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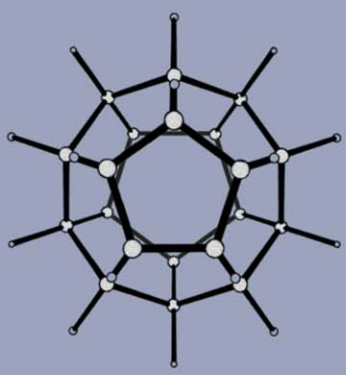
ORGANIC CHEMISTRY IN ACTION

The Design of Organic Synthesis

SECOND EDITION

FÈLIX SERRATOSA
JOSEP XICART



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The Design of Organic Synthesis

SECOND EDITION

PART A:

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with a copy of CHAOS and CHAOSBASE

1996

ELSEVIER
Amsterdam – Lausanne – New York – Oxford – Shannon – Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

ISBN: 0-444-81935-5

This book is printed on acid-free paper.

Printed in The Netherlands

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PREFACE TO THE FIRST EDITION

In 1975, under the title "HEURISKO. Introducción a la Síntesis Orgánica", I published a book which had been written mostly in thhe academic year 1970-71 and copies of which circulated at that time among the graduate students of the Organic Chemistry Department (University of Barcelona). Although in the year 1969 Professor R.E. IRELAND had published his book "Organic Synthesis" (Prentice-Hall), which had a rather classical approach, it was evident that starting from 1967, Professor E.J.COREY, with his methodology and formalisation of the synthetic process, had made a fundamental contribution to the systematisation of organic synthesis which was, from a didactic point of view, a breakthrough in the way Organic Synthesis was taught. Since in my incipient book some of COREY's ideas were already collected, the time seemed ripe for an updating and to look for a publisher. Finally, Editorial Alhambra (Madrid) included it in the collection EXEDRA, a series of monographs on natural and physical sciences. One year later, in 1976, the book by Dr. S. TURNER "The Design of Organic Syntheses" (Elsevier, Amsterdam) was published, thus confirming the expediency of my decision. Later on, S. WARREN published two textbooks: in 1978 a short but really useful book for undergraduates entitled "Designing Organic Syntheses. A Programmed Introduction to the Synthon Approach", and then, in 1982, a larger book "Organic Synthesis: The Disconnection Approach" (both from John Wiley & Sons, Chichester). In 1983, J. FUHRHOP and G. PENZLIN published their book "Organic Synthesis" (Verlag Chemie, Weinheim) and finally, very recently, in the middle of 1989, the book by E.J. COREY and X.M. CHENG "The Logic of Chemical Synthesis" (John Wiley & Sons, New York) appeared.

In the meantime, in 1985, when I started to prepare a second edition of "HEURISKO" I realised that my teaching experience in the last fifteen years had changed my own perspective of the topic sufficiently so as to offer a book essentially different, in which the principles, the strategies and the methodologies for designing organic syntheses could be presented in a simple and yet rigorous way to advanced undergraduate students (corresponding to the fifth year in Spanish Universities). The decision to publish this new book in English was taken later, when Elsevier Science Publishers became interested in the project.

If in the preface of my first book I was pleased to acknowledge my gratitude to Professor E.J. COREY; now, as stated below in the "Acknowledgements", I wish to extend my gratitude to Professor D.A. EVANS.

The treatment given in this book is orientative rather than exhaustive, with special emphasis on the "Lapworth-Evans model" of alternating polarities and the "heuristic principles" governing the different strategies and methodologies involved in the design of organic syntheses. The program, which runs on an IBM PC or a fully compatible microcomputer, allows the "heuristic method" to be used. That is to say, the pupils may be trained to learn and find results by themselves.

This book does not pretend to replace or invalidate any other book on the field. It is one more book in the field of organic synthesis in which teachers and/or students may perhaps find some stimulating ideas and some new examples to deal with.

The title of the book was just a compromise with the Publishers. Because most of the aspects are treated in the book in a rather fragmentary manner and they reflect my own interests which I have freely expressed (sometimes with immoderate enthusiasm and spontaneity) in the classrooms for almost three decades, an appropiate titled could be "Lectures on Organic Synthesis", to which the subtitle "An Introduction to Corey's and Lapworth-Evans Methodologies" might be added. Nevertheless, no matter how fragmentary the different topics may be, I have tried to ensure that the ideas flow smoothly, from a basic introduction to organic synthesis to the methodology of organic synthesis using modern terminology, based on EVANS' work. I hope my efforts will not be in vain and the book will receive an "acceptable" acceptance.

Sitges, New Year's Day, 1990

Fèlix Serratosa
Research Professor, C.S.I.C.

FOREWORD TO THE SECOND EDITION

The cordial reception which the first edition of the book received from teachers and students has prompted us to take the opportunity offered by the publishers to prepare a new revised edition.

Some new material has been added, the more significant changes being:

1) The book has been restructured in two well differentiated parts. Part B deals exclusively with computer-assisted organic synthesis (see 8 and 9).

2) Emphasis on the new objectives and targets, as well as on the role that organic synthesis should play from now on in the new areas of supramolecular chemistry and bioorganic chemistry (Chapter 1), is made.

3) A more extended discussion on synthetic methods and strategies based in radical carbon-carbon bond-forming reactions has been included (Chapter 7).

4) Some new examples to illustrate the heuristic principles have been incorporated (Chapter 4, for instance)

5) The chapter on alicyclic stereoselection has been splitted in two chapters (9 and 10). Chapter 10, which is exclusively devoted to Sharpless' asymmetric epoxidation and dihydroxylation, has been rewritten *de novo*. The most recent advances in catalytic and stereoselective aldol reactions are incorporated in Chapter 9.

6) Chapter 11 is a new one and the aim of it is, on the one hand, to present a panoramic view of the most important methods for the preparation of optically pure compounds in industrial scale (*chirotechnology*) and, on the other, to give a brief inside into the new biological synthetic methodologies, such as the use of *enzymes* and *catalytic monoclonal antibodies* or *abzymes,* which are becoming more and more important and familiar to the synthetic organic chemist. As stated by G. H. Whitesides and C. H. Wong (*Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617-638): "Those unwilling to use these and other biological derived synthetic techniques may find themselves exluded from some of the most exciting problems in molecular science".

7) The chapter dealing with examples of retrosynthetic analysis and the corresponding total synthesis has been enlarged and includes new syntheses of natural products (Chapter 13).

8) The former Chapter 11 and Appendices 2, 3 and 4 devoted to computer-assisted organic synthesis have also been rewritten and constitute now Part B of the book. The following changes have been introduced:

i) CHAOS version 3.0 for Macintosh and version 1.0 for PC Windows® substitute CHAOS version 2.0 for IBM PC and compatibles,

ii) the corresponding "Instruction Manuals" and "Disconnection Tables" of these new versions 3.0 are included,

iii) two 3.1/2 inch diskettes with the new versions of CHAOS and CHAOSDBASE are included instead of the 5 1/4 inch diskette of version 2.0,

iv) a new Appendix (Appendix B-1) with a brief introduction to Ugi's Theory of "Constitutional Chemistry" and to the programs EROS and IGOR has also been added.

9) The main improvements in CHAOS version 3.0 for Macintosh are:

i) The "unique numbering" or "canonical matrices". (Since the program runs slower with this option, for highly complex molecules devoid of any element of symmetry, it may be advisable to deactivate it. See option UNIQUE NUMBERING in menu PROCESS).

ii) New disconnections, which are more selective. Some of them "linked" with previous "activation", as Diels-Alder, Dieckmann or Pauson-Khand reaction.

iii) Besides RINGS and SYNTHETICALLY SIGNIFICANT RINGS, the new version gives, if required, the PRIMARY RINGS. Other new options are SELECT and RESIZE in the menu EDIT, by which one can select part of a synthetic sequence or resize the molecule drawing.

iv) The possibility to introduce new disconnections from inside the program CHAOS itself and work (if it is desired) with one's own chemistry, through CHAOSBASE. The aim of this program is to create DATABASES of new DISCONNECTIONS. Such DATABASES can be opened from the program CHAOS in such a manner that it allows to disconnect molecules according to the DISCONNECTIONS defined in the DATABASE (instead of disconnecting according to the predefined ones implemented in CHAOS).

10) Mistakes and errors detected in the first edition have been corrected.

Barcelona, 1994

Fèlix Serratosa

PREFACE TO THE SECOND EDITION

Professor Fèlix Serratosa died last January 11th after a prolonged liver illness. Fully aware that the end was near, he worked very hard until two or three weeks before his death, in order to finish the second edition of "Organic Chemistry in Action. The Design of Organic Synthesis", the book you are presently reading and to which he had devoted so many efforts.

Although unfortunately Prof. Serratosa could not accomplish his goal, he nonetheless left the revision at a very advanced stage. He had restructured the book into two well-differentiated sections: Part A, dealing with "conventional" organic synthesis, and Part B, devoted exclusively to computer-assisted organic synthesis and based on the former Chapter 11 and Appendices 2, 3 and 4 of the first edition. As decided in advance, Part B was to be the sole responsibility of Dr. Josep Xicart, who had prepared the first versions of the CHAOS (Computerisation and Heuristics Applied to Organic Synthesis) program under the direction of Prof. Serratosa.

Prof. Serratosa had also received the assurance of Prof. Núria Casamitjana that, in any event, she would finish up the job and indeed, despite all the difficulties, she has fulfilled her commitment. She has recovered all materials left on disk by Prof. Serratosa, revised and updated all references, rewritten parts of some chapters and made altogether, I believe, an excellent job.

Though not formally endorsed, but nevertheless fully convinced that, as one of his best friends and colleagues, Fèlix would have liked me to supervise the final stages of his book, I have tried to help in what I could, mostly in proof-reading, general advices and moral support. I hope this second edition of "Organic Chemistry in action. The Design of Organic Synthesis" will be at least as successful as the first one.

Barcelona, December 1995

Dr. Josep Castells
Emeritus Professor. University of Barcelona

COMPLEMENTARY COMMENTS AND ACKNOWLEDGEMENTS

Shortly before his death, Professor Fèlix Serratosa asked us to collaborate in the conclusion of his work. We have tried our best to complete the second edition of his book maintaining as far as possible the ideas and the spirit that have inspired him throughout his life.

Fèlix Serratosa will be missed by all of us for whom he has been not only a professor but a mentor, as well as a colleague and a friend.

The book represents our last homage to a man, who not only taught us Organic Synthesis, but also how to face life with admirable humanity.

First of all, we wish to express our deepest gratitude to Professor Josep Castells, *Emeritus Professor* of the University of Barcelona and one of Fèlix Serratosa's best friends, who has not only encouraged us to carry on the task that Professor Fèlix Serratosa entrusted to us, but has also helped us with his valuable ideas and suggestions in a final revision of the manuscript.

Our thanks to Elsevier Science Publishers for their confidence, first in Professor Fèlix Serratosa and second in our ability to finish the book.

We gratefully acknowledge "Vice-rectorat de Recerca" from the University of Barcelona for financial support that has made the completion of this second edition possible.

Finally, our thanks to all the people whose encouragement has helped us to finish the work that Professor Fèlix Serratosa began.

Barcelona, December 1995

Dr. Núria Casamitjana and Dr. Josep Xicart
Laboratory of Organic Chemistry. Faculty of Pharmacy
University of Barcelona

CONTENTS

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Appendix B-2

Appendix B-3

Appendix B-4

Glossary of abbreviations

acac ..... Acetylacetone
ADH ..... Asymmetric dihydroxylation
ADP ..... Adenosine diphosphate
AIBN ..... 2,2'-Azobisisobutyronitrile
AL ..... Aldolase
ATP ..... Adenosine triphosphate
9-BBN ..... 9-Borabicyclo[3.3.1]nonane
BINAP ..... (2*R*,3*S*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl
BOM ..... Benzyloxymethyl
BSA ..... Bovine serum albumin
BTI ..... Bis(thiocarbonyl)imidazole
Cp ..... Cyclopentadienide anion
DABCO ..... 1,4-Diazabicyclo[2.2.2]octane
DBU ..... 1,8-Diazabicyclo[5.4.0]undec-2-ene
DCC ..... Dicyclohexylcarbodiimide
DET ..... Diethyl tartrate
DHP ..... Dihydropyran
DHQ ..... Dihydroquinine
DHQD ..... Dihydroquinidine
DIPT ..... Diisopropyl tartrate
DIBAL ..... Diisobutyl aluminum hydride
DIOP ..... 2,3-*O*-isopropylidene-2,3-hydroxy-1,4-bis(diphenylphosphino)-butane
DMAP 4-Dimethylaminopyridine
DME ..... 1,2-Dimethoxyethane (glyme)
DMF ..... Dimethylformamide
DMSO ..... Dimethylsulphoxide
DOPA ..... 3-(3,4-Dihydroxyphenyl)-D,L-alanina
DS ..... Diastereoselectivity
ee ..... Enantiomeric excess
ELISA ..... Enzyme-linked Immunosorbent Assay
ES ..... Enantioselectivity
FGA ..... Functional Group Addition

FGI.....Functional Group Interchange
FGR.....Functional Group Removal
HMPA.....Hexamethylphosphoramide
H.D. .....High dilution
HLADH..... Horse liver alcohol dehydrogenase
HP..... Heuristic Principle
Ipc..... Isopinocampheyl
KLH..... Keyhole limpet hemocyanin
LAH.....Lithium aluminum hydride
LDA.....Lithium diisopropylamide
LTMP.....Lithium 2,2,6,6-tetramethylpiperidide
LUMO .....Lowest unoccupied molecular orbital
MCPBA..... *m*-Choloroperbenzoic acid
MED.....2-Methyl-2-ethyl-1,3-dioxolane
MOM.....Methoxymethyl
MOP..... 2-Methoxy-2-propyl
Ms.....Methanesulphonyl (Mesyl)
MS.....Mass Spectrometry
NBS.....*N*-Bromosuccinimide
NMO.....*N*-Methylmorpholine *N*-oxide
PCC..... Pyridinium chlorochromate
PDC..... Pyridinium dichromate
PPTS.....Pyridinium *p*-toluenesulphonate
Red-Al .....Sodium bis(2-methoxyethoxy) aluminum hydride
SOMO.....Singly occupied molecular orbital
TA..... Transaldolase
TBAF..... Tetrabutylammonium fluoride
TBDMS.....*tert*-Butyldimethylsilyl
TBDPS.....*tert*-Butyldiphenylsilyl
TBHP..... *tert*-Butyl hydroperoxide
TBS .....*tert*-Butyldimethylsilyl
TES..... Triethylsilyl
Tf..... Trifluoromethanesulphonyl
TfOH.....Trifluoromethanesulphonic acid
TFA .....Trifluoroacetic acid

THF ..... Tetrahydrofuran
THP ..... Tetrahydropyranyl
TMS ..... Trimethylsilyl
TPP ..... Thiamine pyrophosphate
Ts ..... *p*-Toluenesulphonyl (Tosyl)
TsOH ..... *p*-Toluenesulphonic acid
TK ..... Transketolase
W-K ..... Wolff-Kishner reduction

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PART A. THE DESIGN OF ORGANIC SYNTHESIS

Chapter 1

1. HEURISTICS AND ORGANIC SYNTHESIS. PURE SUBSTANCES

1.1. The chemical and the philosophical concept of «synthesis»: from Aristotle to Kant

With the advent of Ionian natural philosophy during the 5th century B.C., a new way of thinking came into being: *mythos* was replaced by *logos*, and facing the world, man was not anymore satisfied with the mere evidence of things and, as Elisabeth Ströker pointed out, "sought a deeper understanding about what lasts as permanent behind their change" [1].

Although the Greeks dealt with the *Physis -i.e.* Nature-, they did not develop a science of *matter* which could be considered as the precursor of modern chemistry. There were among the Greeks great mathematicians, geometrists, astronomers, physicians, botanists and zoologists, but not chemists properly said. Although Democritus developed an atomistic theory of *matter*, it was Aristotle [2] who, without being a chemist, dealt with concepts which were essentially chemical and would affect, from then on, the future development of this science. It is in the works of Aristotle that the words *synthesis* and *mixis* appear for the first time. But, mind! The easy and direct translation of these words as «synthesis» and «mixture», respectively, has led quite often to a misunderstanding of the ideas of Aristotle. In fact, what Aristotle means by *synthesis* is just a mechanical mixture in which the different components preserve their own identity, and its properties are the sum of the properties of the components. Therefore, the *synthesis* is the reverse process of analysis, since the components of a *synthesis* can be separated by means of an analysis.

By contrast, in what Aristotle calls *mixture* a *henosis* takes place, in such a manner that the properties are not the sum of the properties of the components, but some new properties come out. Since in the *mixis* the components can be also retrieved by analysis, Aristotle must admit that they are also present in the *mixis*, but according to his theory, they are present *in potentia*. In this context, common salt or sodium chloride, for example, would be a *mixis*, the properties of which nothing have to do with those ones of its components. There is nothing in common salt that

reminds us of either the toxicity of chlorine or the aggresiveness of sodium and yet these two elements are present *in potentia*, since they can be recovered, for example, by an electrolytic process. On the other hand, gunpowder would be a *synthesis* in the Aristotelian sense, the elements of which can be separated by a simple analysis, such the selective extraction with different solvents. Nowadays we know that gunpowder is a simple mechanical mixture of its components. That the mixture is explosive is another story.

In summary, to say it in modern terminology, Aristotle clarified the difference between «mixture» and «combination», and for the first time in the human mind there arose some fundamental questions which have affected and concerned the chemists since then. It was not until the 18th century that Antoine Baumé [3] (1728-1804) used, for the first time, the term «combination» instead of *mixis*, as can still be read in the papers of Becher (1635-1682) and Stahl (1660-1734).

In the 17th century, Robert Boyle (1627-1691) established the concept of «structure» by which the Democritean notion that the different forms of matter are mere aggregates of corpuscles or *atoms* in movement was superseded. The «structure» would be the cause and the origen of the *henosis* we have referred to in forming a *mixis*.

According to E. Ströker [1], it was not the Democritean «atomistic theory» of matter which was the precursor of the modern Daltonian atomic theory, as generally accepted, but the Aristotelian concept of *minima naturalia*[1], developed in the Middle Age.

After Aristotle, the word *synthesis* is not found explicitly mentioned in the chemical literature until Dalton used it in his classical book. In the year 1808, Dalton (1766-1844) published his book «A New System of Chemical Philosophy», the chapter III of which is entitled «On Chemical Synthesis». However, in the meantime the word «synthesis» had experienced a semantic change and acquired the modern meaning of «forming a compound». There is, therefore, a time lapse of more than twenty centuries, in which the word «synthesis» was not mentioned by chemists, perhaps because all of them believed as Gerhardt (1816-1856) that: "The chemist's activity is therefore exactly opposed to living nature; the chemist burns, destroys and operates by analysis. Only the life force works by synthesis; it builds up again the edifice torn down by chemical forces" [4]. A better ecological *manifesto* would be

---

[1] *Minima naturalia*, the minimum particles in which a substance can be divided without ceasing to be what it actually is; i.e, without losing those properties which characterise the substance.

difficult to find! However, owing to the fact that many successful results were achieved in the field, in the following years, Gerhardt changed mind and publicly admitted it in 1854.

After Dalton, the word «synthesis» was not usually used yet in chemical parlance. Berzelius (1779-1848), Dumas (1800-1884) and even Wöhler (1800-1882) refer to the classical synthesis of urea -achieved in 1828 by Wöhler himself- as an «artificial production» or «formation» of an organic compound. Only after the publications by Kolbe (1818-1884), Frankland (1825-1899) and Bertholet (1827-1907) was the word «synthesis» normally used and became familiar to chemists.

From the philosophical point of view, although the word «synthesis» has a long tradition, it was Kant (1725-1804) who went deep into the modern meaning of the term, which, in turn, determined the chemical meaning presently accepted by all chemists.

Thus, in philosophy there is a difference between «synthesis» as a method -meaning the way of going from the simple to the complex- and «synthesis» as an operation -in which case means «to com-pose».

In the philosophical literature «synthesis» also means the integration (or junction) of the subject and the predicate. The result of this integration is a proposition which is itself more complex that the components, but on the other hand, it may be said that in «synthesising» the subject and predicate something more simple results. In a more general sense, by «synthesis» is meant the operation of associating the different representations, ones with the others, and to seize what is diverse in just one act of understanding. Nevertheless, what we want to emphasise here is the creative character of synthesis: by joining, something new results.

1.2. Organic synthesis as a heuristic activity

Since Kant, philosophers have recognised two different ways of reasoning. On the one hand, *analytical reasoning*, which is essentially logical and deductive and leads to propositions or explicative statements and on the other, *synthetical reasoning*, which is essentially intuitive and inductive and leads to genuine innovations. This is to say, in contrast with analytical reasoning, synthetical reasoning implies an acquisition of new knowledge.

Using analytical reasoning what already exists can be deduced. Nothing new comes from it: we only discover or unveil the mysteries and secrets of the world in which we live. That was the precise meaning of science according to the ancient

Greeks. By contrast, something really new comes from synthetical reasoning: it is the Christian or modern conception of science. For the Christian and the postchristian, to engage in scientific activity is -as Laín Entralgo stated in his speech "La Ciencia del Europeo", delivered at Geneva after World War II- "to live the intimate *drama* of knowing that every human discovery must necessarily carry around itself a halo of uncertain, audacious, problematical personal creation".

The analysis of a mixture, for instance, gives information about its composition, but the mixture already existed before. We have not created anything new: we have only *deduced* its composition. However, if we synthesise a new compound -a drug, for instance- then we have really created something new that did not exist *a priori.*

If it is true that we demonstrate things by logic, it is only through *intuition* that we discover new things. In fact, as Poincaré pointed out "logic only produces tautologies".

In the same way that syllogisms and theorems are the essence of analytical reasoning, the "heuristic principles" are the essence of synthetical reasoning.

According to "The Oxford Dictionary", the word "heuristic" derives from the Greek *heurisko* ("I find") and it is used as an adjective to describe activities directed towards the act of discovering ("serving to discover"), including all those reasonings and arguments that are persuasive and plausible without being logically rigorous. And it is used as a noun (mainly in the plural) to refer to "the science and art of heuristic activity". The heuristic principles, in contrast with the mathematical theorems and the "rules of proof", do not pretend to be laws, and only suggest lines of activity. It is this heuristic activity that, through some exploratory processes of trial and error, leads finally to discovery. In this context, we can say that organic synthesis is a heuristic activity.

In this book, rather than producing a textbook of organic chemistry, we hope to be able to show the science and art of organic chemistry in action.

1.3. Pure substances. Language: The Classical Structural Theory

Chemistry is the science that deals with matter. The Earth on which we live, as well as the rest of the physical world that surrounds us, is formed by quite different kinds of matter. The first task of the chemist is to identify and isolate all the component entities that, together, constitute the material world. It is interesting to remember here that the old Alchemy was considered as "the noble art of separation".

The different component entities of the tangible physical world are not the atoms and molecules so familiar to chemists, but the so-called "pure substances", meaning by this all the substances that show constant or invariable properties (m.p., b.p., refractive index, specific optical rotation, pharmacological activity, if any, etc.) and are chemically homogeneous (as judged by one or more chromatographic techniques, for instance). Since Lavoisier's classical work, an axiom accepted by the whole chemical community is that only "pure substances" can give relevant information for the further development of chemistry. For this reason, the so-called "purity criteria" were so important in all the classical chemistry textbooks of the first half of this century.

