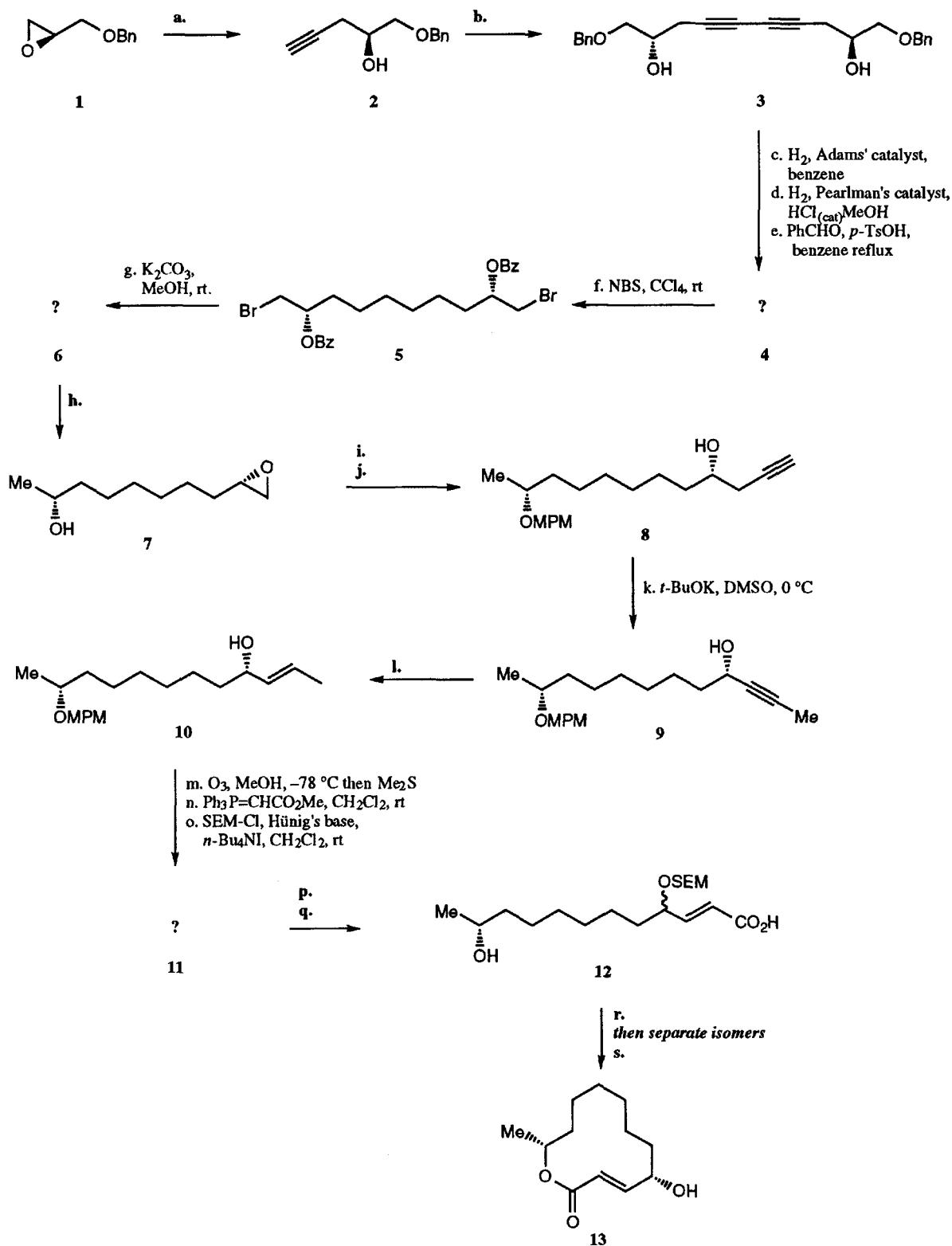
- The sequence from **2** to **3** introduces a tetrahydropyranyl (THP) group. What is the mechanism of this step?
- Following step **d** a quantity of compound **9** was isolable. Suggest a mechanism for its formation.



- Give two alternative methods of removing a SEM group as in step **j**.