All the material world is formed of mixtures, aggregates or more complex combinations of pure substances. For example, it is well known that the bark of the Cinchona tree (*Cinchona calisaya*) shows a remarkable antimalarial activity, which is due, not to the bark as such, but to some "pure substance" which forms an integral part of it. In 1820, the French pharmacists Pelletier and Caventou isolated the active principle of the Cinchona bark, which they called *quinine*, as a pure, crystalline substance, m.p. 177 °C (dec), $[\alpha]_D^{15}$ -169°, and assigned an elemental composition to it of $C_{20}H_{24}N_2O_2$. Once the pure substance has been identified and isolated, the second task of the chemist is to describe it in terms of atoms and molecules according to the general principles of the "Atomic and Molecular Theory", formulated by Dalton and Avogadro at the beginning of the last century (1808 and 1811, respectively) and the "Classical Structural Theory", the bases of which were set up, independently, by Kekulé and Couper in 1858.

Thus, in order to describe adequately any pure substance, its structure must be elucidated. Before the advent of modern analytical techniques, such as X-ray diffraction analysis, structure elucidation was a much more complicated and time-consuming task than the separation and identification of a compound and occupied the life-work of many eminent chemists.

Quinine provides a case in point here, since its structure was not elucidated until 1908, nearly a century after its separation and identification by Pelletier and Caventou.

Once the structure of a molecule has been determined, the next task for the chemist is to synthesise the pure substance. This can be very difficult indeed, but these difficulties notwithstanding, the synthesis of an organic molecule -natural or

non-natural- is always an unique and unforgettable experience which embraces organic chemistry in all its aspects.

As R.E. Ireland [5] has said, the completion of an organic synthesis whatever its complexity is always "a total organic chemistry experience, and it involves the application of the knowledge and techniques of the entire science."

In fact, as we will see, the classical structural theory provides the only means by which a chemist can visualise a synthesis. All science needs a language and the language of organic chemistry is the *Classical Structural Theory*. That this is so can be seen if the first attempts to synthesise quinine are considered.

In the first half of the 19th century, when the colonial expansion of the European nations was at its height, malaria became a serious problem in the newly colonised territories overseas and the price of natural quinine, whose production was at that time monopolised by the Dutch, became exorbitant. In an attempt to provide a cheap alternative to the natural material, the French Pharmaceutical Society offered, in 1850, a prize of 4.000 francs to any chemist who could prepare synthetic quinine in the laboratory.

In England, in 1856, only two years before Kekulé and Couper laid the foundations of the structural theory, W.H. Perkin [6], acting upon the advice of his mentor A.W. Hofmann, attempted to synthesise quinine by the oxidative dimerization of allyltoluidine following the reaction:

$$2\,C_{10}H_{13}N \;+\; 3\,(O) \longrightarrow C_{20}H_{24}N_2O_2 \;+\; H_2O$$

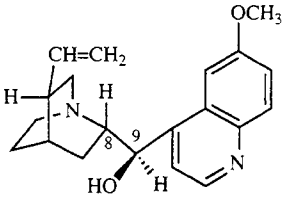
a transformation which if, in terms of the empirical formulae of those days seemed plausible and straightforward, nowadays is known to be highly unlikely if not impossible. The fact that this study of the reaction of simple aromatic amines -in particular, aniline- gave rise to the discovery of the first synthetic dyestuff (*mauveine* or aniline mauve), was due more to the genius of Perkin than to the state of early structural chemical knowledge. Although this discovery paved the way for the great dyestuffs industries, these would not have advanced at such a rate if it had not been for the almost simultaneous publication by Kekulé and Couper, in 1858, of their classical work on the constitution of organic compounds, laying the foundations of the structural theory. The consequences of this work was the assignation of the correct structures to almost all the organic compounds then

known, among them the natural dyestuffs alizarin and indigo, and, moreover, to open up the possibility of synthesising them.

It has been said that the development of organic chemistry in the last hundred years represents the most surprising application of a non-quantitative logical reasoning. Even more surprising is that the structural theory of the organic chemists does not differ too much from the so-called *graph theory* [2]- a branch of mathematics related to topology and combinatorial analysis- developed by Euler and other mathematicians at the beginning of the 18th century.

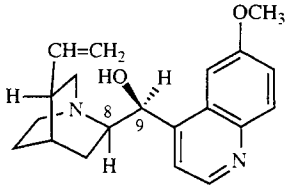
Returning to quinine, the synthesis was not accomplished until 1945, by Woodward and Doering [7] at Harvard University, and it is a moot point whether or not they attempted to collect the 4000 francs prize offered by the French Pharmaceutical Society almost one hundred years earlier.

It must not be forgotten that the concept of pure substance, referred to earlier, is very rigorous and must take into account, not just the constitution and relative configuration of a molecule, but also the absolute configuration of each chiral center that may present. For example, again in relation to quinine (1), quinidine (2) is also known and the only difference between the two molecules is the disposition in space of the groups bonded to C(8). Nevertheless 2 is a different molecule and shows no antimalarial activity. In addition, only one enantiomer of quinine (1), the *laevorotatory,* corresponds to the natural compound and manifests the specific physiological properties associated with this substance.



1

quinine



2

quinidine

Therefore, apart from the problem of linking all the carbon atoms of the carbon skeleton of the molecule, every projected organic synthesis must also take into

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[2] See Appendix A-1.

account the different stereochemical requirements and possibilities inherent in that molecule. The best way of evaluating these is to make use of molecular models.

1.4. The objectives of organic synthesis

As stated by Eschenmoser "the motives for embarking on total syntheses of natural products are manifold" [8]. One of the primary objectives of performing a synthesis was to secure substantial amounts of the product, under acceptable economic conditions. That was the case, for instance, with products such as the natural dyestuffs alizarin and indigo, which were very expensive, and the same holds true in the case of vitamins, hormones, pheromones, etc. which are either difficult to isolate and purify or occur only in minute amounts in Nature. When Nature affords the product in sufficient quantities it might be thought that such an objective would not have any meaning, and yet, even in those cases, the synthesis of a molecule is of paramount importance in organic chemistry. Traditionally, the total synthesis of a compound has been considered to be the definitive and rigorous proof in verifying a proposed structure. In fact, a proposed structure is not accepted as correct until the total synthesis of the molecule has been successfully accomplished. Nowadays, such an arbitrariness is more evident than ever since the physical methods used to determine a structure are the same ones which, in practice, are used to follow the course of a synthetic sequence and to ensure that the events actually go according to plan. The evidence that some of these methods -mainly X-ray crystallographic analysis- may provide is almost absolute.

In fact, the synthesis of a molecule closes the "magic circle" [9] -more magical than logical- which the synthetic organic chemist moves around and comprises the three stages we have referred to: isolation and identification, description and synthesis (see Figs. 1.1 and 1.2).

Occasionally, however, things can go awry and examples exist in the chemical literature (albeit very few in number) of natural products whose structures, even after the "structure confirmation" by total synthesis, were shown to be incorrect in the light of the results obtained by X-ray crystallographic analysis. Patchouli alcohol, a natural sesquiterpene of some interest in the perfumery industry, provides an illuminating example.

Degradation and structure elucidation studies led to structure 3 which was then taken as a target and synthesised by Büchi [10]. Once the synthesis was

successfully accomplished, the identity of synthetic patchouli alcohol with the natural product was verified by direct comparison (Figure 1.3).

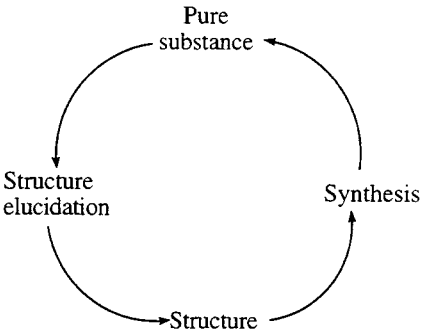


Fig. 1.1

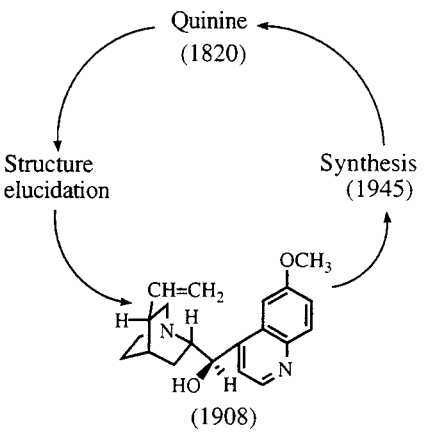


Fig.1.2

Later on, however, X-ray crystallographic analysis by Dunitz of a single crystal of the corresponding chromic diester [11] showed that the actual structure of patchouli alcohol was that of a bridged tricyclic compound (4) (Scheme 1.1), with all its rings having six carbon atoms.

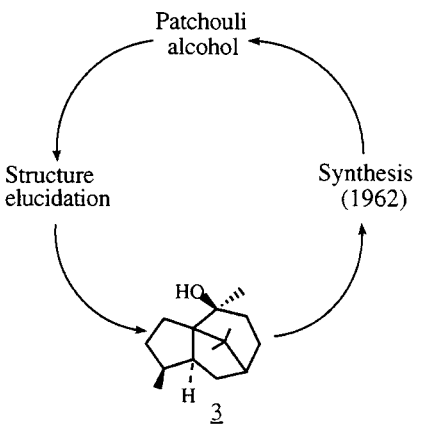
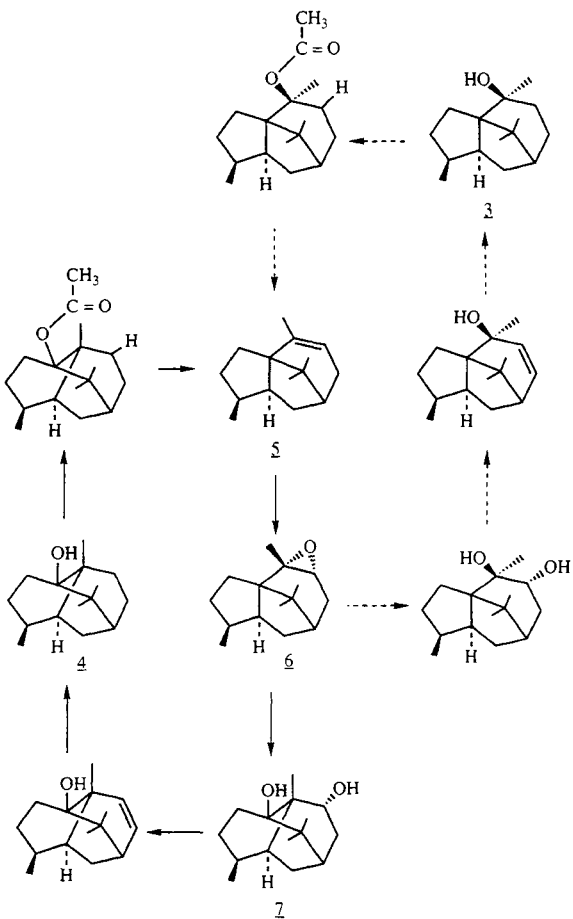


Fig. 1.3

In fact, a "diabolic confabulation" of two rearrangements, one in the course of degradation of patchouli alcohol to α-patchoulene (4 ⟶ 5) and another one in the

exact reverse direction, during the synthesis (6 ⟶ 7), led to this unfortunate mistake. However, if it happened once, in principle it may happen again. It illustrates, therefore, that total synthesis is not necessarily a definitive proof in confirming a proposed structure.

On the other hand, in at least one case, the possibility of assigning incorrect structures on the exclusive basis of X-ray diffraction analysis has been reported, owing to the existence of certain "crystallographic disorders" caused by perturbations of unknown origin [12] [13].



Scheme 1.1

Returning to the motivations for undertaking an organic synthesis, we can say that besides needing sufficient quantities of the product -either to be used as such or

as a "model" for mechanistic and/or spectroscopic studies- the more powerful driving-force is the novelty, the challenge and the risk chemists must face. Robert B. Woodward [14a] explicitly recognised it: "The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men".

To R.B. Woodward undertaking a new synthesis was neither for gain nor simple opportunism. In his own words [14b]: "There is excitement, adventure, and challenge, and can be great art, in organic synthesis", and The Royal Academy of Science of Sweden recognized it, awarding him, in 1965, the Nobel Prize for chemistry "for his outstanding contribution to the art of organic synthesis".

Roald Hoffmann, a former coworker of R.B. Woodward and Nobel Prize as well for his contribution to the frontier orbital theory (the famous Woodward-Hoffmann rules concerning the conservation of molecular orbital symmetry), has also emphasised the artistic aspects of organic synthesis: "The making of molecules puts chemistry very close to the arts. We create the objects that we or others then study or appreciate. That's exactly what writers, visual artists and composers do" [15a]. Nevertheless, Hoffmann also recognises the logic content of synthesis that "has inspired people to write computer programs to emulate the mind of a synthetic chemist, to suggest new syntheses".

In this context it is worth noting that the Nobel Prize for Chemistry, for the year 1990, was awarded to E.J. Corey not only for his outstanding contribution to organic synthesis, but also for his formalisation of the mental process through which a chemist designs a synthesis and for the original way he uses logics, heuristics and computers in designing organic syntheses.

1.5. New times, new targets?

One can easily understand that, after Woodward and Corey, some highly qualified chemists have implicitly concluded that organic synthesis can hardly be a "Nobelable" activity anymore and have put it on trial.

D. Seebach, for example, in a review entitled "Organic Synthesis - Where now?" [15b] explicitly proclaims that "all the most important traditional reasons for undertaking a synthesis -proof of structure, the search for new reactions or new structural effects, and the intellectual challenge and pride associated with demonstrating that 'it can be done'- have lost their validity. Exceptions only prove the rule". Seebach does not wonder "that one often leaves a lecture or a symposium

in which 'something else has just been synthesised' with a feeling of boredom coupled with a sense that the same lecture could just have been delivered 20 years ago!"

Although Seebach recognises that multistep syntheses may provide the broadest possible training for graduate students in organic chemistry, he feels that sponsoring a project for this reason could only be justified from the point of view of teaching responsabilities but not as a commitment to the conduct of basic research within a university environment.

The question Seebach puts on the table is -what should actually be, from now on, the new targets of organic synthesis? In answering this question, Seebach refers to an observation of a theoretical physical chemist who remarked that "nowadays, the molecular program of chemistry has arrived at its successful termination". That is to say, rather than simple molecules, the new generation of targets for the synthetic chemists should be more complicated systems whose structures and properties are determined by non-covalent interactions. In summary, Seebach concludes that "the molecular 'design' of a (super)structure now captures the spotlight, while the synthetic process itself may withdraw into the background".

Quite different are the feelings of Roald Hoffmann, who reminds us once and again that "chemists make molecules"..."Without molecules in hand no property can be studied, no mechanism elucidated" and explicitly proclaims that "it is the making of molecules, chemical synthesis, that I want to praise" [15a].[3]

Somehow, Seebach ends his superb review, in which more than 500 references are quoted, with a rather optimistic message: "that organic synthesis continues to react forcefully and with vitality to new challenges, still ready to pursue old dreams", and he refers to some exciting new targets such as supramolecular structures; inhibitors, suicidal substrates and flustrates; monoclonal antibodies and

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[3] In my opinion (F.S.) and according to my personal experience, I should say that as a Research Professor, I agree with Seebach and my very last contributions to Chemistry, before my official retirement, were on the field of "supramolecular chemistry" and on the field of "computer-assisted organic synthesis". On the other hand, as a teaching Professor, I agree with Hoffmann. If "synthesis is a remarkable activity that is at the heart of chemistry" [15a], I can only introduce my students at the very heart of chemistry by teaching them with *authority*, i.e., only if I am the *author* of, at least, some of the experiences I teach them -whatever how simple or naive my syntheses are. Moreover, as Roald Hoffmann recognises: "The programming is an educational act of some value; the chemists who have worked on these programs have learned much about their own science as they analysed their own thought processes". Again, I agree with Hoffmann.

abzymes systems; analysis, computers and theory; reactivity and transition-metal derivatives; molecular design and catalytic enantioselective syntheses.

The problem behind all these questions is that perhaps we have automatically and uncritically accepted the artificial distinction between Chemistry and Biochemistry (and even perhaps Biology) as a natural and insuperable barrier. But, what does "Molecular Biology" really mean? or "Supramolecular Chemistry"? And what about "Bioorganic Chemistry"? Has it even nowadays any meaning to differentiate between Organic and Inorganic Chemistry?

1.6. Synthesis as a sequence of unequivocal steps. Economy: conversion, selectivity and yield. Starting materials

Synthesis of a more or less complex organic compound implies always a sequence of steps or reactions which go from the starting material to the target. In principle, each one of these reactions may give different products, which are characterised in terms of constitution, configuration and yield. If P_0 are the mole of the starting material,[4] p^1, p^2, p^3...p^i the mole of the different possible reaction products, and P_t the mole of the unreacted starting material after time t,

$$P_0 \longrightarrow p^1, p^2, p^3...p^i, P_t$$

then the following concepts can be defined:

% conversion, %C

$$\%C = \frac{P_0 - P_t}{P_0} \times 100$$

($P_0 - P_t$ = mole of reacted product after time t)

Selectivity (with respect to p^i), S^i

$$S^i = \frac{p^i}{P_0 - P_t} \times 100$$

Yield (with respect to p^i), Y^i

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[4] According to IUPAC, although the SI unit of amount of substance is the mole, the physical quantity 'amount of substance' should no longer be called 'number of moles", just as the physical quantity 'mass' should not be called 'number of kilograms' ("Quantities, Units and Symbols in Physical Chemistry", IUPAC, p. 4, Blackwell Scientific Publications, Oxford, 1988).

$$Y^i = \frac{\%C.S^i}{100} = \frac{p^i}{P_0} \times 100$$

It should be realised that the experimental conditions not only affect conversion and yields -as it is, for instance, in the case of using appropriate catalysts that accelerate the rate of the desired reaction, or in the cases where the use of pressure and/or temperature would favor the displacement of the equilibrium to the reaction products side-, but they may also sometimes affect selectivity controlling, for example, the formation of either the kinetic or the thermodynamic enolate as may be required. Nevertheless, selectivity is usually attained by using the appropriate *control elements* (protecting or blocking groups, activating groups, conformational or configurational control, etc) (see Chapter 8).

From a synthetic point of view it is convenient to distinguish the following kinds of selectivity:

i) Chemoselectivity: differentiation of identical or very similar chemical reactivity.

ii) Regioselectivity: refers to the orientation between reactants and differentiates positions or regions of a molecule similarly activated by identical or similar functional groups.[5]

iii) Stereoselectivity:

a) Diastereoselectivity: relative stereochemical control.

b) Enantioselectivity: absolute stereochemical control.

The first two classes of selectivity distinguish between constitutional isomers; the last one between stereoisomers (configurational isomers and, eventually, conformational isomers).

The reaction sequence (steps) of a synthesis may be linear (i) or convergent (ii) [16]. Because the total yield $\underline{Y}$ of a synthesis is the product of the partial yields $\underline{y}$,

$$\underline{Y} = \left[\frac{\underline{y}}{100}\right]^n \times 100 \qquad (n = \text{number of steps})$$

-and "the arithmetic demon dictates one of the major axioms of synthesis: 'Get the most done in the fewest steps and in the highest yield'" (R.I. Ireland)-, in a linear

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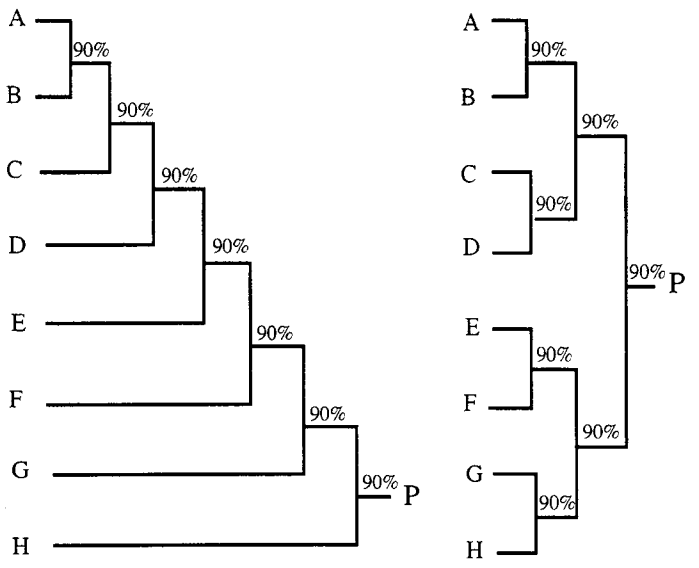
[5] Some authors prefer to distinguish between *regioselectivity* and *situselectivity*, respectively.

synthesis $\underline{Y}$ decreases rapidly with the number of steps n, resulting in a waste of intermediates which are more and more expensive at every new step. By contrast, a convergent synthesis is much more economical because each intermediate is obtained from a combination of two precursors and the formation of the most expensive intermediates is delayed to the last steps of the synthesis. Moreover, in a convergent synthesis the demand of intermediates is more easily satisfied since each one of them is nearer to the starting materials.

Compare, for instance, the overall yield ($\underline{Y}$) of a seven-step synthesis (n = 7) in each one of the two versions-(i) and (ii)-, assuming an average yield *per* step ($\underline{y}$) of 90% (see Fig. 1.4)



$\underline{Y} = 0.9^7 \times 100 = 47.8\%$

$\underline{Y} = 0.9^3 \times 100 = 72.9\%$

Fig. 1.4

Other things being equal, the superiority of convergent strategies (ii) over linear strategies (i) is really dramatic when dealing with polypeptides, the synthesis of which would require several steps. Considering, for instance, a convergent synthesis of a polypeptide with 64 aminoacids, and assuming that the average yield

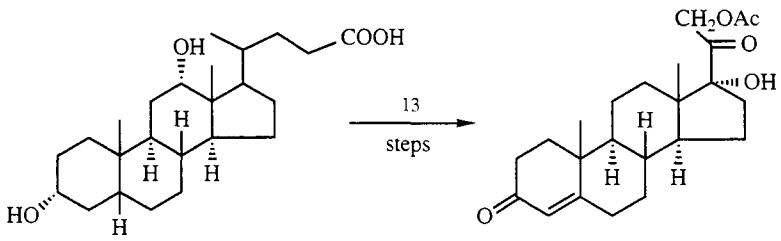
per step is 90%, the overall yield is 53%, in contrast with only 0.13% yield for the linear synthesis.

Moreover, if the average yield *per* step decreases only slightly, let us say down to 85%, the overall yield of the convergent synthesis is still quite acceptable -37%-, but now the overall yield of the linear synthesis would be only 0.004%. It is clear, therefore, that for polypeptides of any complexity and for proteins, linear syntheses in solution are not practicable even if the yields of each step are kept high. However, solid-phase peptide synthesis can be quite efficient. This is because solid-phase synthesis represents an improvement in linear methodology which has, as yet, not found an equivalent in convergent methods [17].

These reflections are of special interest in the case of industrial syntheses in which the economic aspects are important. In these syntheses there is another factor to be kept in mind that may be illustrated by considering the industrial syntheses of steroids developed by Velluz and his coworkers in 1960 [18]. In contrast with other syntheses in which the intermediates are racemates and are only resolved into their optical active forms in the last step, the industrial syntheses require the resolution of the racemic mixture at the first possible opportunity, in order to exclude the unwanted isomer and thus avoiding the expenses of its processing. For recent advances in enantioselective synthesis see *Heading 9.3.*

With regard to *starting materials*, a *total synthesis* must start from materials that, ultimately, can be reduced to the elements. Since the only organic compounds, apart from urea, that can be prepared from the elements are acetylene, methane and methanol, a total synthesis must be reduced to them. This does not mean that the chemist must always start from these basic materials, but from compounds -the more elaborated the better- that are derived from them rather than from natural compounds with the basic carbon skeleton already present, but not previously synthesised, since in such a case, we should refer to *partial synthesis.*

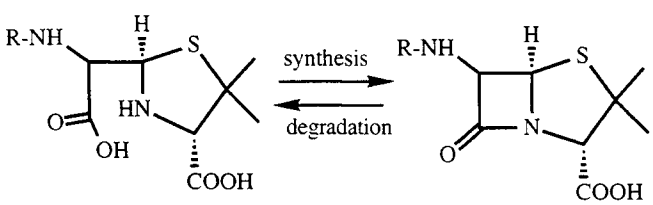
The first synthesis of cortisone (8), for instance,was a partial synthesis from desoxycholic acid (9), performed in 1948 by a group of chemists at Merck and Co under the leadership of Kendall [19], three years before Woodward [20] and Robinson [21], independently, accomplished the first total synthesis of steroids.



9 8 (acetate)

However, if those natural products have been previously synthesised one may start from them, provided that it simplifies the synthesis, since repetitions and waste of time should be avoided. Moreover, once a key intermediate has been synthesised, but may also be obtained easily by degradation from some other product, including the same natural product that is being synthesised, the chemist should resort to such a source and use it to continue the synthesis. This approach to total synthesis is referred to as the *relay approach.*

Examples of such an approach are found in the synthesis of strychnine [22] and morphine [23], labours which have been said to bear resemblance to *Sysiphus's torment* [24], since they involve linear sequences of more than 25 steps. However, the most illustrative example is found, perhaps, in the synthesis of penicillin (10), in the course of which the penicilloic acid derivative 11 was synthesised, though through a laborious and lenghty route. Because this intermediate was easily available from natural penicillin, it was convenient to resort to such a method of degradation in order to make it available in sufficient quantities for studying the last step -that requires the formation of a β-lactam- and thus accomplishing successfully the total synthesis [25].



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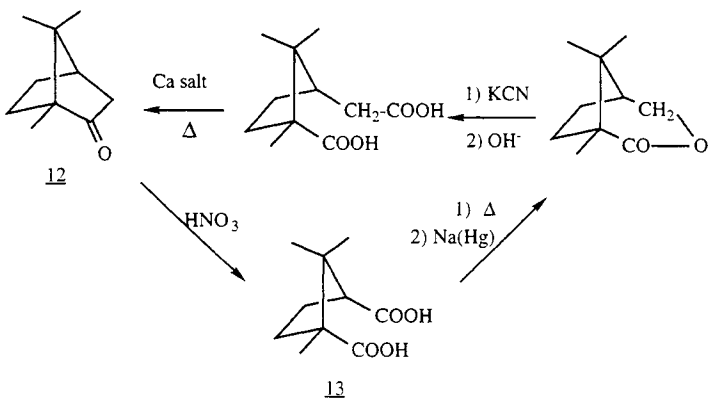
Another type of synthesis is the so-called *formal total synthesis.* In this case, a degradation product had been previously transformed into the desired natural

product, the structure of which was under investigation. The synthesis of the degradation product then constitutes a formal total synthesis. Although this procedure does not afford any of the target molecule, a formal synthetic scheme is established from the elements. For example, in the case of camphor (12), the sequence shown in Scheme 1.2 had been established by degradation.

The total synthesis was restricted then to the synthesis of camphoric acid (13), since it had been previously reconverted to camphor [26].

In fact, the total synthesis of chlorophyll was also a formal total synthesis, since the problem was to synthesise chlorin e_6, which had been obtained by degradation and then reconverted into chlorophyll [27].



Scheme 1.2

1.7. Carbon skeleton, functional group manipulation and stereochemical control. Rule of maximum simplicity

As has been mentioned, the synthesis of an organic compound always implies a sequence -either linear or convergent- of oriented steps that go from some starting materials to the target. Each one of these steps involves joining some structural units or *synthons*, and the following aspects must be taken into account:

i) the formation of the carbon-carbon (or carbon-heteroatom) bonds leading to the "carbon skeleton" of the molecule,

ii) the manipulation of functional groups; i.e., introduction, interconversion and elimination of them, and

iii) all the related stereochemical problems.

Although the three aspects are not strictly independent, sometimes, from a didactic point of view, and to simplify the synthetic analysis, they may be considered separately. However, their mutual interaction must be allowed for in some further stage of the analysis, in order to introduce the pertinent modifications into the process and to arrive at the simplest possible solution (see Diagram 1.1): this means that the maximum correlation must exist among the different individual synthetic operations, so that each one of them allows, facilitates or simplifies, in some way, all the other ones ("rule of maximum simplicity").

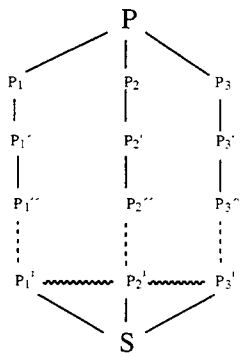


Diagram 1.1

In order to illustrate what "the maximum correlation" and "the simplest possible solution" mean, we can compare the formation of ring A of the steroidal skeletons, in the synthesis of cortisone (8) by Sarett *et al.*, accomplished in 1952 [28], with the synthesis of conessine (14) by Stork and his co-workers, accomplished ten years later, in 1962 [29] (Scheme 1.3).

These two compounds have in common the presence of a polycyclic steroidal skeleton, and although in both syntheses the same strategy is used to build up ring A, the synthesis of cortisone shows a greater simplicity than the synthesis of conessine.

The key intermediates from which ring A must be constructed -which were synthesised through a sequence that will not be considered here- are, respectively, 15a and 15b.

Notice that, in spite of the *trans*-junction of rings B and C present in the target molecules, both synthesis start from intermediates with a *cis*-B/C configuration in

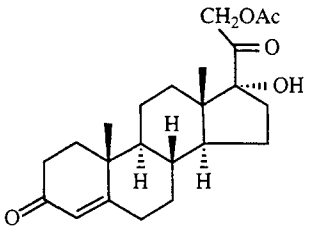
order to exercise regioselective as well as stereoselective control. In fact, intermediates 15a and 15b are *cis*-decalins and are, therefore, "folded" molecules in which the convex face (α) and the concave face (β) are clearly differentiated. Since the electrophilic Michael acceptors attack the corresponding enolates from the back side (α), the methyl group at C(10) is forced to adopt the β configuration as it is found in the final product.

On the other hand, the formation of the perhydrophenanthrene system instead of the linear anthracene system is favored by the fact that *cis*-decalones form almost exclusively the Δ^1-enolate (according to the conventional numbering of decalins) and consequently alkylation takes place selectively at C(10) instead of C(6) (according to the conventional numbering of steroidal systems).

Once regioselective and stereoselective controls have been exerted, the *cis*-decalins must be isomerised to *trans*-decalins, the configuration present in the target molecules. Since *trans*-decalins are thermodynamically more stable than the corresponding *cis*-decalins, it is possible to isomerise the latter through enolisation, a process that can be favored by the presence of a carbonyl group near to the centre to be inverted.

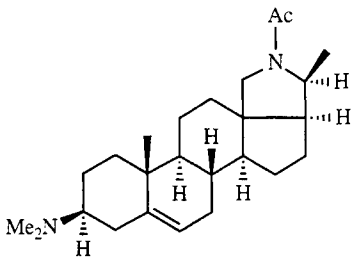
In the case of the synthesis of cortisone, Oppenhauer oxidation of hydroxyl group at C(14) -after the necessary acetalisation of the unsaturated carbonyl group- leads to intermediate 16a, which, under the basic conditions of Oppenhauer oxidation, spontaneously isomerises to 17a, with the more stable *trans*-B/C junction. An additional advantage of this sequence is that the carbonyl group activates the C(13) vicinal position, and allows not only the introduction of the methyl group, but facilitates the construction of ring D of the cortisone molecule.

By contrast, in the synthesis of conessine there is not such an efficient and elegant correlation among the different synthetic operations. Of course, we refer only to the construction of the A ring and do not mean to imply any demerit in Stork's synthesis of what is, after all, a more complex molecule.



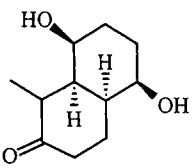
8

cortisone (acetate)

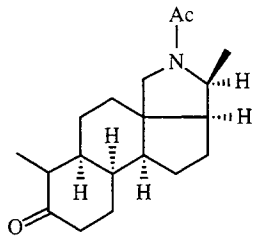


14

conessine

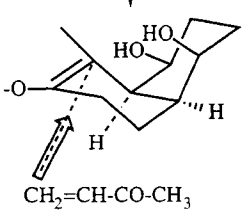


15a

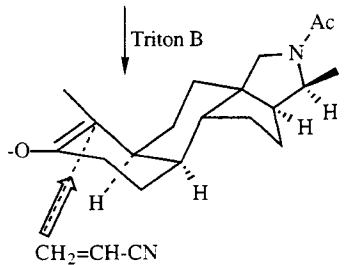


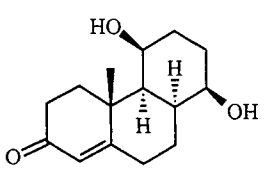
15b

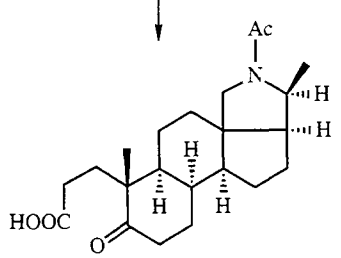
Triton B



Triton B







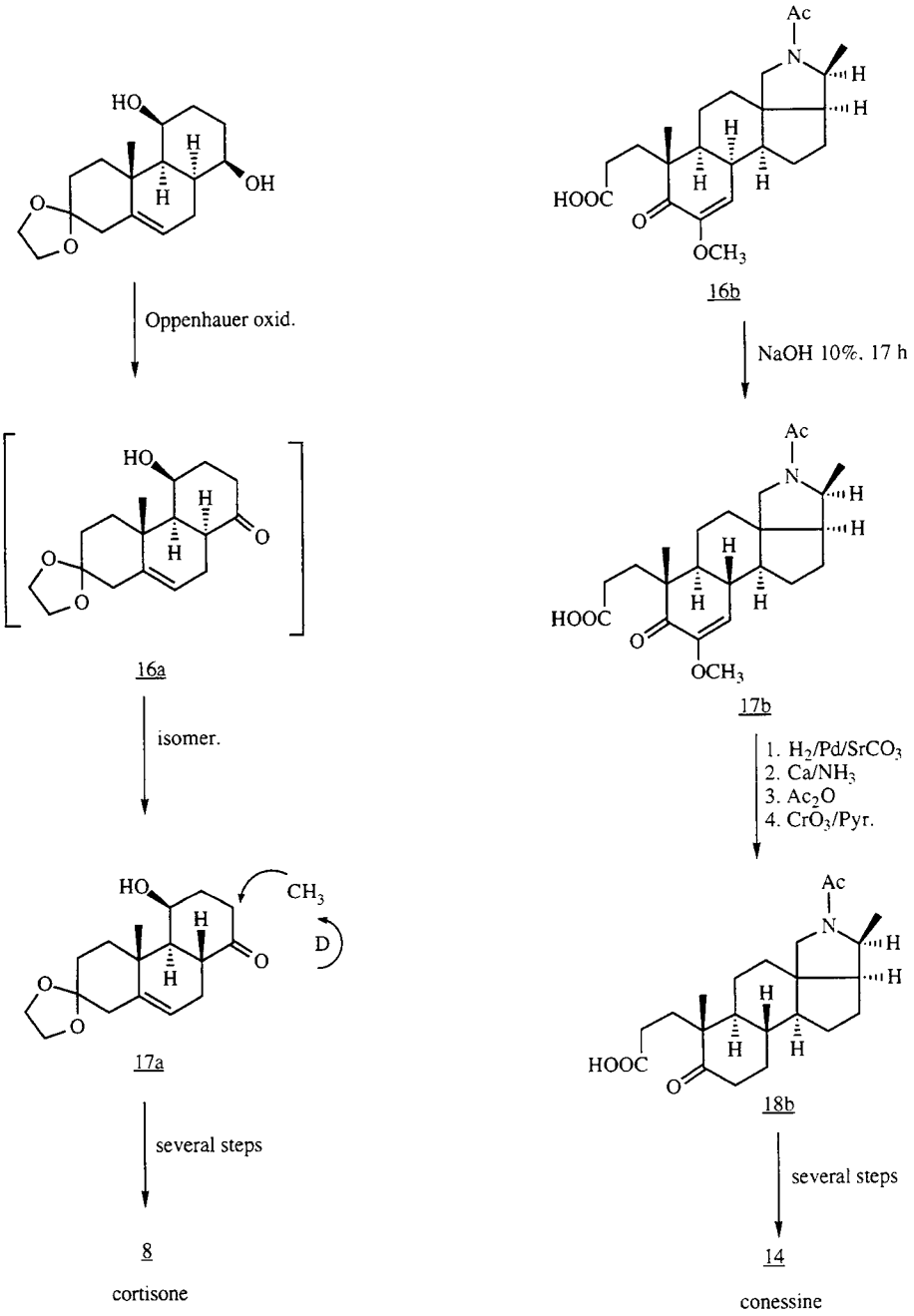
$(CH_2OH)_2$

$TsOH/C_6H_6$

1. Br_2 ; 2. OH^-

3. Oxid.; 4. Me_2SO_4

Scheme 1.3



Scheme 1.3 (continued)

As shown in the synthetic sequence, to induce isomerisation of the *cis*-B/C junction to a *trans* configuration, a double bond between C(6) and C(7), that can transmit the electronic effects of carbonyl group at C(5) must be created *ex profeso.*[6] This relatively simple structural modification requires no less than five different synthetic operations: i) bromination at C(6); ii) substitution of the bromine atom by an OH group; iii) oxidation; iv) *O*-methylation with dimethyl sulphate, and v) isomerisation in alkaline medium (16b ⟶ 17b). But then, once isomerisation has taken place, four further steps are necessary to eliminate the double bond: vi) catalytic hydrogenation of the double bond; vii) elimination of OCH_3 by Ca dissolved in ammonia, which causes two unwanted side-reactions, reduction of the carbonyl group and the loss of the acetyl group of the nitrogen; viii) re-acetylation of the amino group, and ix) oxidation to restore the carbonyl group originally present (17b ⟶ 18b).

Therefore, nine steps or synthetic operations are necessary in the conessine synthesis for isomerising the *cis*-B/C decalin system to *trans*-B/C, a transformation that in the cortisone synthesis is accomplished without any *extra* step, since it takes place spontaneously in the oxidation step, which, in turn, is necessary to introduce the second angular methyl group and build up ring D of cortisone in a stereoselective manner. Better correlation amongst different synthetic operations would be difficult to find in more recent synthesis of similar complexity and magnitude than that of Sarett.

1.8. Molecular complexity and synthetic analysis

On the basis of graph theory and information theory, Bertz [30] has proposed, in the past few years, the first general index of molecular complexity (η), so introducing a quantitative concept of "molecular complexity" which may be applied to synthetic analysis.

In terms of complexity, the "rule of maximum simplicity" means that the complexity of the intermediates throughout the synthetic sequence must be kept as near as possible to the complexity of the starting materials, C_0, and to that of the

---

[6] In contrast with the cortisone synthesis, in which ring A is constructed in a straightforward manner by a Robinson annulation, the synthesis of ring A of conessine is constructed in a stepwise fashion in order to have, at this stage, the carbonyl group free. Ring A will then be "closed" by nucleophilic attack of CH_3MgBr on the enol lactone.

final product, C_f [30c] [31]. This means that the area below the curve given by the expression:

$$F = \int_0^{f-1} C(k)d(k)$$

where molecular complexity, C, is function of the steps, k, of the synthetic sequence, must be minimised. The function may be represented by a coordinate system, such as the one shown in Fig. 1.5.

C(k) is a polygonal function, and, accordingly, F can be expanded into the sum:

$$F = 1/2(C_o + C_1)k_1 + 1/2(C_1 + C_2)k_2 + ... + 1/2(C_{f-1} + C_f)k_f = \sum_{i=1}^{f-1} C_i + 1/2(C_o + C_f) \quad \textbf{(a)}$$

in which the "size" of each one of the steps k_i is taken equal to 1.

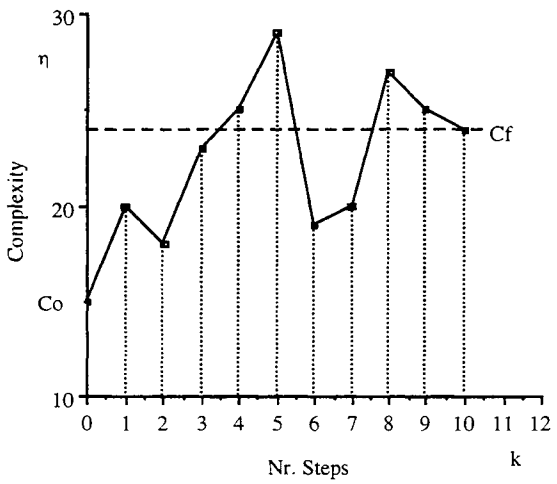


Fig. 1.5

Since maximum simplicity would be attained in the "ideal" case of a one-step synthesis,

$$F_0 = 1/2(C_0 + C_f) \quad \textbf{(b)}$$

the excess complexity, C_x, is given by the difference between (**a**) and (**b**)

$$F - F_o = C_x = \sum_i C_i$$

that is to say, by the sum of the complexities of the intermediates.

For the various "indices of complexity" which have been proposed and the minimum requirements they must meet in order to be really useful, see Bertz [30a]. The "complexity index" η, proposed by Bertz, is based on the number of connections and is defined as the number of adjacent pairs of bonds existing in one molecule.

Curves such as the one shown in Fig. 1.5 are useful when comparing different synthetic approaches to the same target. For instance, Fig. 1.6 compares the linear syntheses of dodecahedrane by Paquette [32] and Prinzbach [33] with the "ideal" one-step synthesis and two theoretically possible convergent syntheses [34] [35]. As can be seen, whereas in the linear synthesis, intermediates of similiar or greater complexity than the dodecahedrane molecule itself are reached in very few steps, in the convergent syntheses the complexities of the intermediates are kept quite near to that of the starting materials and the dodecahedrane complexity is only reached in the final steps. Since the greater the complexity the greater the risk of unwanted side-reactions, the lower complexities of the convergent syntheses is another factor -apart from the number of steps required- which must be taken into account, and which also plays a part in their greater efficiency (see Hendrickson, [36]).

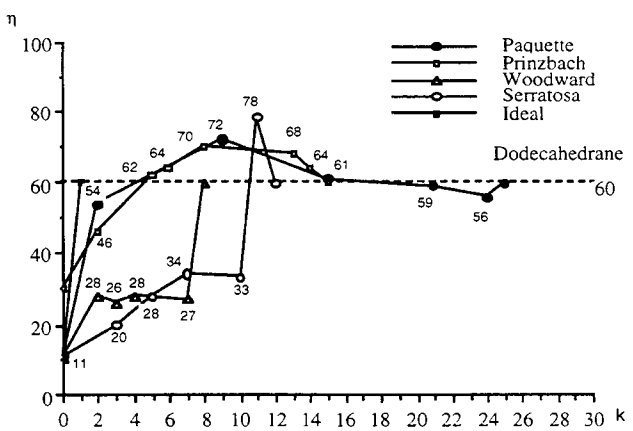


Fig. 1.6

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Appendix A-1

GRAPH THEORY. MOLECULAR COMPLEXITY INDICES

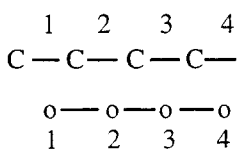
"Molecular complexity" is a rather subjective concept. Although the structural features which contribute to the complexity of a molecule have been pointed out by different authors [1] [2] [3] [4], only recently Bertz has defined a quantitative and unified index embracing the size, symmetry, branching, unsaturation, and heteroatoms chatracteristic of a complex molecule [5] [6].

According to *Graph Theory*, a molecule may be represented by its *skeletal molecular graph* which, from a mathematical point of view, is the union of a set of points, symbolising the atoms other than hydrogens, and a set of lines, symbolising bonds. Its properties can be then expressed in terms of *graph-theoretical invariants*, $N_{i,j}$, which have been defined as "the number of distinct ways in which skeleton *i* can be cut out of skeleton *j*". The simplest invariant which takes into account both points and lines is N_{2j}, the number of ways that propane can be cut out of a saturated hydrocarbon, which has been used succesfully as a branching index. A more general index proposed by Bertz, which may be applied to unsaturated systems, is based upon η, the number of *connections*, defined as "the number of pairs of adjacent lines".

So, the number of connections can be determined either from the "bond graph" [7], or even better, from the number of "propanes" that can be derived from the skeleton of the molecule under consideration.

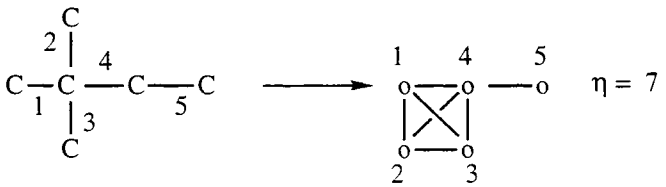
To build up a "bond graph", the bonds of a given molecule are enumerated and represented by a point, and then each pair of points is connected with a line whenever the corresponding bonds are adjacent. Therefore, the number of the resulting lines gives the number of "adjacent pairs" or connections (η). For example,

n-pentane

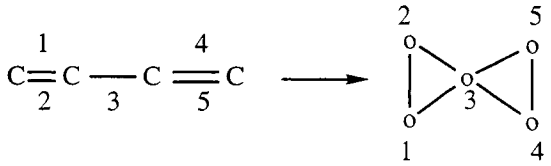


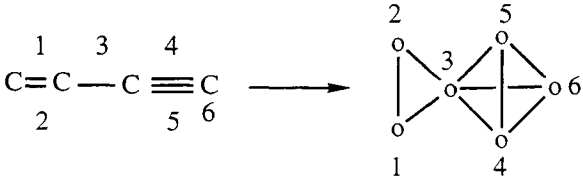
$\eta = 3$

In the case of branched molecules it is necessary to draw the points appropriately in order to get "graphs" as simple as possible in which the adjacent bonds are easily detected. For a tertiary carbon atom, for instance, where there are three adjacent bonds, the three corresponding points are disposed in a triangle; for a quaternary carbon atom, the four points are arranged in a square:

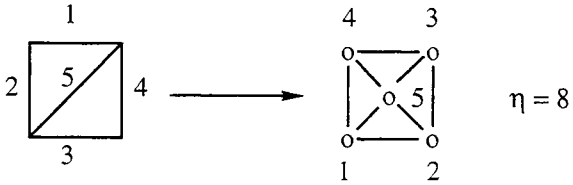
2,2-dimethylbutane  $\eta = 7$

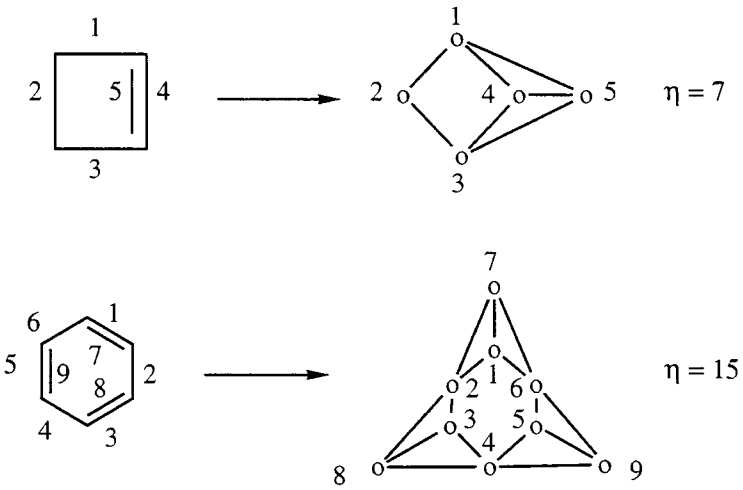
On the other hand, in molecules with multiple bonds, each "component bond" of double and triple bonds is numbered independently, and keeping in mind the geometrical distribution of points we have just referred to. For example,

butadiene  $\eta = 6$

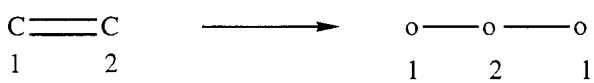
vinylacetylene  $\eta = 9$

With fused polycyclic systems and cycles bearing double bonds, in order to obtain simple "bond graphs", a careful distribution of points must be carried out,

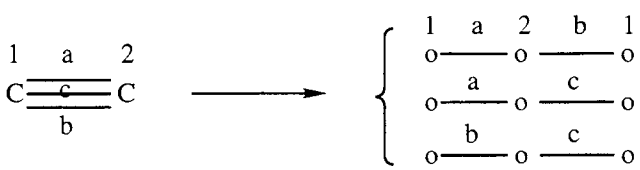
 $\eta = 8$



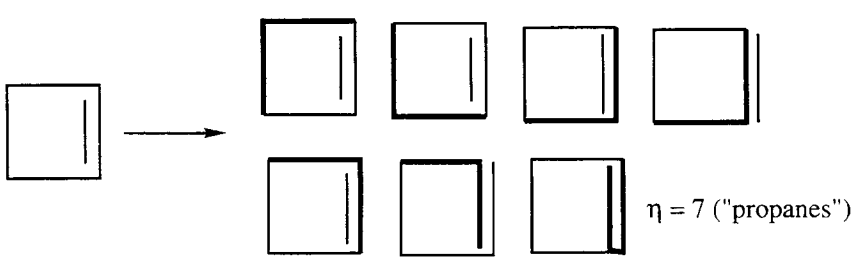
The alternative procedure to determine the number of connections is, as we have already mentioned, to calculate the number of "propanes" within the molecular skeleton, bearing in mind that a double bond is equivalent to one "propane";



and a triple bond to three "propanes",



For instance, in the case of cyclobutene we will have,



In the "general index of complexity" (C_t) proposed by Bertz, besides the number of connections, symmetry is also taken into account. Such an index, that incorporates concepts from the "graph theory" and the "theory of information" [7] is defined as:

$$C_t = C(n) + C(E)$$

in which

$$C(n) = 2n \log_2 n - \Sigma n_i \log_2 n_i$$

and

$$C(E) = E \log_2 E - \Sigma E_i \log_2 E_i$$

where n represents any *invariant* of the graph; E the total number of atoms present in the molecule; n_i the number of symmetry equivalent invariants in the graph, and E_i the number of atoms of the same element i.