4. Total Synthesis of (+)-Patulolide C

S. Takano, T. Murakami, K. Samizu and K. Ogasawara, *Heterocycles*, 1994, 39, 67.

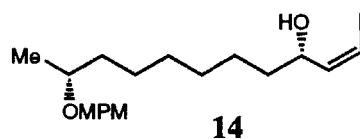


Abstracted with permission from *Heterocycles*, 1994, 39, 67 ©1994 The Japan Institute of Heterocyclic Chemistry

4. Total Synthesis of (+)-Patulolide C

Discussion Points

- What is the mechanism of steps **b** and **k**?
- Give a method for the formation of the *Z*-olefin **14** from alkyne **9**.

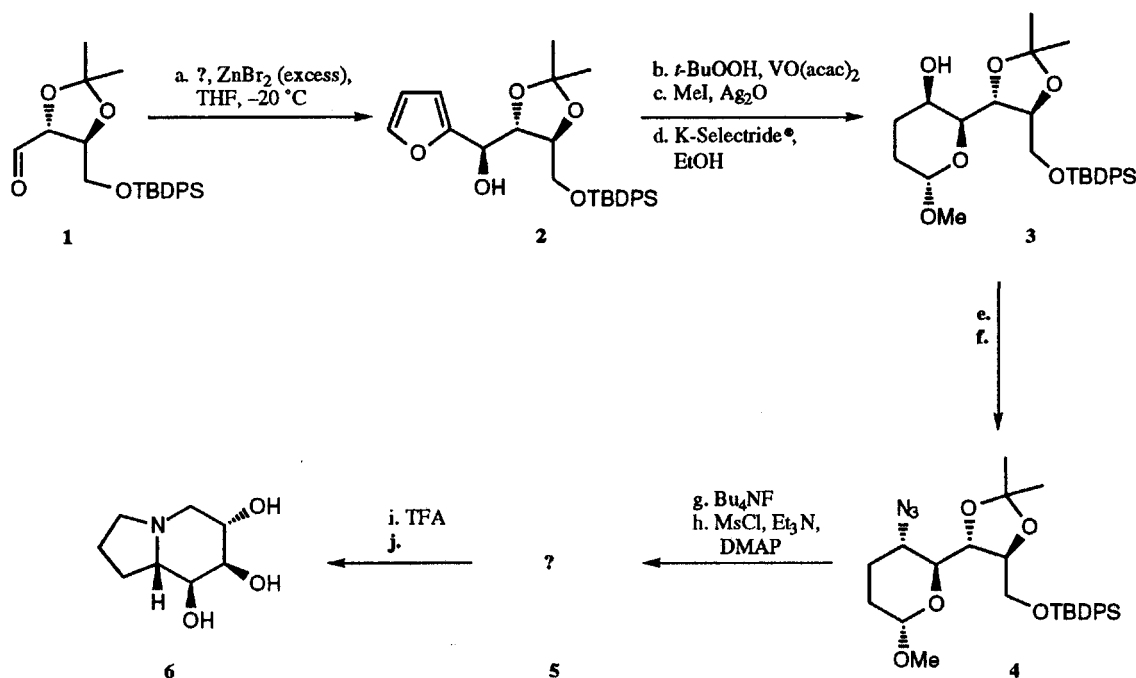


Further Reading

- A similar approach to that described above was used by the authors in the synthesis of a milbemycin K fragment, see: S. Takano, Y. Sekiguchi and K. Ogasawara, *Heterocycles*, **1994**, *38*, 59.
- For an excellent review on the two-directional chain synthesis strategy see: C. S. Poss and S. L. Schreiber, *Acc. Chem. Res.*, **1994**, *27*, 9. Another elegant application of this strategy to the synthesis of (–)-parviflorin has recently been published: T. R. Hoyer and Z. Ye, *J. Am. Chem. Soc.*, **1996**, *118*, 1801.
- For a review of macrocyclic ring formation methods see: Q. C. Meng and M. Hesse in *Top. Curr. Chem.*, **1992**, *161*, 107.
- A more recent chemoenzymatic synthesis of the related (*R*)-patulolide A has also been published: A. Sharma, S. Sankaranarayanan and S. Chattopadhyay, *J. Org. Chem.*, **1996**, *61*, 1814.