Although n can represent any graph-theoretical invariant, the choice is quite critical if chemically meaningful results are to be obtained. For example, if n is taken to symbolise points, cyclobutane and tetrahedrane are assigned equal complexities [C(points) = 8.00]; if n is taken to represent lines, cyclohexane and tetrahedrane have the same value [C(lines) = 15.51]. Since "branching" must also be taken into account, besides the size and the symmetry, C(connections) give the following order: tetrahedrane (43.02) > cyclohexane (15.51) > cyclobutane (8.00), which makes sense considering that tetrahedrane contains three cyclobutane subgraphs in addition to four cyclopropane subgraphs. Henceforth $n = \eta$, giving the index $C(\eta)$.

On the other hand, the complexity of a molecule increases with the number of heteroatoms, the symmetrical disposition of which is a simplifying factor just as it is for carbon atoms. When all the atoms are the same, C(E) = 0 and the total complexity C_t is equal to $C(\eta)$; i. e, the complexity due to connectivity.

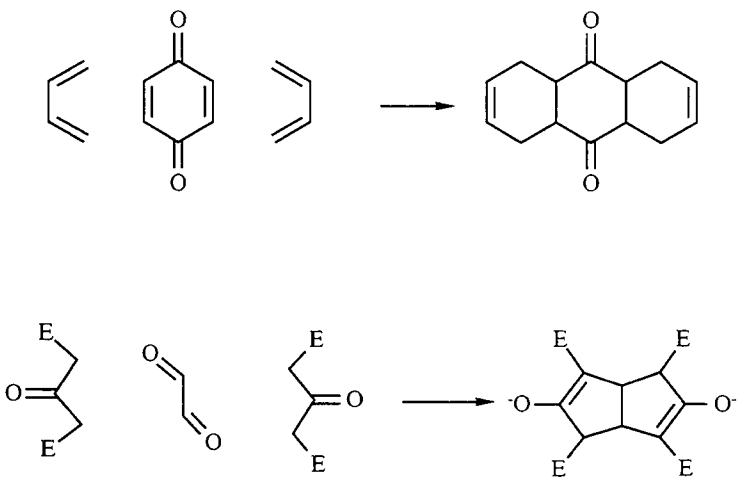
With such a "general index of complexity" it is possible to calculate the complexity of any molecule and, therefore, the complexity of all the intermediates of a synthetic sequence, and, in principle, it is also possible to calculate[7] the change of complexity, ΔC_t, upon going from the starting materials to the target.

---

[7] To calculate C_t it is convenient to take into account that:

$$\log_2 x = (\log 2)^{-1} . \log x = 3.32 \log x$$

In Scheme A-1.1 [7] a comparison of a typical Diels-Alder reaction (butadiene + *p*-benzoquinone) with a typical Weiss reaction (dimethyl 3-glutarate + glyoxal), in terms of ΔC_t, is shown. The stereochemistry of the products is implicit in the assignment of symmetry, i.e., equivalent connections: the Diels-Alder adduct is *cis-anti-cis* (C_{2h}) and the Weiss reaction product is *cis*, with the *exo* ester groups (C_2) (the complexity of the ester groups is ignored, since they do not undergo any change).



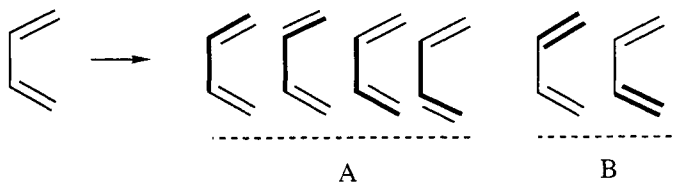
Scheme A-1.1

In the case of butadiene, the calculation of the number of connections by the "propane method" gives $\eta = 6$ (connections), distributed in two groups: one of four equivalent substructures and another group of two equivalent substructures.

Therefore,

$$C(\eta) = 2 \times 6 \log_2 6 - 4 \times \log_2 4 - 2 \times \log_2 2 = 21.0$$

Similarly, for the *p*-benzoquinone the "propane method" gives an index of complexity of $\eta = 22$, distributed in two groups of eight equivalent substructures and three groups of two equivalent substructures each.



Therefore:

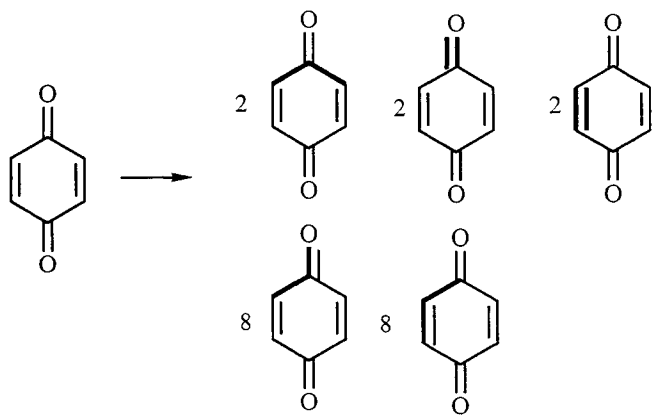
$$C(\eta) = 2 \times 22 \log_2 22 - 2 \times 8 \log_2 8 - 3 \times 2 \log_2 2 = 142.2$$

and, owing to the presence of heteroatoms, their contribution must also be taken into account.

$$E = 8, E_0 = 2, E_c = 6$$

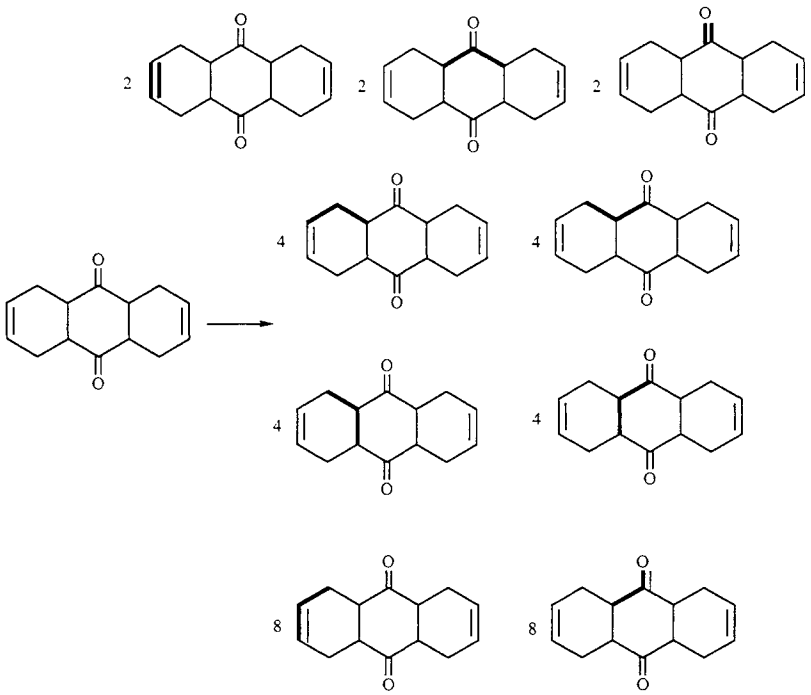
$$C(E) = 8 \log_2 8 - 6 \log_2 6 - 2 \log_2 2 = 6.5$$

The total complexity of *p*-benzoquinone will be:



$$C_t = 142.2 + 6.5 = 148.7$$

On the other hand, the complexity index of the Diels-Alder adduct is $\eta = 38$, with two groups of eight, four groups of four and three groups of two substructures each.



Therefore,

$$C(\eta) = 2 \times 38 \log_2 38 - 2 \times \log_2 8 - 4 \times 4 \log_2 4 - 3 \times 2 \log_2 2 = 312.8$$

the contribution of the heteroatoms being,

$$E = 16, E_0 = 2; E_c = 14$$
$$C(E) = 16 \log_2 16 - 14 \log_2 14 - 1 \log_2 2 = 8.7$$

and the total complexity:

$$C_t = 312.8 + 8.7 = 321.5$$

So, for the Diels-Alder condensation the change in complexity is:

$$\Delta C_t = 321.5 - 148.7 - 21.0 - 21.0 = 130.8$$

Proceeding in a similar way, the reader may substantiate, as an exercise, that the change in complexity for the Weiss reaction is substantially larger (ΔC_t = 195.8).

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Chapter 2

2. THE REACTIVITY OF ORGANIC MOLECULES

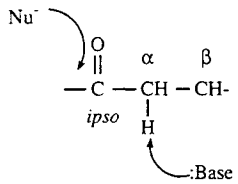
2.1. Some general remarks on the reactivity of organic compounds

In the first Chapter we have seen how the solution of a synthetic problem involves three aspects, which are more or less related: i) formation of the carbon-carbon (or carbon-heteroatom) bonds that comprise the molecular skeleton; ii) manipulation of the corresponding functional groups, and iii) all the related stereochemical problems. Although the "rule of maximum simplicity" demands the maximum possible correlation amongst the three aspects, in the present approach only the formation of the carbon skeleton and the manipulation of functional groups are considered together, the problems related to stereochemical control being treated separately. It is necessary that the two first aspects are treated together since the formation of a carbon-carbon (or carbon-heteroatom) bond usually requires the manipulation of some functional groups. It is as well to remember here that saturated hydrocarbons, devoid of functionalisation, do not exhibit any of the "typical" organic reactions -except for certain radical reactions, which are nevertheless of great industrial importance- for which reason they are known as "paraffins" (from Latin *parum* + *affinis* = little affinity).

Keeping in mind these considerations we can make the following generalisations about the reactivity of organic molecules [1]:

1) The typical reactions of organic compounds are basically the reactions of their functional groups or heteroatoms. Notice that functional groups may be considered as being "inorganic accidents" within the typically organic carbon skeleton.

A functional group may act either as a reactive group (reactions at the *ipso*-carbon atom) or as an activating group (reactions at the α- and/or β-carbon atoms and only very seldom at the γ-carbon atom):

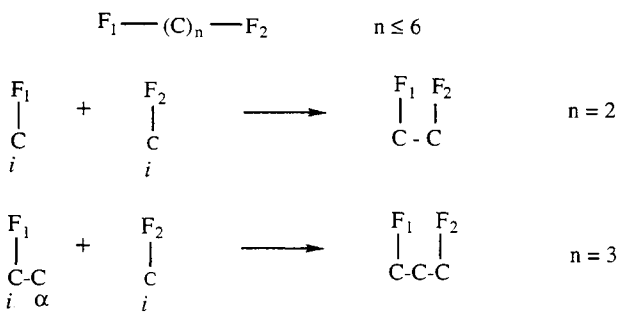


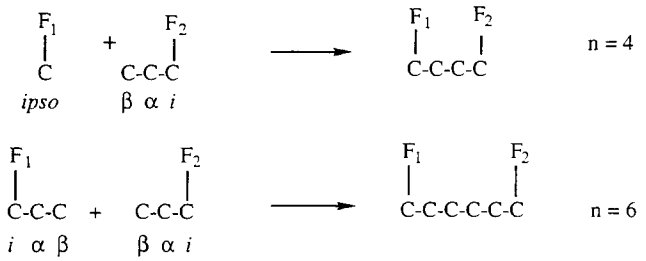
2) The problem of creating the carbon-carbon (or carbon-heteroatom) bonds is not strictly separable from the problem of functional group manipulations. In fact, as has been stated by Ireland [2]: "Synthetic planning, then, is a balance between the problem of framework construction through the use of carbon-carbon bond-forming reactions and the problem of subsequent functional group manipulations" (*Cf.* the "rule of maximum simplicity").

3) Notwithstanding what has been stated above (generalisation 2), the construction of the molecular framework has priority over the oxidation levels of the functional groups and even of the carbon skeleton itself. This means that all the following compounds are synthetically equivalent:

CH_3-CH_2-CH_2-OH	CH_3-CH_2-CH=O	CH_3-CH_2-COOR
CH_2=CH-CH_2-OH	CH_2=CH-CH=O	CH_2=CH-COOH
HC≡C-CH_2-OH	HC≡C-CH=O	HC≡C-COOR

4) The synthesis of a polyfunctional molecule can always be reduced to the problem of constructing differently paired functional group relationships, which (keeping in mind generalisation 1) usually requires the creation of a carbon chain with a number of carbon atoms equal to or smaller than 6 ($n \leq 6$).





5) The most important organic reactions -*in vitro* as well as *in vivo*-, leading to the formation of carbon-carbon (or carbon-heteroatom) bonds are, generally speaking, of ionic or polar nature (see, however, *Heading 5.5*).

6) Keeping in mind the above "generalisation" organic molecules may be considered, at least formally, as aggregates of ions (and will be eventually, represented with formal charges on the atoms).

$$A^{(+)} + B^{(-)} \longrightarrow A\text{-}B$$

7) The distribution of formal charges in the carbon skeleton is determined by the functional groups (or heteroatoms) present on it. In this context is very useful to use the "Lapworth model" of alternating polarities.

2.2. Molecules as ionic aggregates. The Lapworth-Evans model

The idea that chemical bonds in organic compounds are partially polar and can be associated with alternating positive and negative charges, has a long tradition in organic chemistry.

Cuy [3], for example, observed that certain physical properties, such as melting points, boiling points, molecular volumes, densities and viscosities, are an alternating function of the number of carbon atoms in any homologous series, in such a manner that if melting points, for instance, are plotted against the number of carbon atoms the curve has a saw-tooth appearance (see Fig. 2.1).

Cuy assumed that the physical properties are directly related to the polarity of the constituent atoms and that the carbon atoms will tend to become polarised, alternatively positively and negatively.

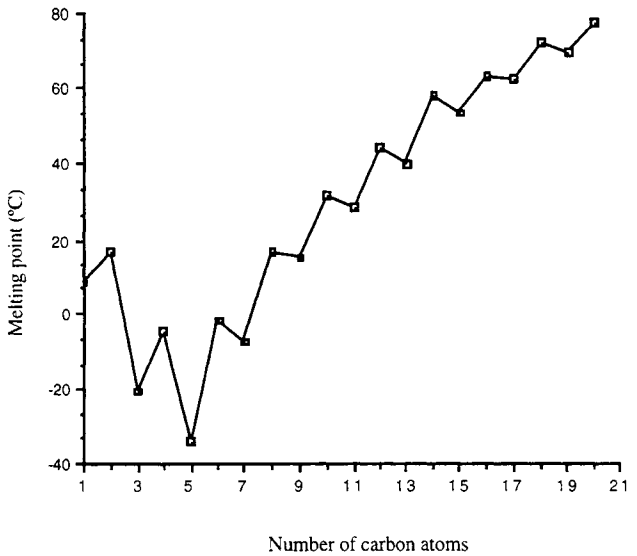


Fig. 2.1. Melting points of linear monocarboxylic acids

In addition, Cuy observed that the reaction of propene with HBr gives 2-bromopropane, according to the equation,

$$\overset{(-)\quad(+)\quad(-)}{CH_3 - CH = CH_2} \xrightarrow{HBr} CH_3 - CH(Br) - CH_3$$

a product whose formation is in keeping with the result predicted both by the idea of alternating polarities and also by the Markownikoff rule.

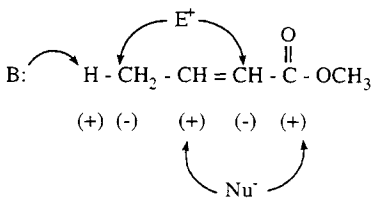
In fact, Cuy's idea was not completely original. Many years before, Flürscheim [4] and Fry [5], had postulated similar theories of alternating polarities, and the idea was soon extended by Hanke and Koessler [6], Kermack and Robinson [7] and Stieglitz [8] in order to predict the site of reactivity in both aliphatic and aromatic systems. However, as has been stated by A.E. Remick [9], "it would profit us but little to pursue further the similarities and differences of these theories of alternating polarity. Suffice it to say that they were eventually shown to be wrong [10] [11] at least in regard to saturated molecules". In spite of this, it is worthwhile referring here to the work of Lapworth.

A. Lapworth proposed a theory of alternating polarity [12] in the same year that Cuy's paper was published, demonstrating that he was more than fifty years

ahead of his fellow colleagues in regard to organic synthesis. In this context, the following words by Sir Robert Robinson [13] [14] are of particular significance: "When, in the early Manchester days, one discussed synthetical projects with Lapworth, it was quite clear that he had some unusual way of deciding they would 'go' or not. It turned out to be a scheme of alternating polarities in a chain of atoms".

Lapworth's model was based upon the polarised character of organic bonds and the "alternating latent polarities", induced by the presence of some "key-atoms" or hetero-atoms (such as oxygen or nitrogen) in a chain of atoms. The idea behind Lapworth's "unusual way" to visualise organic synthesis was revived by David A. Evans fifty years later [15, 16] and "operates from the premise that synthetic target molecules may be viewed in terms of their ionic components", the alternating polarities being assigned according to the electronic character of the functional group or heteroatom attached to the carbon chain.

For example, methyl crotonate shows the following pattern,



the electrophilic or nucleophilic character of each one of the carbon atoms (eventually even hydrogen atoms) being in accordance with that found experimentally. Thus, a nucleophile, such as a Grignard reagent, reacts with the electrophilic *ipso*- carbon atom (1,2-addition), but the same reagent, in the presence of copper (I) or as an organocuprate, reacts at the β-carbon atom in a Michael reaction (1,4-addition). On the other hand, whereas an electrophile such as a proton, will react with the nucleophilic α-carbon atom, a positive bromine ion will react with the nucleophilic γ-carbon atom. That the alternating polarities can even be extended to hydrogen atoms, is clear from the ready substitution of the γ-hydrogen atom observed by Lapworth in 1901 [12], which provides "an exact parallel with the behaviour of the hydrogen atoms in the methyl group of *o*- and *p*-nitrotoluene" (for a more recent approach to the "charge alternation concept", see Klein [17]).

Although Evans was the first one to propose a heuristic classification of functional groups (see below 2.3) and to classify the bifunctional relationships as "consonant" and "dissonant" -depending upon whether the alternating polarities are "matched" or not-, at the turn of the century Lapworth was completely aware of the differences existing between what he called "homogeneous" and "heterogeneous" arrangements of atoms or atomic groups in the molecules, as well as the reversible character of the former and the importance of "depolarisation effects", analogous to oxidation and reduction, for synthesising "heterogenous" arrangements (or bifunctional dissonant relatioships, according to Evans's terminology). In his classic paper of 1920 [12], Lapworth not only referred to "amphoteric groups like $^{-}$CN", but even the idea of "reactivity inversion" (or *Umpolung*) [16] was probably present in his mind after his pioneering work on the cyanide-mediated benzoin condensation [18] (Lapworth, 1903, 1904).

2.3. Classification of functional groups according to D.A. Evans

Before proceeding to the heuristic classification of functional groups by Evans, it is as well to remember here that in classical organic chemistry when the heteroatom that determines the functionality is attached to an sp^3 carbon atom, this atom is usually not included as forming part of the functional group. However, if the heteroatom is attached to an sp^2 or *sp* carbon atom, then in these cases the carbon atoms are included in the functional group (see Table 2.1).

TABLE 2.1. Classical functional groups in organic chemistry

Compound	Functional group	Heteroatom	Hybridisation
CH_3-CH_2-OH	-OH	-OH	sp^3
CH_3-CH_2-NH_2	-NH_2	-NH_2	sp^3
CH_3-CH_2-Cl	-Cl	-Cl	sp^3
CH_3-CO-CH_3	C=O	=O	sp^2
CH_3-C≡N	-CN	≡N	*sp*

In order to avoid any ambiguity, in Evans' classification only the heteroatom is considered as the functional group, whether it is attached to an sp^3, sp^2 or *sp* carbon

atom. Keeping this in mind, Evans considers three types of hypothetical "ideal" functional groups:

1) Functional groups of type E which confer electrophilic character upon the *ipso* carbon atom to which they are attached.

2) Functional groups of type N or G (after Seebach [16],1979) that -in contrast with the type E- confer nucleophilic character upon the *ipso*-carbon atom to which they are attached.

3) Functional groups of type A, which exhibit an ambivalent character, conferring both electrophilic and nucleophilic character upon the carbon atom to which they are attached. Whichever character is manifested will depend upon the reaction conditions and/or the structure of the molecule to which the functional group is attached.

Table 2.2 gives the more important and characteristic functional groups or heteroatoms found in organic molecules, which have been classified according to the observed reactivity, into the corresponding hypothetic ideal type. Whereas functional groups of type E are constituted by highly electronegative elements, the groups of type G are constituted by electropositive metals. On the other hand, the functional groups of type A are heteroatoms or polyatomic groups which can stabilise a negative charge on the *ipso* carbon atom (characteristic of G groups) and, at the same time are good leaving groups (generating therefore an incipient positive charge at the *ipso*-carbon atom, as groups of type E do). It must be kept in mind that the classification of Evans is purely *heuristic*, in the sense that *it works*, and its purpose is not to give a rigid classification based on theoretical considerations about the reactivity of organic molecules, but to differentiate between those groups strongly polarised either towards typical E or typical G behavior.

Notice that whereas compounds with functional groups of type E are the "normal", relatively stable and storable organic chemicals such as alcohols, ethers, aldehydes, ketones, acids, esters, amines, etc., compounds with functional groups of type G are "reagents" that must usually be prepared *in situ*, such as organometallic compounds (organolithiums, Grignard reagents, etc.). Compounds with functional groups of type A, on the other hand, can be either "normal" chemicals (such as nitrocompounds, nitriles, alkenes, alkynes, etc.) or reagents (organoboranes, Wittig ylids, etc.), as well as derivatives of the E-group (oximes, hydrazones, *N*-nitrosoamines, etc.).

TABLE 2.2. Classification of functional groups according to D.A. Evans

(+)	(-)
C - E	C - G
-OH, -OR	metals of groups 1, 2 and 12
=O	$-AlR_2$, $-SiR_3$
$-NR_2$, =NR	
X (halogen)	

(±)

C - A

(+)

$-NO_2$, =NOH, =N-NHR, =N(O)R, -N(R)-NO, $=N_2$, ≡N, $-NR_3$

(+)

-SR, -S(O)R, $-SO_2R$, $-SR_2$, (and the corresponding Se derivatives)

(+)

$-PR_2$, $-P(O)R_2$, $-PR_3$

$-BR_2$, $=CR_2$, ≡CR

transition metals

Thus, starting from the electronic character of the heteroatom attached to the carbon chain, it is possible to assign positive and negative formal charges, in an alternate fashion, to all the carbon atoms of the molecular skeleton:

(+) (-) (+) (-) (+) (-) (±) (±) (±)

C - C -C - E C - C - C - G C - C - C - A

Specific examples are:

(+) (-) (+) (+) (-) (+) (+) (-) (+)

CH_3-CH_2-CH_2-Cl CH_3-CH_2-CH=O CH_2=CH-CH_2-OMs

(+) (-) (+) (+) (-) (+) (-) (-) (+) (-)

CH_2=CH-CO_2CH_3 CH_3-CH_2-CH_2-CH_2-Li CH_2=CH-CH_2-MgBr

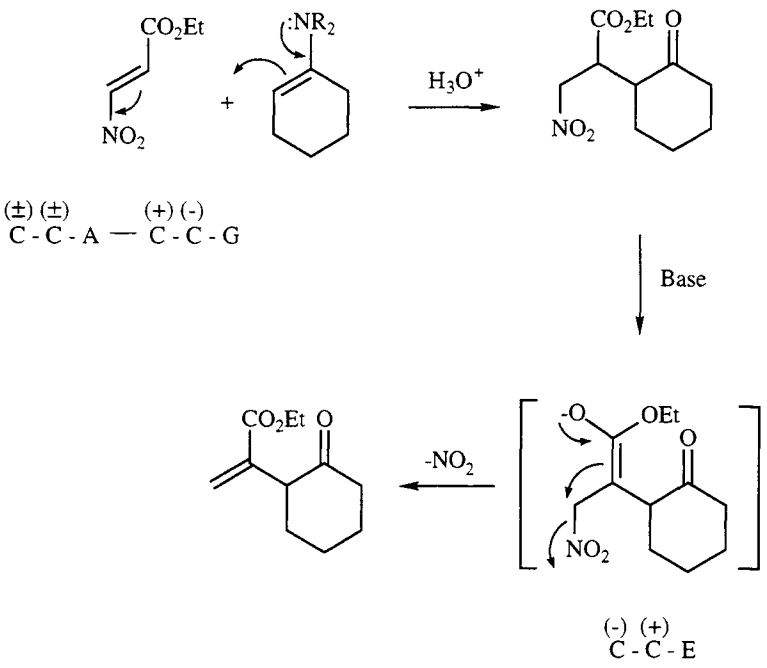
An important point to be considered here is that interchanging a type G functional group for one of type E (or *vice versa*), not only inverts the reactivity of the *ipso*-carbon atom but also the "latent polarities" of each of the carbon atoms of the skeleton (see below "reactivity inversion" or "*Umpolung*"). A classical example is the transformation of alkyl halides -which are typical electrophiles- into the corresponding alkylmagnesium halides ("Grignard reagents"), which are excellent nucleophiles.

Grignard, in developing such a reaction, practically doubled the possibilities of synthetic organic chemistry and was awarded the Nobel Prize for Chemistry, in 1912.

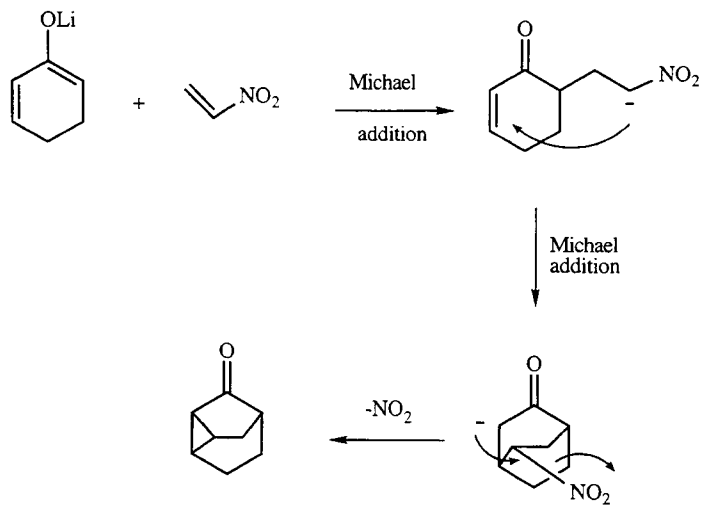
With regard to functional groups of type A, their interest lies in the ambivalent character exhibited by such groups, which not only confer a double electrophilic and nucleophilic character to each of the carbon atoms of the carbon chain, but they may even violate, in some cases, the rule of alternating polarities postulated by Lapworth.

Double and triple bonds are classified as type A because a non-symmetrical reagent -such as water, hydrogen halides, etc.- can be added to them either in a Markownikoff or in an anti-Markownikoff manner. The nitrile group on one hand, stabilises a negative charge at the α-carbon atom and shows the typical reactivity of an electrophile at the digonal carbon atom -as in the Thorpe-Ziegler condensation for instance- but, on the other hand, owing to the stability of the cyanide anion, may behave as a leaving group conferring then an electrophilic character upon the α-carbon atom.

Nitro-groups are the most versatile functional groups of the type A used in organic synthesis (see *Heading 5.1*, "illogical disconnections" and "reactivity inversion" in the synthesis of dissonant systems). The following reactions (Scheme 2.1 and 2.2) [19] illustrate the ambivalent character of the NO_2 group, and how it may manifest either one of the two possible characters, depending upon the reaction conditions and/or the characteristics of the corresponding substrate:

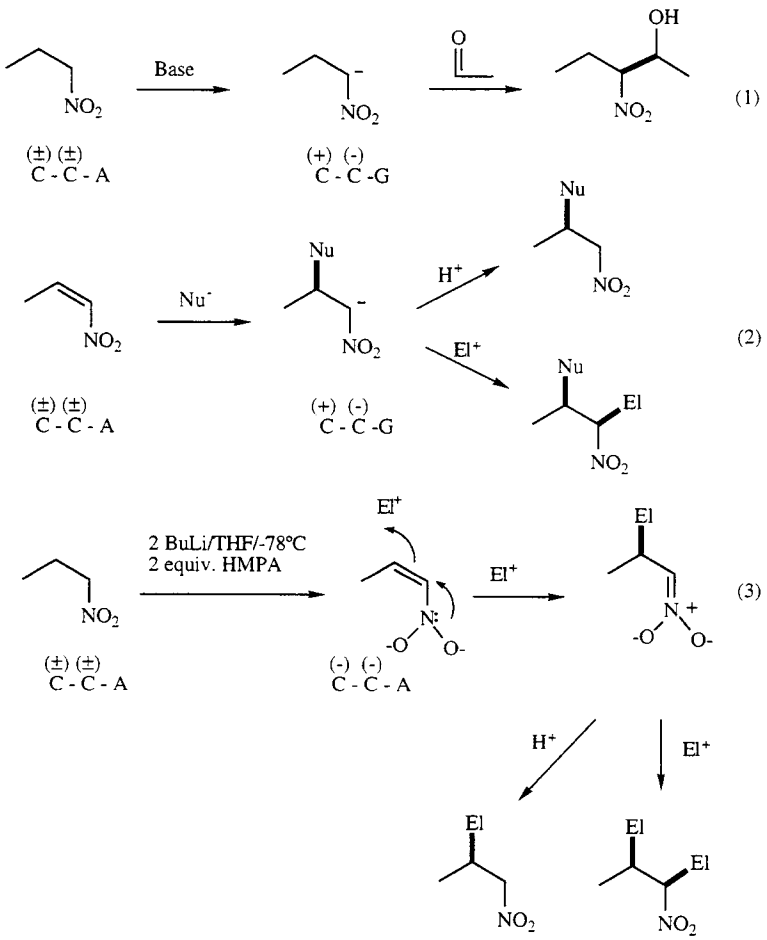


Scheme 2.1



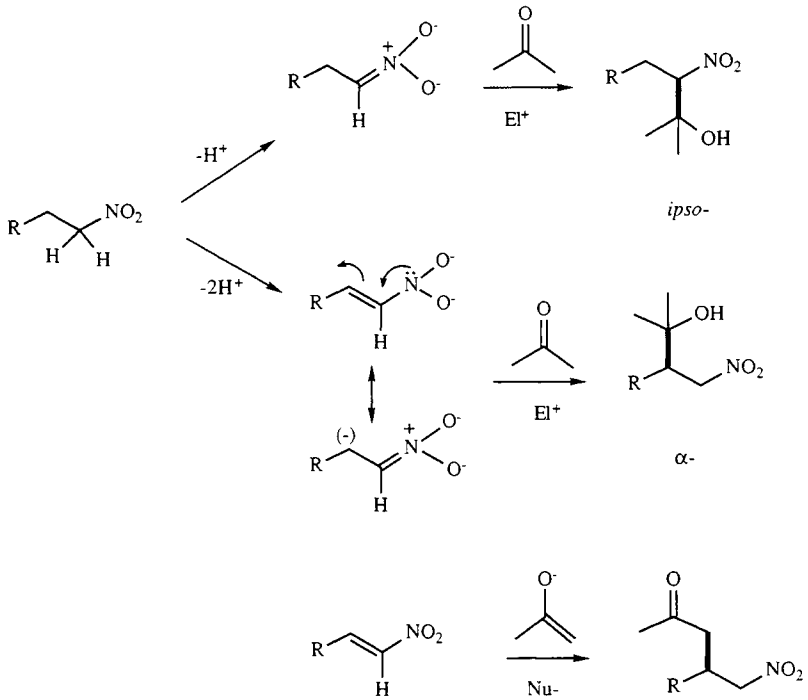
Scheme 2.2

A special case are the reactions in which a double deprotonation of a nitro-compound is involved [20], because then the "Lapworth model" does not apply anymore and the rule of alternating polarities is clearly violated (reaction 3, Scheme 2.3; see also *Heading 5.5.5*):



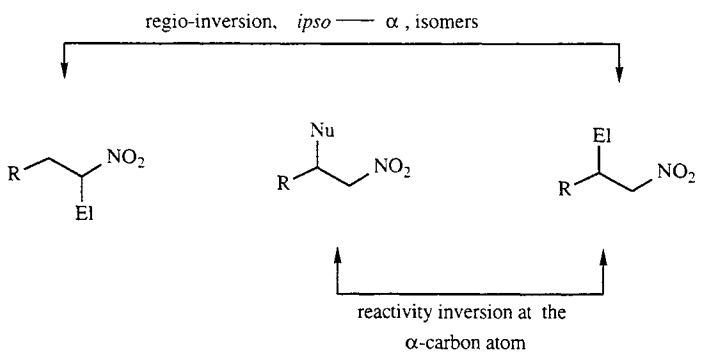
Scheme 2.3

The synthetic implications [21] of either a conjugated double bond or the double deprotonation in derivatives of nitroethane are summarised below (Scheme 2.4):



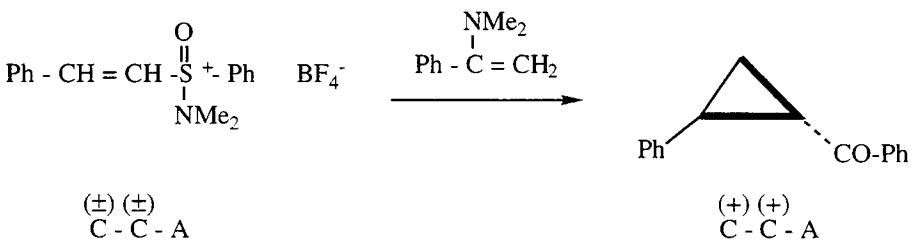
Scheme 2.4

These illustrate how different oxidation states of the same carbon skeleton, with the same functionality, give different regioisomeric reaction products (Scheme 2.5):



Scheme 2.5

Another example of violation of the "alternating polarities rule" is provided by the reaction of *trans*-(dimethylamino)phenyl(2-phenylvinyl)oxosulfonium tetrafluoroborate with the corresponding enamine of acetophenone (Scheme 2.6), in which the typical ambivalent pattern of a carbon chain bearing a group of type A becomes defined finally as a pattern with two vicinal positive charges:



Scheme 2.6

2.4. Consonant and dissonant bifunctional relationships

As stated in "generalisation 4", from a synthetic point of view it is convenient to analyse the organic molecules in terms of paired functional group relationships. Since there are two hypothetical "ideal" groups, E and G, it is possible, according to Evans, to define two different bifunctional relationships: the "consonant systems (or molecules)", in which the alternating latent polarities always match whatever the starting functional group from which the polarities are assigned, and the "dissonant systems (or molecules)" in which the alternating latent polarities do not match (see Table 2.3). Besides, in this book (see *Heading 5.1*) we will refer to the molecules (or systems) involving bifunctional relationships in which one or both groups are of type A as "assonant molecules (or systems)" (1,*n*-A, $n \leq 6$).

Notations 1,2-D, 1,3-C, 1,4-D, etc., refer to the relative position of the two functional groups within the carbon chain. Notice that rings, even if they have no functionality, can be classified as either consonant or dissonant depending upon whether they have an even or an odd number of carbon atoms. Table 2.4 summarises all the possibilities for bifunctional relationships as well as for rings, whether they are carbocycles or heterocycles, and whether they are funtionalised or not.

TABLE 2.3. Consonant (C) and dissonant (D) bifunctional relationships

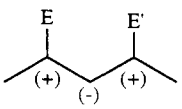
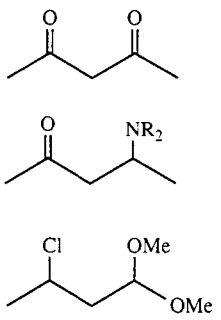
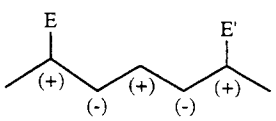
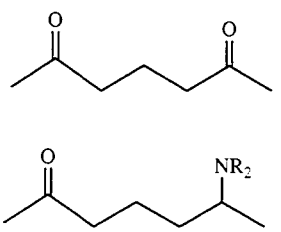
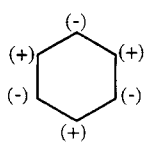
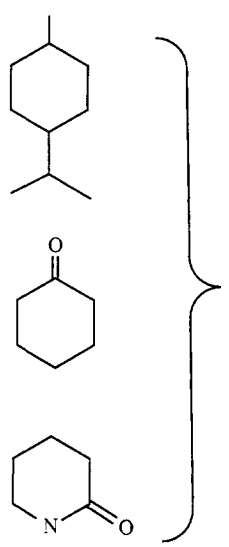
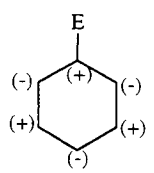
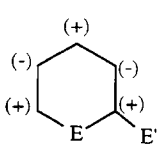
Bifunctional relationship	Example	Notation
		1,3-C
		1,5-C
		C-ring
		
		

TABLE 2.3 (cont.)

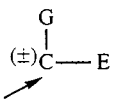
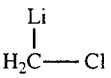
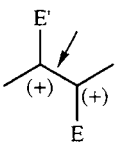
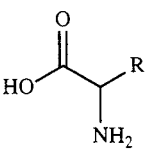
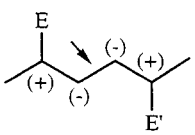
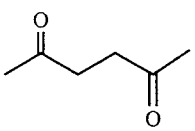
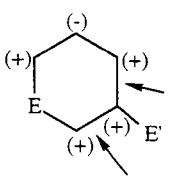
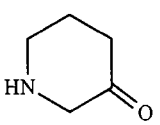
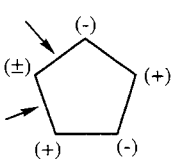
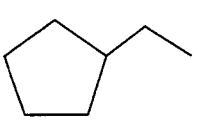
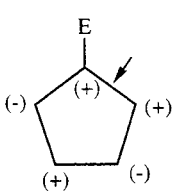
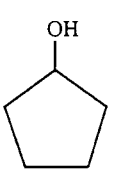
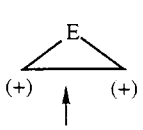
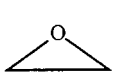
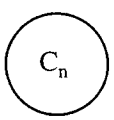
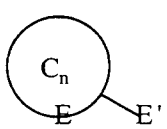
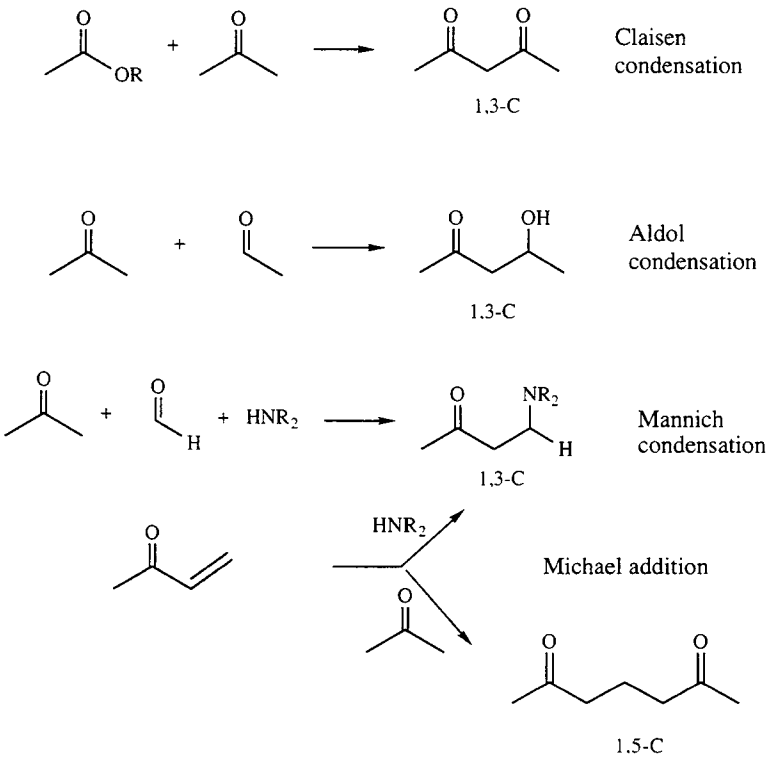
Bifunctional relationship	Example	Notation
		1,1-D
		1,2-D
		1,4-D
		1,2-D; 1.4-D
		D-rings
		
		

TABLE 2.4. Consonant and dissonant linear bifunctional relationships, carbocycles, and heterocycles

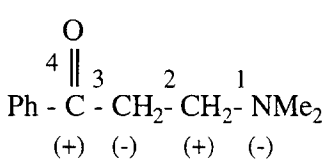
Bifunctional relationship	n even	n odd
E - $(C)_n$- E'	dissonant	consonant
G - $(C)_n$- G'	dissonant	consonant
E - $(C)_n$- G	consonant	dissonant
	consonant	dissonant
	dissonant	consonant

In principle, the synthesis of a consonant molecule or a bifunctional relationship within a more complex polyfunctional molecule, does not offer too many difficulties. In fact, all the classical synthetic methods of carbon-carbon bond formation that utilise reactions which are essentially reversible, lead to consonant relationships. For instance, the book by H.O. House "Modern Synthetic Reactions" [22], after dealing, for almost 500 pages, with functional group manipulations, devotes the last 350 pages to carbon-carbon bond formation, all of which lead to consonant relationships. These methods can, actually, be reduced to the following four classical condensations (and their variants): Claisen condensation, aldol condensation, Mannich condensation and Michael addition (Table 2.5).

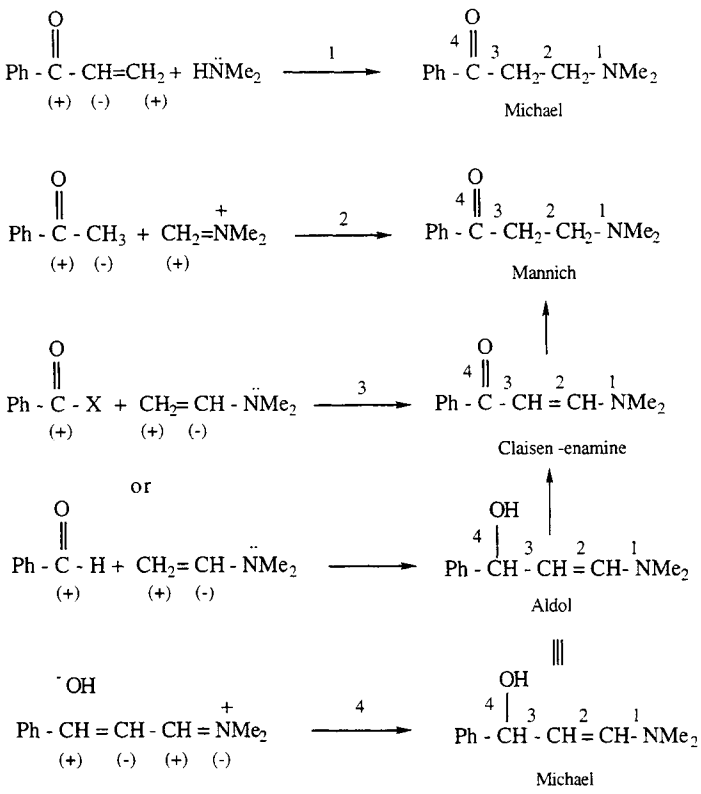
Table 2.5. Classical synthetic methods leading to consonant relationships



Keeping in mind "generalisation 3" concerning the priority of the carbon skeleton over the oxidation state of the functional groups (or even of the carbon chain itself), the synthesis of a consonant molecule (or system) with n bonds between the two functional groups has, in principle, n possible different synthetic pathways. For instance, the 1,3-amino-ketone,



numbering arbitrarily the bonds from 1 to 4, offers the following possibilities:



As can be seen , the same four classical condensations which were mentioned before, are again present; i. e., Claisen, aldol, and Mannich condensations and the Michael addition.

As we will see later, in contrast to consonant molecules or systems, the synthesis of dissonant molecules is always a more complex problem, that involves a larger number of steps and intermediates and takes place through essentially irreversible processes, which require more critical and sophisticated experimental conditions.