5. Asymmetric Synthesis of 1-Deoxy-8,8a-di-epi-castanospermine

S. F. Martin, H.-J. Chen and V. M. Lynch, *J. Org. Chem.*, **1995**, *60*, 276.



Abstracted with permission from *J. Org. Chem.*, **1995**, *60*, 276 ©1995 American Chemical Society

Discussion Points

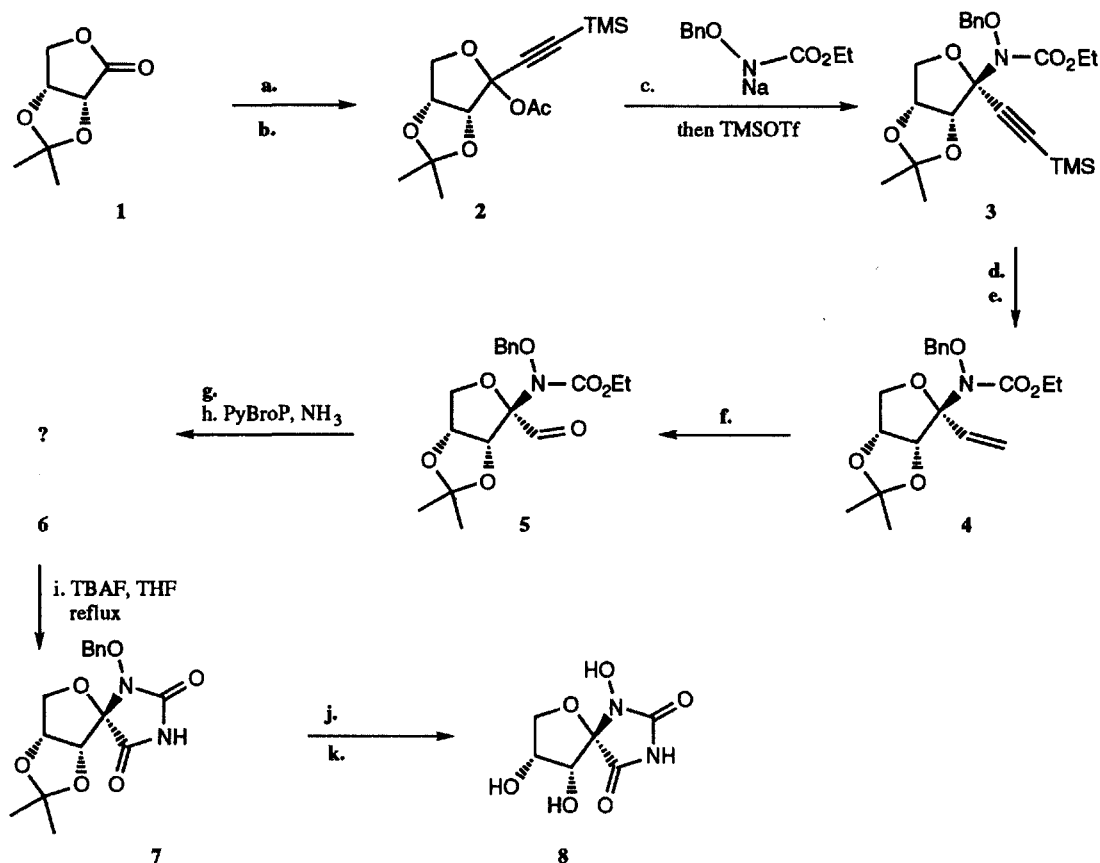
- Explain the stereoselectivity obtained in step a.
- Propose a mechanism for the conversion of 2 into 3.
- Suggest a structure for the intermediate formed in step j.

Further Reading

- For oxidative opening of furans, see: B. M. Adger, C. Barrett, J. Brennan, M. A. McKerverey and R. W. Murray, *J. Chem. Soc., Chem. Commun.*, **1991**, *21*, 1553.
- For an analysis of chelation-controlled carbonyl addition reactions, see: M. T. Reetz, *Acc. Chem. Res.*, **1993**, *26*, 462.