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Chapter 3

3. METHODOLOGIES. SYNTHESIS TREE

3.1. The retrosynthetic process. Methodologies for the design of organic synthesis. The synthesis tree

If there is any "golden rule" for success in planning a synthesis of a more or less complex organic compound, it is to work the problem backwards [1]; i.e., the chemist must follow the reverse path that in practice will be followed in the laboratory . For this, the target molecule is submitted to some type of "dissection" or "mental degradation" which gives structural subunits named *synthons*, which are then "dissected" again and the process repeated until different sequences of intermediate precursors, that go from the target down to possible starting materials are generated. In contrast to the synthetic process in the laboratory, Corey [2] refers to this process as a "retrosynthetic" process and represents it by a double arrow $\Longrightarrow$, introducing also the terms *transform* and *retron* [3], as opposed to *reaction* and *synthon.*

$$A \xrightarrow{\text{reaction}} B \quad \text{synthetic process}$$

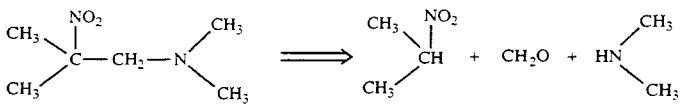
$$B \xRightarrow{\text{transform}} A \quad \text{retrosynthetic process}$$

According to the formalisation of E.J. Corey, the retrosynthetic process, through which the organic chemist establishes a synthetic plan of an organic compound, implies the disconnection of some bonds as the result of applying a *transform* to a given *retron,* to give *synthons* which, after being conveniently elaborated, constitute the intermediate precursors for the synthesis of the target molecule

In fact, this is an oversimplification of a process that very often may be quite complex and elaborate. Corey [4] differentiates between two extreme methodologies for planning organic syntheses which differ with respect to analytical and logical

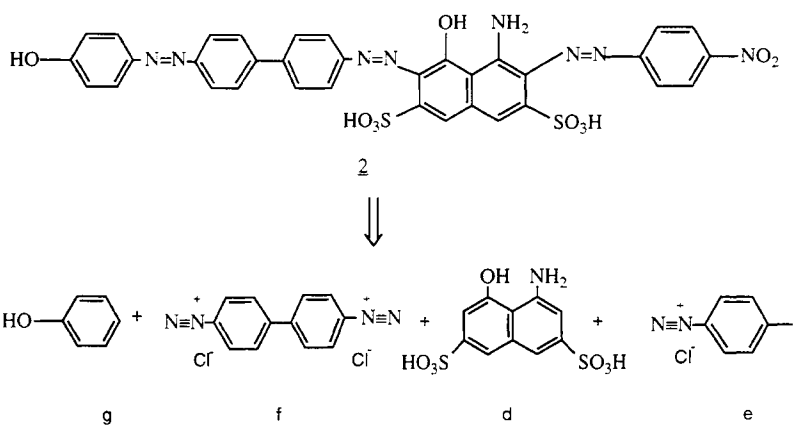
sophistication and generality, that can be termed: 1) the "direct associative approach", and 2) the "logic-centred methodology".

In the direct associative approach, which is applied in the case of relatively simple molecules, the chemist directly recognises within the structure of the target molecule a number of readily available structural subunits which can be properly joined, by using standard reactions with which he is very familiar. For instance, it is easy to see that structure 1 can be obtained by bringing together, the fragments a, b and c, in a Mannich condensation:



1 a b c

It is also easy to see that the dyestuff 2 (diamine green B) can be synthesised by joining the fragments d, e, f, and g , in this precise order, by controlling the pH of the medium. Such an example illustrates how the molecular magnitude does not necessarily imply greater complexity in the synthetic planning (for a discussion of "molecular complexity" *versus* "synthetic complexity" see ref. [5]).



2

g f d e

In the synthesis of peptides and proteins, recognition of the constituent aminoacids is almost immediate; however, the realisation of the synthesis in the laboratory may be one of the most arduous tasks which the synthetic organic chemist faces. The molecular magnitude and the strong polarity which tends to make the reaction intermediates very insoluble, as well as the problem of conservation of

the chiral centres are, amongst others, some of the factors which must be taken into account and which require the use of some special techniques.

With respect to the "logic-centred methodology", which is used in the planning of complex organic molecules, it implies choosing some specific strategies and using the tactical application of the different resources that modern organic chemistry offers to the chemist. The central point of this methodology is a rational and penetrating analysis of the structure of the target molecule. Such an analysis leads to a limited logical set of intermediate structures which can be transformed into the original in just one reaction or synthetic step. Every structure generated is then carefully analysed as before to give another set of structures, which can be transformed into the preceding structures in one step. The process is repeated for every intermediate until a "tree" of such intermediate structures is obtained. By this process a set of possible alternative synthetic pathways is generated which correspond to sequences of synthetic intermediate structures that go from possible starting materials I^o to the target molecule T: it is the so-called "synthesis tree" (Diagram 3.1) [2] [4].

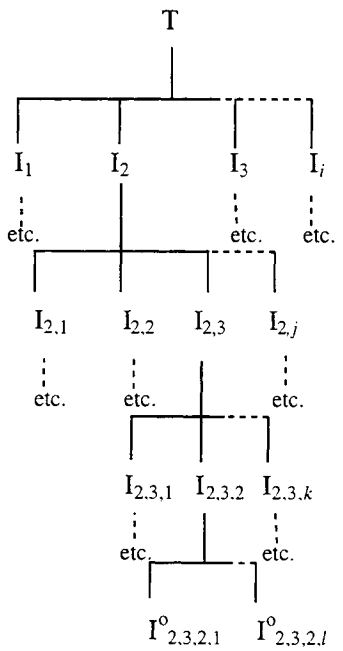


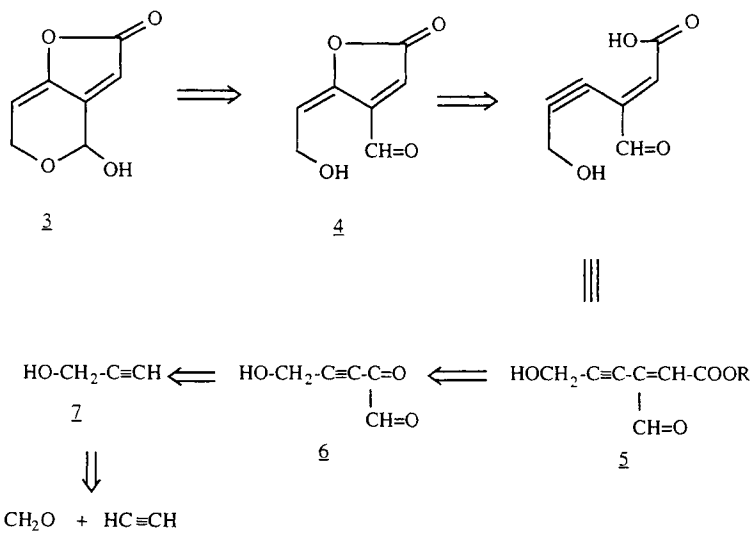
Diagram 3.1
"Synthesis tree"

The "synthesis tree" illustrates diagrammatically the above mentioned "golden rule". That is to say, the derivation of the different synthetic pathways is carried out in the opposite direction to which the synthesis will be performed in the laboratory and, in this sense, the analysis follows the exact opposite direction of the synthesis. The evaluation of the different alternative pathways is sometimes immediate, but in general is not so easy and several factors must be taken into account: number of steps, availability of starting materials, well known reactions that give high yields, etc., which -together with the chemist's own experience in some specific field (acetylenes, for instance)- always introduces some element of subjectivity in making the choice.

Nevertheless, most chemists design their syntheses -or they have designed them in the past- with a minimum of logic-centred analysis, using the two extreme approaches simultaneously, a methodology to which Corey refers as the "intermediate approach". Essentially, this method implies the recognition of a structural relationship between a fundamental or critical unit within the structure of the target molecule and a structure which corresponds to a known or, at least, to a potentially available compound. This compound is, in fact, the actual starting point of the synthesis. Although the deduction and elaboration of the specific sequences for attaining the goal may require a complex logic-centred analysis, the choice of the starting point greatly restricts the different possibilities, ruling out some solutions which could be better.

In order to illustrate how the "intermediate approach" works, let us analyse the planning of a synthesis of patulin carried out in our laboratory [6]. Patulin (3) is an antibiotic with a relatively high degree of structural complexity. As Woodward (1950) has said "few known substances contain as many reactive groupings, combined so compactly, as does patulin". Proceeding in a retrosynthetic manner, patulin may be *dissected* as shown in Scheme 3.1, thus arriving at propargyl alcohol (7) as the starting material, which is a commercially available compound, prepared by reaction of acetylene with formaldehyde (since this basic chemical compound is obtained from methanol, the whole sequence represents a true total synthesis from the elements). The fragments or *synthons* resulting from the *dissection* must indeed be properly elaborated, so that a sequence of intermediate precursors, that lead to the target molecule by means of known or conceivable reactions, is established. On the other hand, performing the synthesis in the laboratory requires the use of some protecting groups in order to control the reactivity of the different functional groups

and to direct the synthesis along the route already planned. Though all this elaboration required a more or less complex logical analysis, the design of the synthetic planning is, in fact, a typical example of the "intermediate approach" because a γ-yliden-α,β-butenolide was recognised as the fundamental structural subunit of patulin, which, in turn, was automatically associated with a propargylidenacetic acid 5, certainly not known, but potentially available. Owing to our previous experience on the field, we knew that such acids cyclise intramolecularly to butenolides, provided that the double bond has the required stereochemistry. Therefore, the starting point of the synthesis was already determined, without exploring other solutions that could have been more atractive and promising.

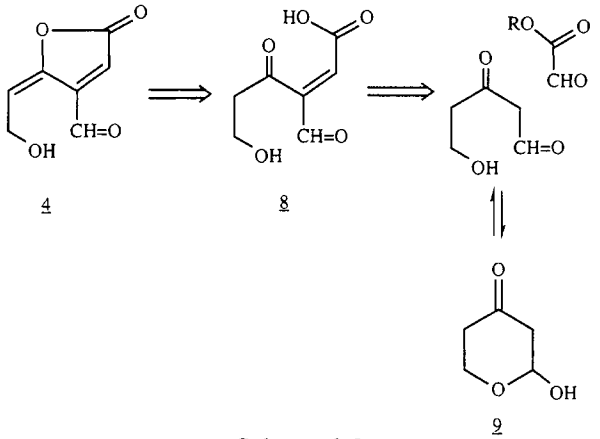


Scheme 3.1

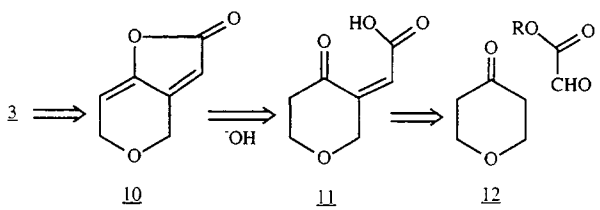
However, intermediate precursors other than 4 could be generated (see Scheme 3.2) and a "synthesis tree" would finally have resulted. For instance, the intermediate precursor of 4 could be 8, which would generate another "lineage" of intermediate precursors.

Or, alternatively (see Scheme 3.3), the immediate precursor of patulin could be 10, arriving through this new route to tetrahydro-γ-pyrone 12, as the starting material, together with the synthon =CH-COOR, which conveniently elaborated gives either a glyoxylic ester, OCH-COOR, or an oxomalonic diester,

$O=C(COOR)_2$. This last sequence was the one used by Woodward [7] in his total synthesis of patulin.



Scheme 3.2



Scheme 3.3

In summary, had the "logic-centred methodology" been used, a "synthesis tree" such as the one shown in Diagram 3.2 would have resulted and the different alternative synthetic sequences generated would have been evaluated.

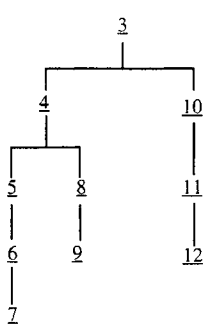
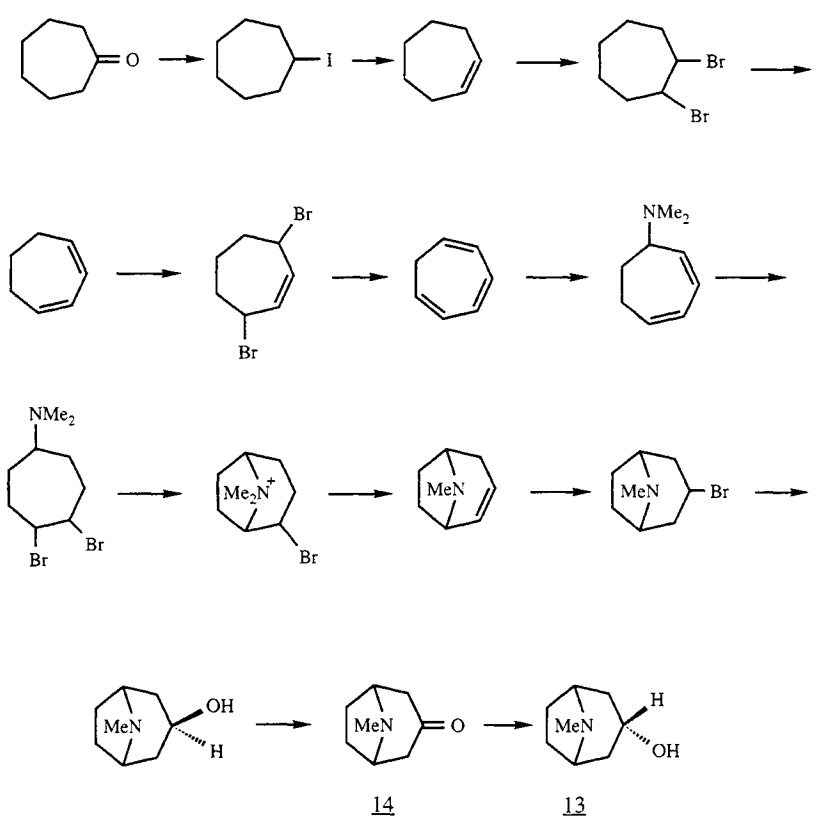


Diagram 3.2

3.2. Biogenetic considerations. Biomimetic synthesis

In the particular case of natural products, once all the possibilities that the "logic-centred methodology" offers have been explored, it is pertinent to consider the biogenetic pathways by which they are synthesised in Nature since these can be a source of inspiration and may introduce an intrinsic element of elegance into the synthetic plans. In this context, tropine (13) offers a unique example in the history of organic synthesis. In 1902 this rather simple alkaloid was synthesised by Willstätter from cycloheptanone [8] through a sequence of about twenty steps, as shown in Scheme 3.4.

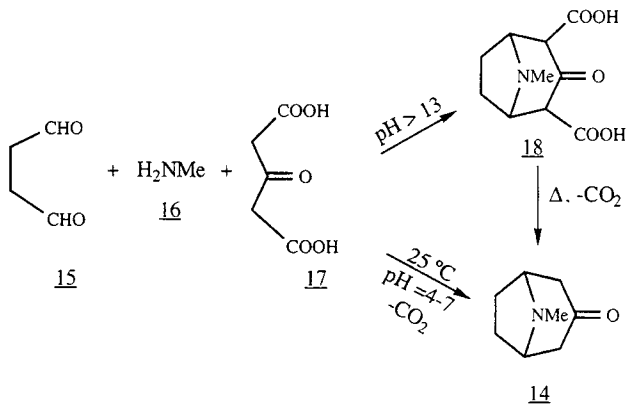


14 13

Scheme 3.4

In 1917, Sir Robert Robinson [9] suggested that tropinone (14) could be synthesised in Nature from succinic dialdehyde (15), *N*-methylamine (16) and acetonedicarboxylic acid (17), or some of their "equivalents", according to a double

Mannich-type condensation. In order to test his hypothesis, Robinson carried out the reaction in the laboratory, verifying that it takes place in strong alkali medium to give, after protonation, the diacid 18 which decarboxylates on heating to afford tropinone 14. Later on, in 1937, Schöpf [10] showed that the reaction actually takes place in one single step working under physiological or cellular conditions, i.e., in aqueous medium at room temperature and neutral pH, affording tropinone in yields higher than 90% (Scheme 3.5).



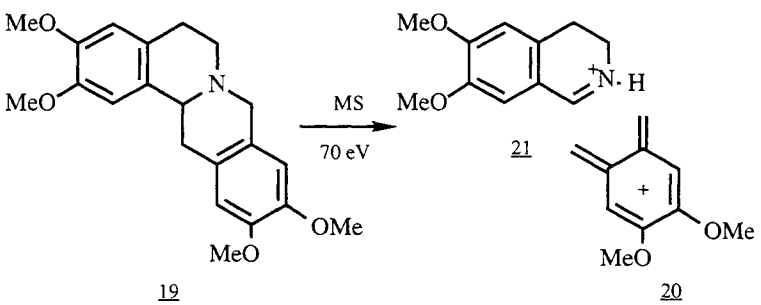
Scheme 3.5

More recent examples of biomimetic synthesis are the syntheses of thebaine [11] and usnic acid [12], as well as strychnine [13], morphine alkaloids [11] [14] and a great number of terpenic compounds [15]. On the other hand, hypothetic prebiotic considerations may also simplify tremendously the synthetic plans. Such is the case, for example, of the work of Eschenmoser on vitamin B_{12} who, after synthesising it in collaboration with Woodward by a linear sequence of almost fifty steps [16], investigated the prebiotic origen of this complex molecule. The experimental work undertaken in this direction demonstrates that the amount of "external instruction" required for "self-assembling" the different structural elements present in this molecule is surprisingly small. This fact could eventually lead to a very simple synthesis of vitamin B_{12} starting from α-amino nitriles which would involve only a few steps [17].

3.3. Mass Spectra and Retro-Mass Spectral Synthesis

Another alternative approach for the planning of syntheses of natural products is "retro mass-spectral synthesis" developed by Kametani [18]. Since mass spectroscopy is a bond breaking process, it can be used as an alternative to the retrosynthetic process for designing syntheses of natural products. It is well known that the fragmentations in a mass spectrometer resemble those found in purely thermal fragmentations. A classical example is the retro-Diels-Alder reaction in compounds bearing cyclohexene rings, which afford the corresponding ethylene and the radical ion of a diene.

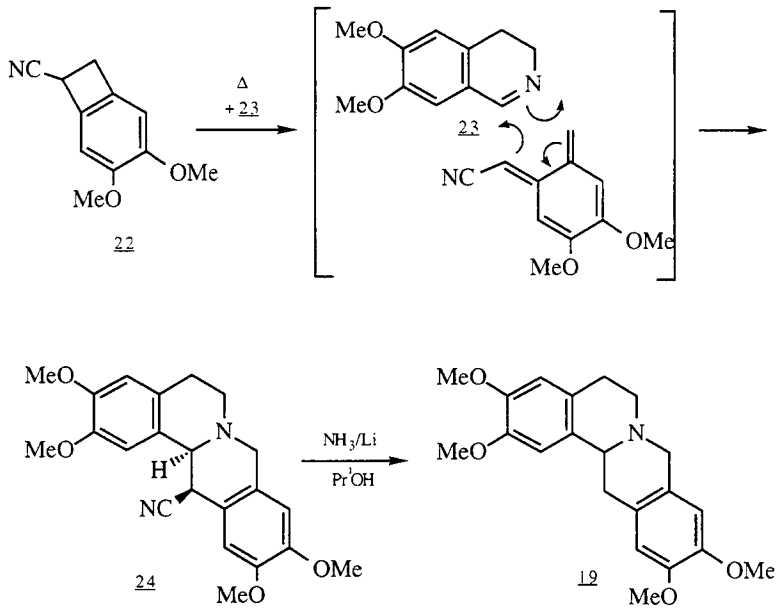
The mass spectrum of xylopinine (19), a protoberberine alkaloid, shows an ion 20, having an *o*-quinodimethane system, together with a 3,4-dihydroisoquinolinium ion (21) (Scheme 3.6).



Scheme 3.6

This fragmentation process suggests that a Diels-Alder condensation of the compounds corresponding to the two ions should afford xylopinine 19.

In practice, the equivalent synthon of 20 was 1-cyano-4,5-dimethoxybenzocyclobutene 22 (Scheme 3.7) which on heating generates a reactive *o*-quinodimethane by a conrotatory electrocyclic ring opening process (*Cf.* Scheme 3.7) and reacts, at 150-160 °C, with the 3,4-dihydroisoquinoleine 23 to give 80-88%yield of 13-cyanoprotoberberine 24. A simple reductive decyanation with lithium in liquid ammonia in the presence of isopropyl alcohol afforded xylopinine (19) in 84.6% yield [19].



Scheme 3.7

3.4. The mathematical model of constitutional chemistry. The programs EROS and IGOR

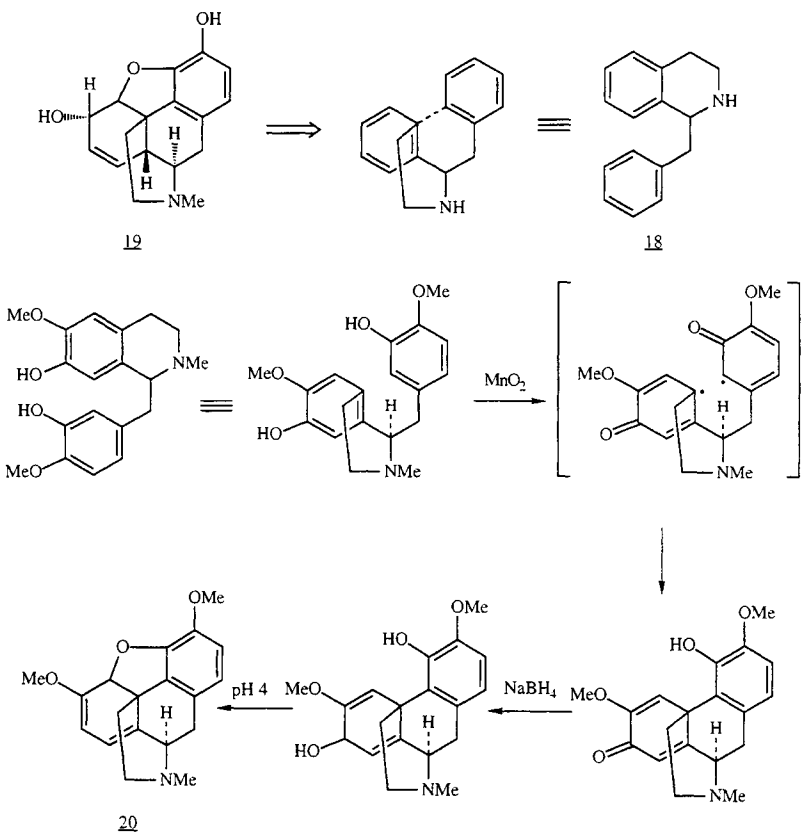
Finally, a completely different approach to the design of organic synthesis are the computer programs developed by Ugi and his colleagues, which can be applied to any kind of molecules whether they are natural or not [20] [21]. These programs are not intended only as a tool to generate new synthetic routes of a given target molecule, but constitute a general mathematical approach to the logical structure of chemistry. The molecules are represented by matrices and the chemical reactions as recombinations of such matrices. Instead of resorting to a "library" of known reactions, the program attacks the problem of designing a chemical synthesis as a game, using combinatorial analysis. For an introduction to Ugi's method see Appendix B-1.

3.5. Structural synthetic analysis, simplification and generation of the intermediate precursors of the "synthesis tree". Principle of microscopic reversibility

In connection with the "logic-centred methodology" we have referred to the elaboration of a "synthesis tree" by a process that involves the stepwise generation

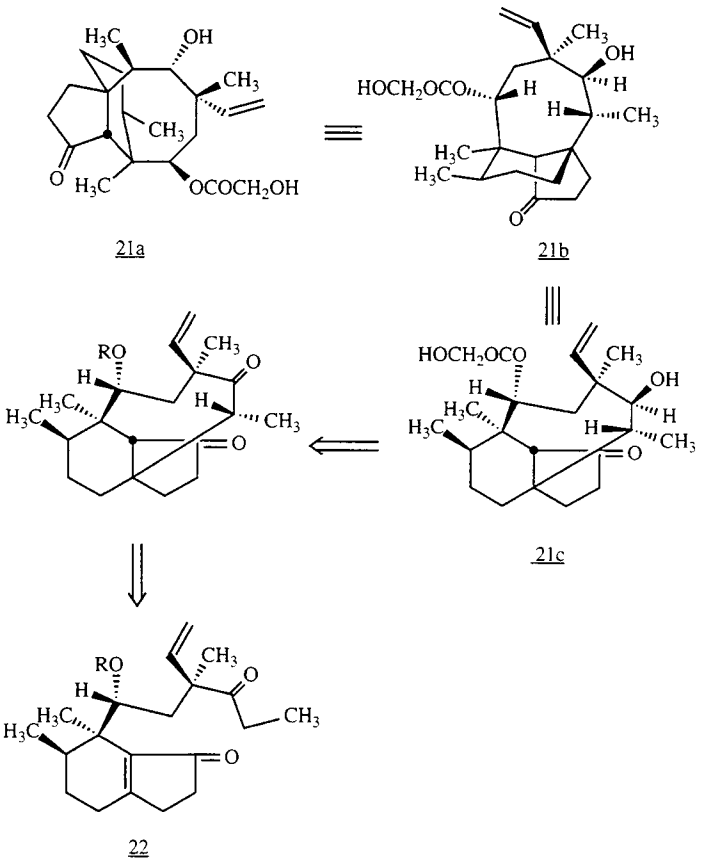
in the retrosynthetic direction, of some intermediate precursors from the target molecule. Such a process implies different stages:

1) In the first place, the structure of the target molecule is submitted to a rational analysis in order to perceive the most significant structural features, and it may be useful to use different types of molecular models at this point. It should be remembered that a molecular structure has "thousand faces" and finding the most convenient perspective may greatly simplifly the synthetic problem. The synthesis of opium alkaloids, for instance, is much simplified if one realises that they are, in fact, derivatives of benzyltetrahydroisoquinoline (18) (see Scheme 3.8). This was indeed the inspired intuition of Sir Robert Robinson which led to the structural elucidation of morphine (19) and to a first sketch of the biogenetic pathway [22], and later on to the biomimetic synthesis of thebaine 20 [23] [24].



Scheme 3.8

A more recent example is provided by the synthesis of (+)-pleuromutilin 21a by Paquette [25], a diterpene antibiotic produced by several basidiomycetes through an unprecedented biosynthetic pathway. The structure of this antibiotic which is constituted by a tricyclic carbon skeleton can be represented by the following equivalent formulae 21a = 21b = 21c. Paquette undertook a synthesis of this compound through a substituted tetrahydroindanone 22, in which there are already four of the eight chiral centres present in the molecule, in its absolute configuration, and which may be also obtained by degradation of natural (+)-pleuromutilin ("relay approach"). The retrosynthetic analysis leading to such an intermediate involves a retro-Michael disconnection as can be easily visualised starting from pleuromutilin in the "perspective" shown in 21c (Scheme 3.9).



Scheme 3.9

In the synthetic analysis of any organic compound, the structural features that must be taken into account are:

a) the actual or potential symmetry of the molecule,

b) the functional groups present in the molecule, including the reactivity, sensitivity and unstability at every site of it,

c) the carbon skeleton, including carbon chains, rings and appendages attached to them,

d) all the stereochemical aspects, with emphasis on:

i) chiral centers,

ii) conformation and configuration of rings, and

iii) proximity effects (or "propinquity").

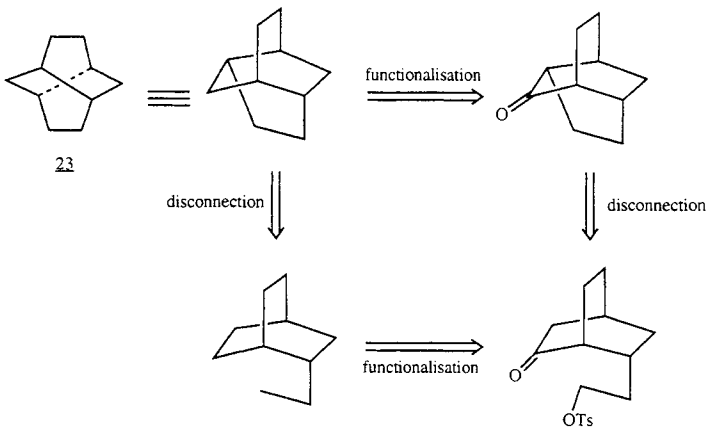
e) biogenetic considerations (only when dealing with natural products).

2) Upon the perceived structural features a process of simplification of the molecular complexity is then carried out.

3) Once the simplification has been carried through up to a limit, the next stage is to generate a set of intermediate precursors. In some simple cases, the simplification may have led directly to some useful intermediates (see, for instance, the synthesis of indigo), from which is possible to establish a general synthetic plan. However, in most cases, the simplification process will be applied to each one of the generated intermediates until suitable starting materials are arrived at.

The generation of the intermediate precursors and the synthetic sequences is carried out by a retrosynthetic process that involves the disconnection of bonds. For this, the chemist must use a set of fundamental "heuristic principles", which cannot be logically proved or demonstrated, but whose validity and efficiency are beyond question, and lie in the general synthetic methods familiar to any experienced synthetic chemist. In this context, it should be emphasised that all we have said about the nature of the organic bond-forming reactions applies equally to the retrosynthetic disconnective processes. That is to say, the process of bond disconnections is not strictly separable from functional group manipulations and, therefore, it happens very often that the disconnections can only be made once the target molecule has been properly functionalised. Or, alternatively, one can proceed directly to the disconnection of strategic bonds (i.e., bonds whose disconnection leads to especially simple precursors: see *7.2.1*), and to functionalise then *a posteriori* the resulting synthons, so that they can revert to the target molecule by a

well defined sequence of reactions. For instance, twistane (23) -which is a molecule without functionality- may be "dissected" as follow (Scheme 3.10):



Scheme 3.10

By analogy with the organic bond-forming reactions, it is assumed that bond disconnections take place heterolytically, being classified as "logical disconnections" if the three following criteria are met:

i) that a reasonable disconnection mechanism exists,

ii) that the disconnection leads to stable fragments -ions or molecules-, and

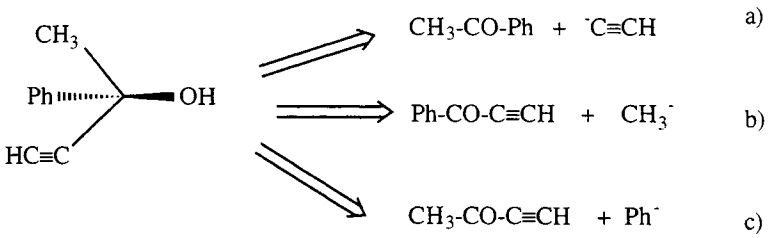
iii) that the disconnection represents the greatest possible simplification.

The "principle of microscopic reversibility", which indicates that the forward and the reverse reactions must proceed through the same pathway, assures us that we can use the same reaction mechanism for generating the intermediate precursors of the "synthesis tree", that we use for the synthesis in the laboratory. In other words, according to the "principle of microscopic reversibility", [26] two reciprocal reactions from the point of view of stoichiometry are also such from the point of view of their mechanism, provided that the reaction conditions are the same or at least very similar. A corollary is that the knowledge of synthetic methods and reaction mechanisms itself -according to the electronic theory of valence and the theory of frontier molecular orbitals- must be applied in order to generate the intermediate precursors of the "synthesis tree" and which will determine the correctness of a synthesis design and, ultimately, the success of it.

It must not be forgotten that the retrosynthetic bond-disconnections are only *mental processes* [27], which may however, coincide with actual processes in the laboratory provided that the reactions under consideration are reversible. Another immediate consequence is that only consonant systems (or molecules) can offer, properly speaking, reasonable bond-disconnection mechanisms, as it is required by "logical bond disconnections".

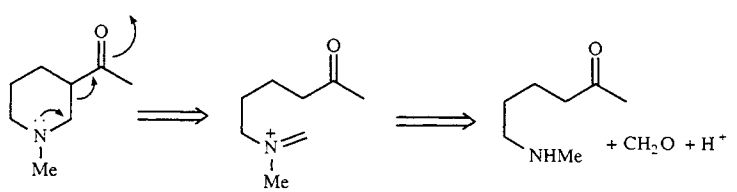
Some illustrative examples of all these considerations are given below:

a) Nucleophilic dealkylation of a tertiary alcohol (equivalent to the "S_N2 transform"),

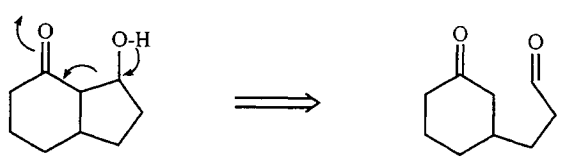


of the three possible disconnections the first one meets best the requirements for a "logical disconnection", since a reasonable mechanism exists that generates two stable fragments, such as acetophenone and the highly stabilised acetylide anion, and represents the maximum possible simplification.

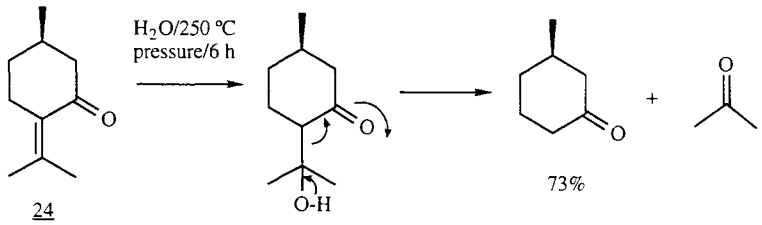
b) Retro-Mannich disconnection (equivalent to the "Mannich transform"),



c) Retro-aldol disconnection (equivalent to the "aldol transform"),

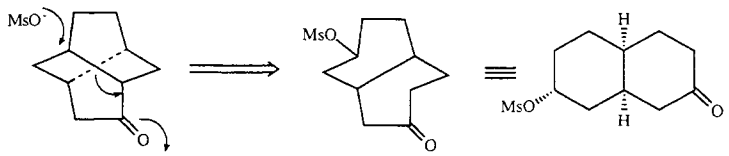


An example which illustrates that the retrosynthetic process may sometimes find a parallel in the laboratory is provided by the preparation of (*R*)-(+)-3-methylcyclohexanone from (+)-pulegone (24), described by Wallach in 1896, [28] in which the experimental conditions are such that the equilibrium is displaced to "reagents",



24

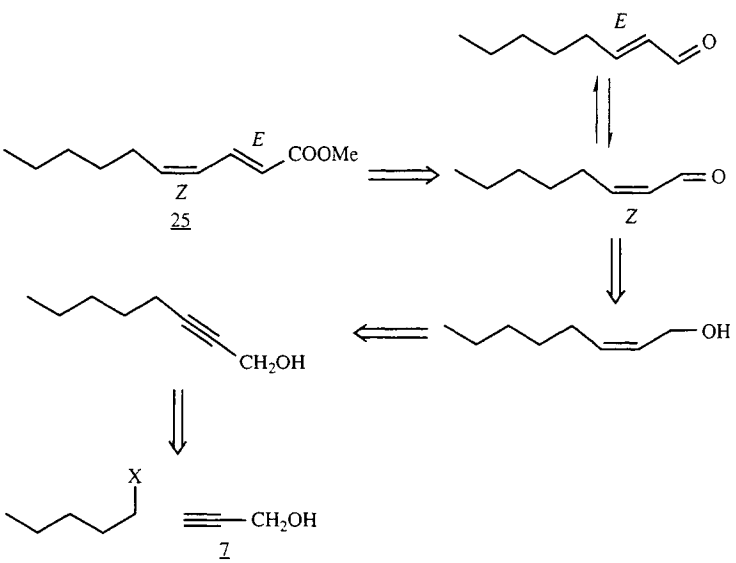
d) Intramolecular nucleophilic dealkylation



Here, in contrast with the above examples, the retrosynthetic process is purely "mental", since the mesylate, as a good leaving group, is a poor nucleophile and the "reaction" will never take place whatever the reaction conditions.

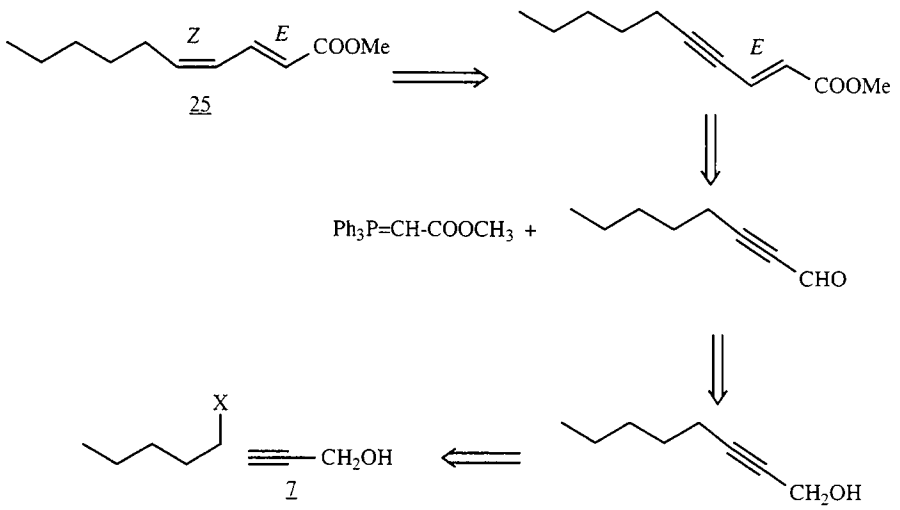
It should be kept in mind that the different stages involved in the process -analysis, simplification and generation of the intermediate precursors- are not strictly separable. In fact, it may happen very often that during the simplification stage a set of valid intermediate precursors are already generated or, conversely, the most important simplifications can only be made during the process of generating synthetic intermediate precursors. Moreover, the design of the synthesis of an organic molecule is always an *iterative* process, so that, as a new intermediate precursor is generated, all the other previously generated intermediates must be subjected to possible modifications evolved in connection with new requirements developed in a further stage of the analysis. For instance, considering a theoretically possible synthesis of the unsaturated ester 25, known as "essence of pear" and of great importance in the perfumery and flavour industry, we may imagine a retrosynthetic process, such as the one shown in Scheme 3.11, in which it is highly

convenient to introduce a triple bond into the intermediate precursor in order to proceed then to a disconnection which leads to the highly stabilised acetylide anion of propargylic alcohol (7), according to a reasonable dealkylation mechanism. The disconnection means, on the other hand, a great simplification. However, the requirements evolved towards the end of the analysis, which "advise" the substitution of a triple bond for a double bond, "compel" reconsideration of the previously generated intermediate precursors and to establish that it is more convenient to introduce the triple bond at the first step of the retrosynthetic process, so that the manipulation of a relatively unstable α,β-unsaturated aldehyde of (*Z*)-configuration which could partially isomerise to the more stable (*E*)-configuration, is avoided in the actual synthesis in the laboratory. After the iteration the retrosynthetic plan would be the one shown in Scheme 3.12.



Scheme 3.11

The last step, in the synthetic direction, would therefore be the catalytic hydrogenation of a triple bond to a double bond, a reaction that performed with Lindlar catalyst would assure the correct (*Z*)-configuration.



Scheme 3.12

Once the "synthesis tree" has been elaborated, we must proceed to the evaluation of the alternative pathways and compare them with possible synthetic schemes in order to optimise the chosen route and make it as self-consistent as possible. However, all synthetic plans must be flexible enough to allow new alternative solutions when things do not happen as anticipated. In this sense, Woodward referred very often to opportunism and of taking advantage of the "surprises" which may occur during the execution of a synthesis. Through the different stages of a synthesis new aspects may evolve and even important discoveries may be made. Such was the case, for instance, in the vitamin B_{12} synthesis in which the considerations of the stereochemistry of an intermediate, opposite to the one anticipated, led Woodward to the discovery of the principle of conservation of orbital symmetry [29].

3.6. Auxiliary physical techniques in the synthesis of organic compounds

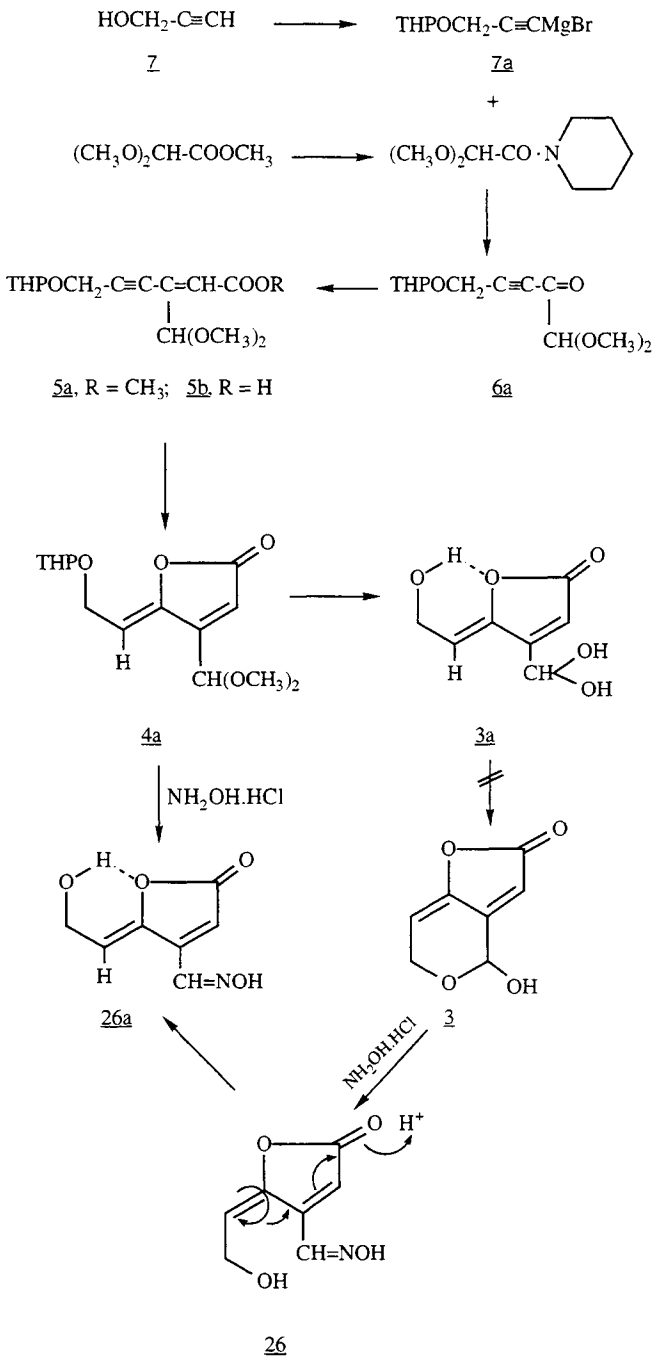
Since an organic synthesis of any magnitude is always a total experience in organic chemistry that involves the application of the knowledge and techniques of the entire science [1], before considering the details involved in the generation of the intermediate precursors and the elaboration of the "synthesis tree", let us consider very briefly the importance of the auxiliary physical techniques in performing a relatively complex synthesis.

We have already referred to the "golden rule" for designing an organic synthesis. Another key principle, which refers to the actual execution of the synthesis in the laboratory, is that the chemist must use whenever possible all the available physical techniques to control every step and determine that every reaction takes place, from a *chemo-*, *regio-* and *stereochemical* point of view, as anticipated.

A classical example in which an intensive and systematic application of all the auxiliary physical techniques -including X-ray diffraction analysis- was made, is provided by the total synthesis of cephalosporine C by Woodward and coworkers [30]. However, in order to illustrate this important principle, we will consider a much more simple example, that is already familiar to us. Let us consider the synthesis of patulin as originally planned in our laboratory (see above 3 $\Longrightarrow$ 7).

The experimental execution of the synthesis in the laboratory involved the sequence of reactions shown in Scheme 3.13.

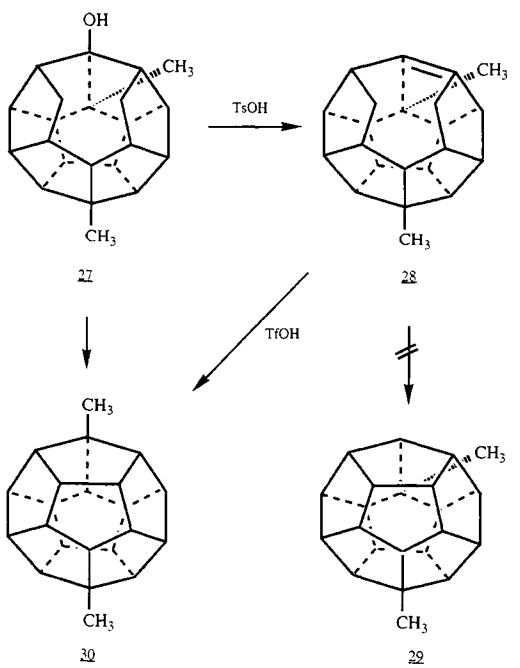
As can be seen, the synthesis afforded patulin-oxime (26a) rather than patulin itself, a fact that was from a theoretical point of view, of some interest since it demonstrates that carbonylic derivatives of patulin are formed with inversion of configuration and must be considered as derivative of the hypothetical *trans*-patulin (3a). However, the example is still valid for illustrating the usefulness of physical techniques in organic synthesis. In such a case, owing to the presence of different chromophores in the intermediates, the application of UV spectroscopy was the method of choice (without neglecting to use any of the other techniques available at that moment). In fact, from the starting propargyl alcohol (7) up to patulin (3), as the synthesis proceeded, a progressive bathochromic shift (to larger wave lengths) in the ultraviolet spectrum would be expected in the synthetic intermediates. Thus, for propargyl alcohol, with an isolated triple bond, one would expect an absorption below 200 nm, i.e., beyond of the capability of the commercial spectrophotometers usually used in an organic laboratory. For the acetylenic ketone 6a, with a carbonyl group conjugated with a triple bond, an absorption about 215-220 nm would be expected; for the ester 5a, as well as for the corresponding acid (5b), around 250 nm, and for the lactone 4a, a γ-yliden-α,β-butenolide, an absorption identical to patulin itself, i.e., 276 nm. Verification of these values after every reaction indicated, therefore, that the synthesis went forwards in the expected way. In practice the values found were: 223 nm for the ketone 6a, 257 nm for the ester 5a, 246 nm for the (*E*)-acid (*cis*) (5b) and 250 for the (*Z*)-isomer (*trans*), and, finally, 276 nm for the lactone 4a.


HOCH2-C≡CH
7
THPOCH2-C≡CMgBr
7a
+
(CH3O)2CH-COOCH3
(CH3O)2CH-CO·N
THPOCH2-C≡C-C=O
CH(OCH3)2
THPOCH2-C≡C-C=CH-COOR
CH(OCH3)2
5a, R = CH3; 5b, R = H
6a
THPO
CH(OCH3)2
4a
3a
NH2OH.HCl
CH=NOH
26a
3
NH2OH.HCl
CH=NOH
OH
26

Scheme 3.13

A much more complex example, since the molecule has a high order of connectivity and has no functional groups, is found in the synthesis of 1,16-dimethyldodecahedrane (30) by Paquette and coworkers [31] (see Scheme 3.14). This synthesis illustrates how ^{13}C NMR spectroscopy and X-ray analysis are the methods of choice, since they are the only two auxiliary physical techniques capable of giving the necessary information for correct structural assignations.

In the final stages of the synthesis, Paquette arrived at intermediate 27 which, after treatment with *p*-toluenesulphonic acid in refluxing benzene, gave alkene 28. This olefin was treated then with a superacid, such as trifluorosulphonic acid, to afford a dimethyl derivative of dodecahedrane, to which the structure 29 should, in principle, be assigned. Since this structure exhibits C_2 symmetry, the ^{13}C NMR spectrum should have eight lines. However, in practice, the spectrum showed only four lines, indicating that the structure actually belongs to the D_{3d} point group. In fact, the superacid medium induced a 1,2-shift of a methyl group and the most symmetrical 1,16-dimethyldodecahedrane 30 was formed as confirmed by X-ray diffraction analysis.