6. Synthesis of a Structure Related to Hydantocidin

S. Hanessian, J.-Y. Sancéau and P. Chemla, *Tetrahedron*, 1995, 51, 6669.



Abstracted with permission from *Tetrahedron*, 1995, 51, 6669 ©1995 Elsevier Science Ltd

Discussion Points

- Propose a mechanism for step c with a rationalisation of the stereochemical outcome.
- What is the role of TBAF in step i?

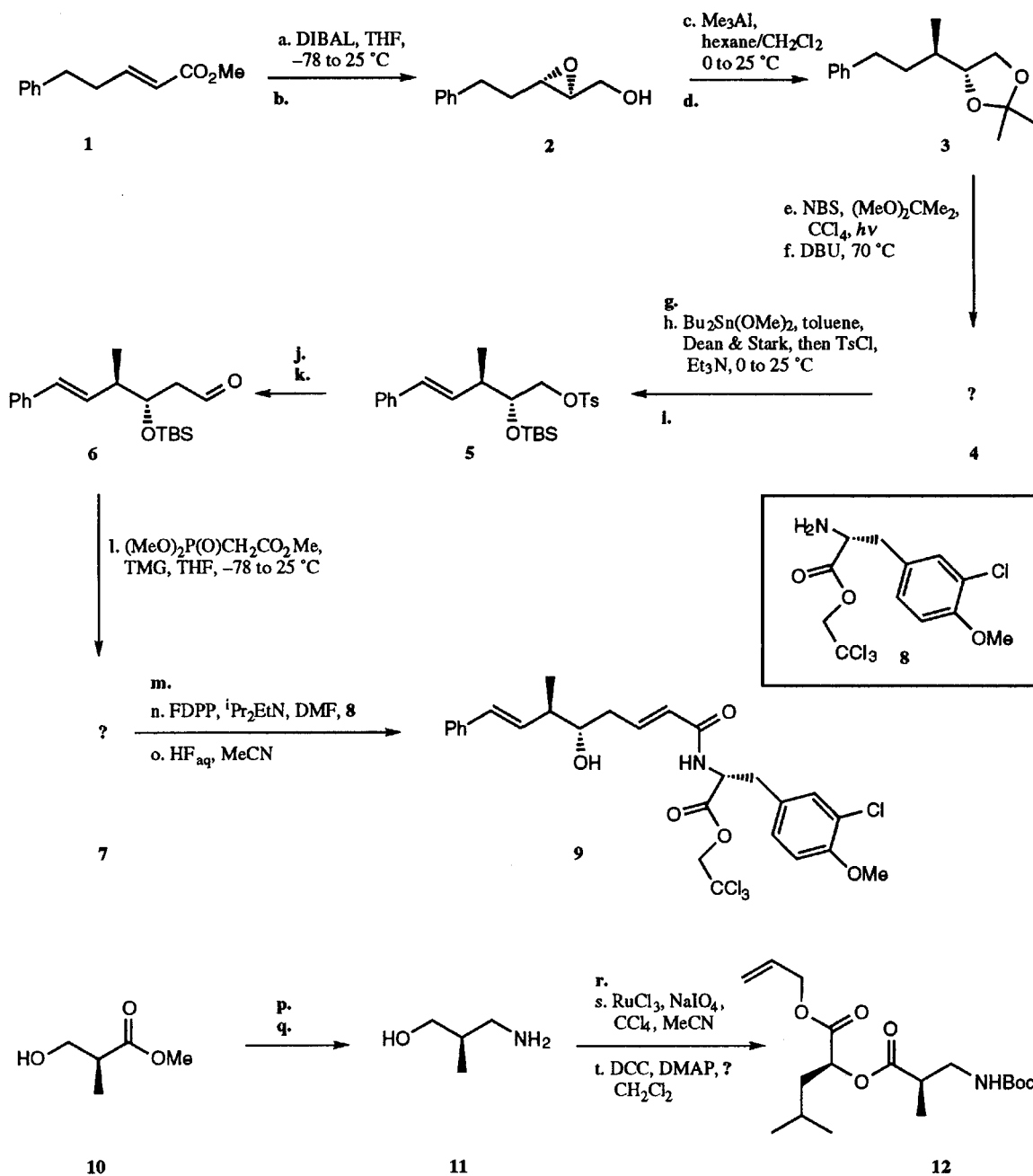
Further Reading

- For recent examples of the use of fluoride ion as a base, see: T. Sato and J. Otera, *J. Org. Chem.*, 1995, 60, 2627; see also: T. Sato and J. Otera, *Synlett*, 1995, 845.

7. Total Synthesis of Cryptophycin C

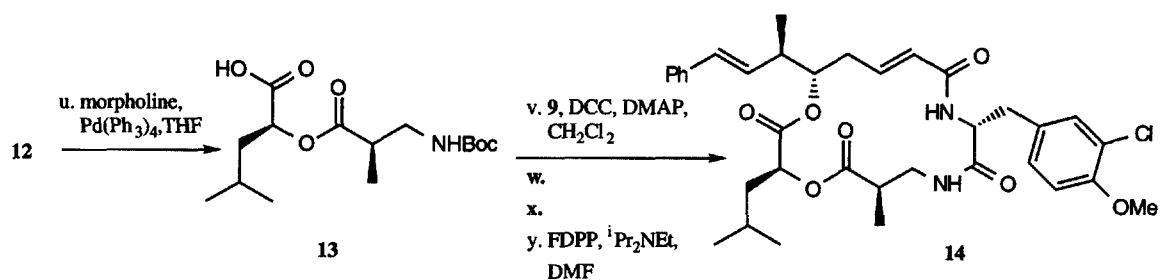
R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore and M. A. Tius,

J. Am. Chem. Soc., 1995, 117, 2479.



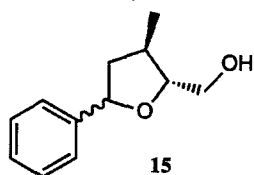
Abstracted with permission from *J. Am. Chem. Soc.*, 1995, 117, 2479 ©1995 American Chemical Society

7. Total Synthesis of Cryptophycin C



Discussion Points

- Suggest a synthesis for compound 1.
- Explain the regioselectivity in the epoxide opening of step c.
- A considerable amount of compound 15 was formed when step e was carried out in the absence of 2,2-dimethoxypropane.



Suggest an explanation for the formation of this compound and the function of 2,2-dimethoxypropane.

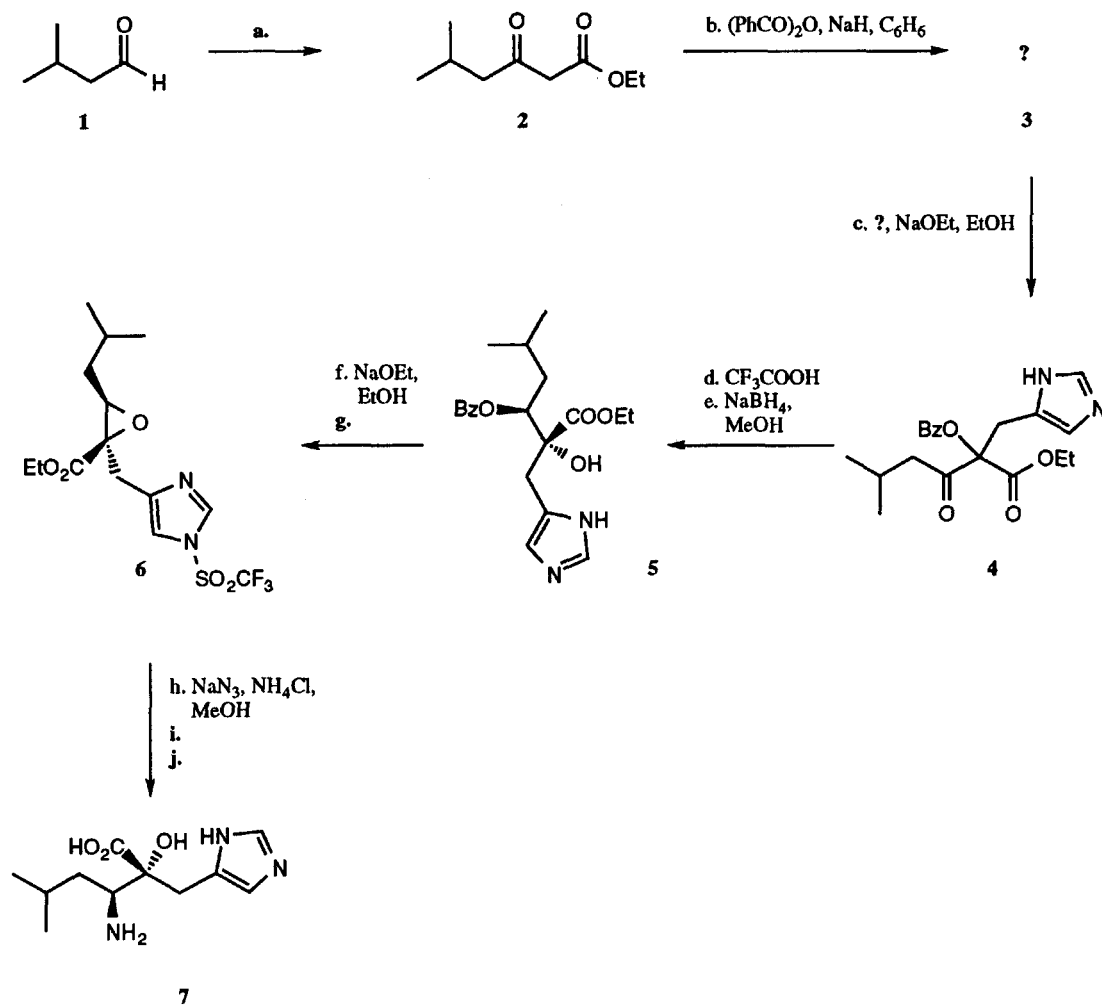
- Give mechanisms for steps h and u.

Further Reading

- For studies on the regioselectivity in epoxide opening, see: M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E. Giovani, F. Macchia, M. Pineschi, *J. Org. Chem.*, **1993**, 58, 1221; M. Chini, P. Crotti, C. Gardelli and F. Macchia, *Tetrahedron*, **1994**, 50, 1261.
- For a review on ring-closure methods in the synthesis of natural products, see: Q. C. Meng and M. Hesse, *Top. Curr. Chem.*, **1992**, 161, 107.
- For a modification of the allyl group removal procedure, see: A. Merzouk and F. Guibè, *Tetrahedron Lett.*, **1992**, 33, 477.

8. Total Synthesis of (±)-Leuhistin

S. J. Hecker and K. M. Werner, *J. Org. Chem.*, 1993, 58, 1762.



Abstracted with permission from *J. Org. Chem.*, 1993, 58, 1762 ©1993 American Chemical Society

Discussion Points

- Suggest a possible reason for the selectivity observed in step e.
- Explain the migration of the benzoate group observed in transforming compound 4 into 5.

Further Reading

- For the use of activated alumina in the synthesis of 3-oxoesters, see: D. D. Dhavale, P. N. Patil and R. S. Raghao, *J. Chem. Res., Synop.*, 1994, 4, 152.
- For reviews on catalytic transfer hydrogenation, see: R. A. Johnstone, A. H. Wilby and I. D. Entwistle, *Chem. Rev.*, 1985, 85, 129; G. Brieger and T. J. Nestruck, *Chem. Rev.*, 1974, 74, 567.

- [Second Language Identities pdf, azw \(kindle\), epub](#)
- [read online Shadowlands pdf, azw \(kindle\), epub](#)
- [The Hegel Variations: On the Phenomenology of Spirit here](#)
- [download Winter Numbers: Poems](#)
- [download Unfinished Agenda: Urban Politics in the Era of Black Power pdf, azw \(kindle\), epub](#)

- <http://paulczajak.com/?library/Naked-Chocolate--The-Astonishing-Truth-About-the-World-s-Greatest-Food.pdf>
- <http://xn--d1aboelcb1f.xn--p1ai/lib/Shadowlands.pdf>
- <http://jaythebody.com/freebooks/The-Language-of-the-Papyri.pdf>
- <http://flog.co.id/library/Strange-Tools--Art-and-Human-Nature.pdf>
- <http://junkrobots.com/ebooks/Unfinished-Agenda--Urban-Politics-in-the-Era-of-Black-Power.pdf>