Scheme 3.14

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Chapter 4

4. SYNTHETIC STRUCTURAL ANALYSIS. SIMPLIFICATION. HETEROLYTIC DISCONNECTIONS: HEURISTIC PRINCIPLES

From this chapter onwards, we will consider in some detail each of the different structural features that the chemist must perceive in order to proceed first to the simplification of the synthetic problem and then to the generation of the intermediate precursors of the "synthesis tree".

4.1. Symmetry

"Symmetry" (from Greck word συμ–μετρια) means "the same measure" or "due proportion" and, like the concept of "synthesis", involves an intrinsic paradox: a symmetrical object by becoming simpler -owing to the fact that it is a compound of two equal parts- it becomes more complex -because there is a higher level of interrelationships between the two parts [1].

From this general law it is possible to infer probable properties, since according to the principle of Neumann the properties cannot be less symmetrical than the structure. Neumann's principle states that: "The symmetry elements of any physical property of a crystal must include the symmetry elements of the point group of the crystal". Thus, a centro-symmetric crystal cannot by pyroelectric, since it would require that the two symmetrically related ends behave differently towards a change of temperature.

A complete set of symmetry elements[8] is known to be intrinsic only to the sphere. However, objects may be referred to as *symmetrical* if they retain certain elements of symmetry. The term *asymmetrical* [9] should be applied only to those objects where not a single element of symmetry is present

The recognition of symmetry -either *real* or *potential*- in the structure of the target molecule may be of paramount importance not only in the simplification step,

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[8] Symmetry elements (which should not be confused with the elements in a set) are the operators that generate the repeated pattern of symmetry.

[9] For quite a long time, such objects have been called *dissymmetric*, thereby emphasizing the lack of a part of a complete set of symmetry elements.

but also in the generation of the intermediate precursors as well. A molecule is said to have *real symmetry* if the structure possesses some symmetry element (centre, axis, plane, etc.), and is said to have *potential symmetry* when though it is an asymmetrical molecule, it may be disconnected to give either a symmetrical structure or two synthetically equivalent structures [2].

High-symmetry molecules can sometimes be conveniently synthesized by joining together isometric segments[10] or *synthons* through a convergent synthesis [3] [4]. In such a case, the segments may be identical (achiral or *homochiral* segments) or enantiomeric pairs (*heterochiral* segments).

The convergent synthesis from homochiral segments and its reciprocal process, the bisection of an achiral molecule into homochiral fragments, are usually referred to as *la Coupe du Roi* [3]. On the other hand, the coupling of heterochiral segments to produce an achiral molecules has been named *narcissistic coupling.*[11] This strategy has two major advantages: it is convergent and reflexive [5], and it does not require the resolution of the starting materials into optically pure enantiomers. Such strategy has been proposed for the synthesis of dodecahedrane [6], though enthalpic as well as entropic factors seem to play against such a simple entry to the most symmetrical existing organic molecule [7].

A classical example of how symmetry in the target molecule can greatly simplify the synthesis is provided by indigo [8], a natural dyestuff which has been known for more than 4000 years and which has experienced a boom in recent times thanks to "blue jeans" being so popular.

The structure of indigo was determined in 1870, only 12 years after Kekulé and Couper settled the bases of the *Structural Theory*, and the first synthetic indigo appeared on the market as early as in 1897. The strucure of indigo (1) is shown in Figure 1.1, though the *trans* configuration of the double bond was not established until later, by X-ray crystallographic analysis [9].

The recognition of a C_2 axis of symmetry (or a plane, when the double bond was thought to have the *cis* configuration), allows the disconnection of the molecule into two identical moieties of indoxyl (2). The synthesis is therefore reduced to the

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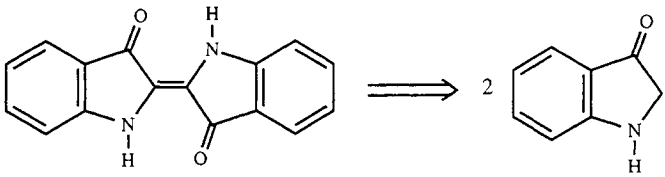
10 Two molecules are isometric if their labeled graphs are the same, i.e., if the atoms and their connectivity (bonds) are the same. See ref. 3 and references therein.

11 "*Narcissistic*, from *Narkissos*, youth who fell in love with his reflection in water", *The Oxford English Dictionary*.

synthesis of this simple compound since it was already known that its oxidative dimerisation leads directly to indigo.



1 2

Fig. 1.1

In fact, indigo is isolated from the leaves of *Isattis tinctoria*, a plant indigenous to Europe, and from *Indigofera sumatrans,* native to India and Java, as a glucoside of indoxyl (2). Immediately after harvesting, the leaves and stalks of the plant are steeped in water. Fermentation sets in and the glucoside is hydrolysed to glucose and indoxyl. The resulting aqueous solution is decanted and aerated to give the blue dyestuff 1. From the very beginning it was recognised that this compound was in fact the simplest member of a large family of many other dyestuffs, in which one or both -NH- groups are replaced by sulphur atoms and bear different substituents on the aromatic rings.

Once the structure of indigo was established in 1870, it was quite logical to attempt its synthesis, not only as an intellectual challenge, but also as a profitable source of cheaper indigo that could advantageously compete with the natural dyestuff. The first industrial synthesis used by "Badische Anilin und Soda Fabrik" (BASF) was the procedure developed by Karl Neumann, which utilised the reaction of aniline with chloroacetic acid and then cyclisation of the resulting product to indoxyl promoted by $NaNH_2$ at high temperatures (over 200 °C). However, the first really lucrative procedure was offered by Adolph von Baeyer to the same company, which paid to him the equivalent of $100,000 for the rights to his invention. In all, BASF spent over $5,000,000 in developing a technically feasible process [9].

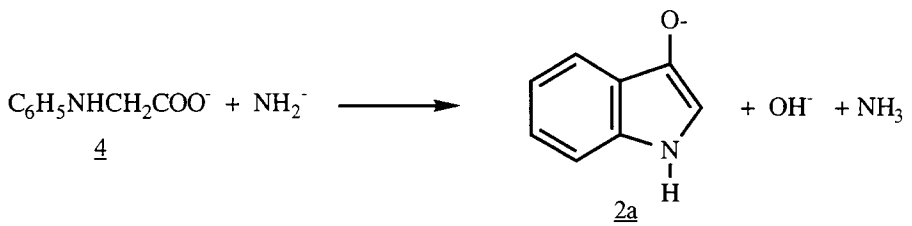
In the synthesis developed by von Baeyer the starting material is also aniline, which is treated with a buffered solution of sodium bisulphite, cyanide and formaldehyde, to give a nitrile, in a reaction which, at least formally, resembles a Mannich condensation:

$$C_6H_5NH_2 + HCHO + CN^- \longrightarrow \underset{\underline{3}}{C_6H_5NHCH_2CN} + OH^-$$

The resulting nitrile 3 is then hydrolysed,

$$\underset{\underline{3}}{C_6H_5NHCH_2CN} + OH^- + H_2O \longrightarrow \underset{\underline{4}}{C_6H_5NHCH_2COO^-} + NH_3$$

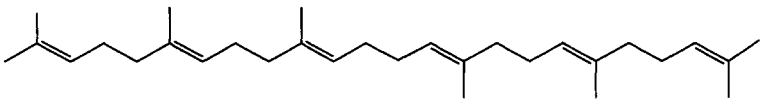
The cyclisation of phenylglycine (4) to indoxyl (2) requires heating in the presence of strong bases (Scheme 4.1). The best results are obtained using sodamide at temperatures near 190 °C, preferably mixed with sodium and potassium hydroxides which give a eutectic of low melting point.



Scheme 4.1

The process used nowadays differs only slightly from the original developed by von Baeyer, and excellent yields can be obtained, at economically profitable expenses, provided that the products are recycled and the byproducts recovered.

Other molecules in which the presence of a C_2 axis of symmetry also simplifies the syntheses are squalene (5) and β-carotene (6). Notice that in such cases the simplification derives from the fact that the syntheses are convergent and reflexive; i.e., syntheses which start from identical precursors [5]. In practice, the synthesis of these two substances may be carried out not only by dimerisation of two identical moieties [10] [11] -which may lead to a mixture of isomers-, but preferentially by addition of two identical fragments to a central bifunctional unit according to the scheme: $C_x + C_y + C_x = C_n$ (squalene: $C_{11} + C_8 + C_{11} = C_{30}$ [12]; β-carotene: $C_{16} + C_8 + C_{16} = C_{40}$ [13] or $C_{19} + C_2 + C_{19} = C_{40}$ [14].



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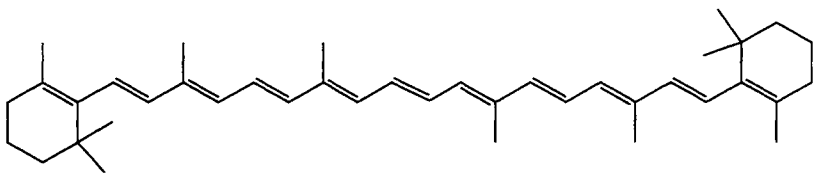
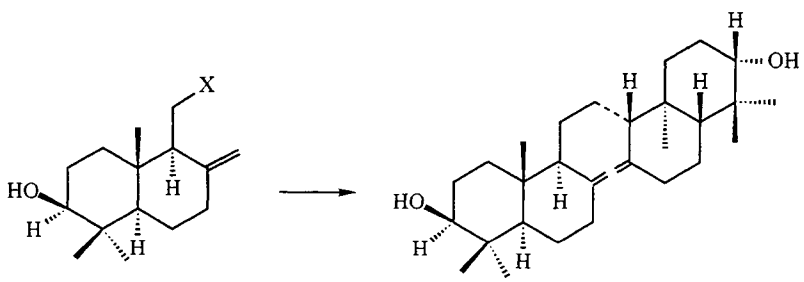


6

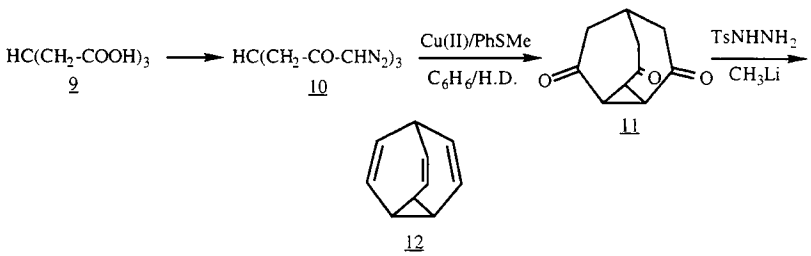
A more complicated example, in which the presence of symmetry reduces the problem of creating eight chiral centres to only four, is the case of (+)-α-onocerine (8), the synthesis of which [15] was performed by coupling of the two enantiomerically pure C_{15} units (7, X = COOH), with the correct stereochemistry, in order to prevent the formation of the unnatural *meso* form (*d,l* + *l,d*) (Scheme 4.2).



7 8

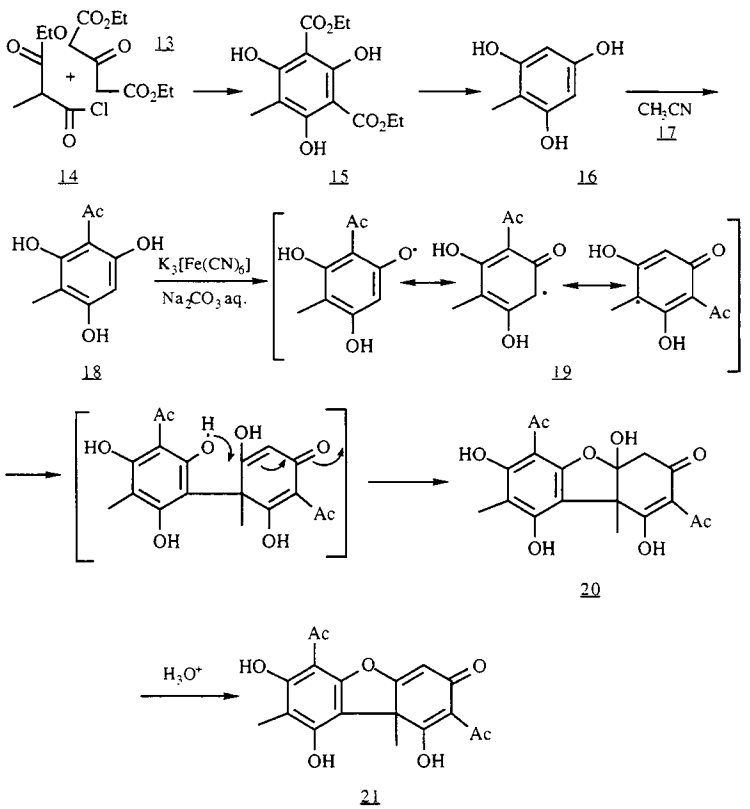
Scheme 4.2

The presence of symmetry is also an important factor in linear syntheses provided that an element of symmetry is maintained during the course of a synthetic sequence. For instance, one of the syntheses of bullvalene (12) -a molecule that possesses a C_3 axis of symmetry- starts from chloroform, and proceeds then through methane(triacetic) acid (9), the corresponding tris-α-diazoketone (10) and bullvalanetrione (11), molecules which all have a C_3 axis of symmetry (Scheme 4.3) [16].



Scheme 4.3

Much more subtle are those molecules which exhibit only *potential symmetry*. Usnic acid (21), for instance, which does not exhibit any kind of symmetry, can be synthesised in two steps by the unsymmetrical coupling of two molecules of the same phenoxy radical 19 (Scheme 4.4) [17], which is prepared from readily accessible starting materials: 13 and 14.



Scheme 4.4

Bertz [5] has drawn the attention to the relationship existing between the concept of *potential* symmetry and the symmetry present in the corresponding "synthesis tree" (or "synthesis graph") [18]. In the abovementioned synthesis of usnic acid both branches of the synthesis tree are identical, and collapse into a single path, a fact that is most easily visualised by comparing synthetic trees for labelled (a) and unlabelled (b) usnic acid (see Diagram 4.1).

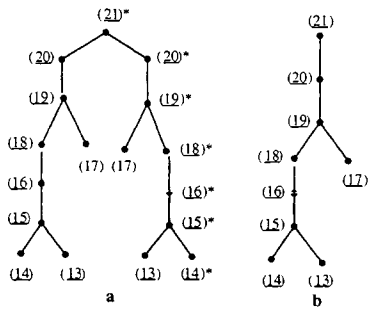
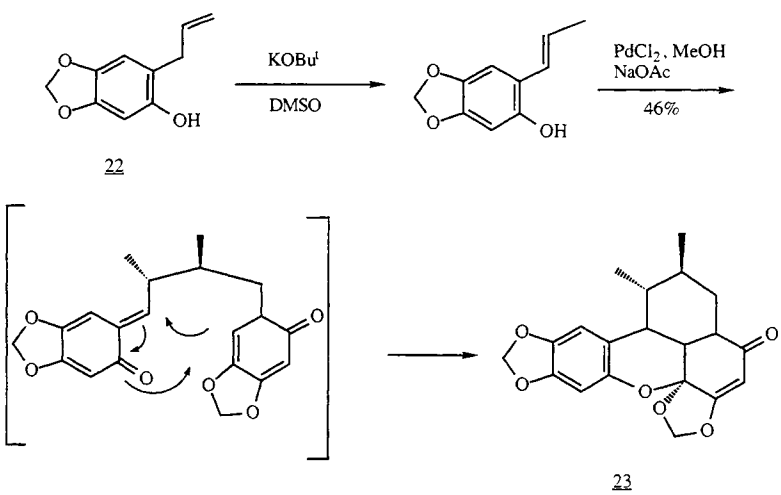


Diagram 4.1

Synthesis graph for **a**) labelled and **b**) unlabelled usnic acid according to Scheme 4.4.

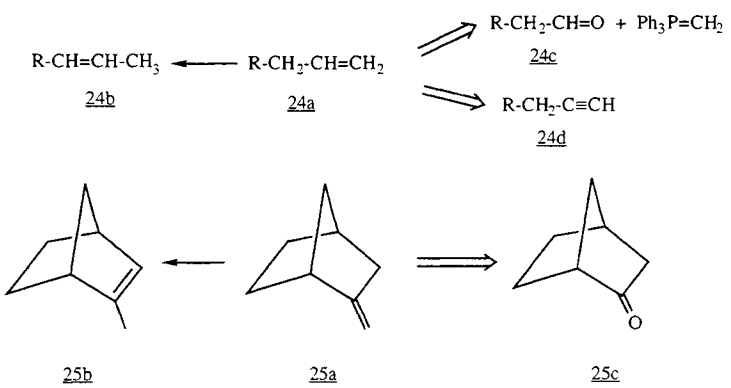
Another example is the synthesis of carpanone (23), which takes place by a two-step dimerisation of two identical moieties (22), the second step proceeding via a hetero-Diels-Alder cycloaddition [19] (Scheme 4.5).



Scheme 4.5

4.2. Functional groups

Since a practical rule in organic synthesis is that the unstable or highly reactive functional groups must be introduced as late as possible in the synthetic sequence, one of *the first simplifications is to remove* (FGR = *"functional group removal") or modify* (FGI = *"functional group interconversion") the unstable or highly reactive groups present in the target molecule* (Heuristic Principle n° 1 = HP-1). For example, since a terminal (24a) or an exocyclic double bond (25a) may easily isomerise to the thermodynamically more stable disubstituted or endocyclic alkene (24b or 25b) when considering a possible synthesis of a molecule in which a terminal or an exocyclic double bond is present, the first thing to do is to replace it (FGI) by a more stable group, such as a carbonyl group (24c and 25c) or an acetylene (24d). In the synthetic direction, the triple bond and the carbonyl group may be then converted in the last step into the desired methylene groups by familiar and well known reactions, such as a Wittig reaction or a partial reduction.

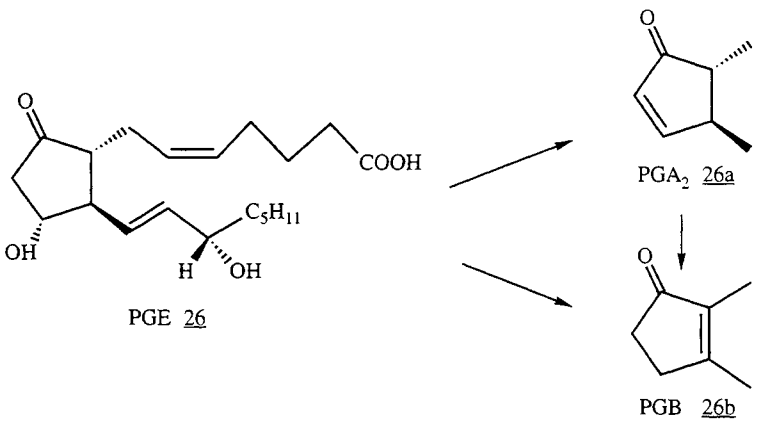


Another important "heuristic principle" regarding functional groups, refers to the *necessity of examining all possible pairs of functional groups* (HP-2) in order to detect:

i) the origin of possible instabilities, and

ii) the consonant and dissonant relationships.

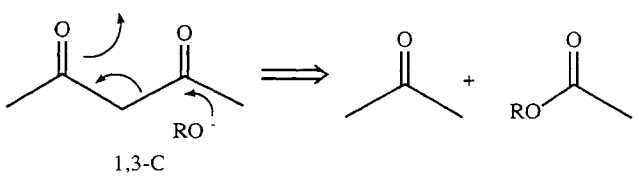
For instance, the marked lack of stability of prostaglandins of the E series (26), [20] in acid as well as in basic medium, is due to the presence of a β-hydroxyketone system in the structure which, under these conditions, is dehydrated to give in the first place the secondary prostaglandins of the A series (26a) and later on, under more drastic conditions, the prostaglandins of the B series (26b) (Scheme 4.6).



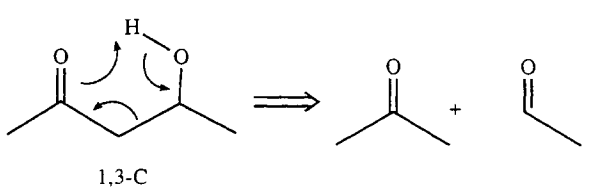
Scheme 4.6

The recognition of consonant bifunctional relationships in the target molecule allows their disconnection by a retro-Claisen, a retro-aldol or a retro-Mannich condensation or by retro-Michael addition [equivalent, according to Corey's formalisation, to the application of the corresponding *transforms (≡ operators)* to the appropriate *retrons*].

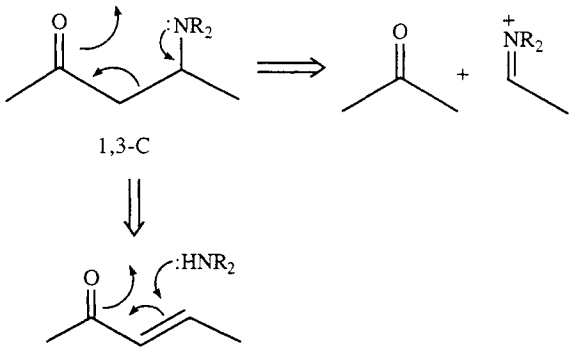
Retro-Claisen:



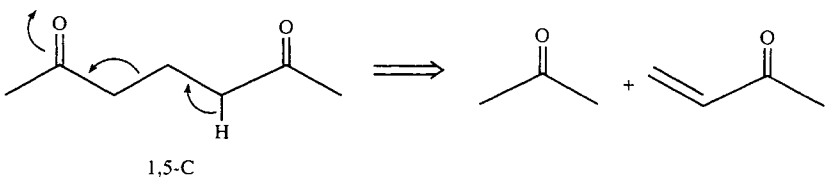
Retro-aldol:



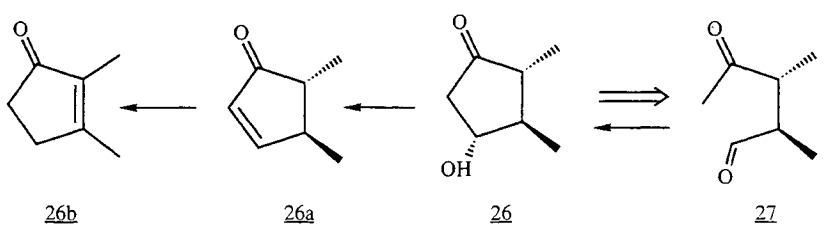
Retro-Mannich:



Retro-Michael:



According to these heuristic principles, a possible synthesis of prostaglandins that proceeds via an aldol condensation in the last step, would be in principle valid for synthesis of prostanoids of the A and the B series (26a or 26b), but not for those of the E series owing to the great unstability of the resulting aldol (β-hydroxyketone or 1,3-C system) under the reaction conditions [20] (Scheme 4.7).

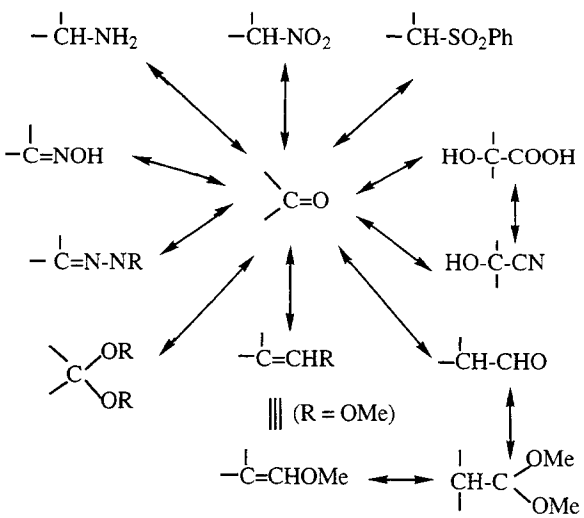


Scheme 4.7

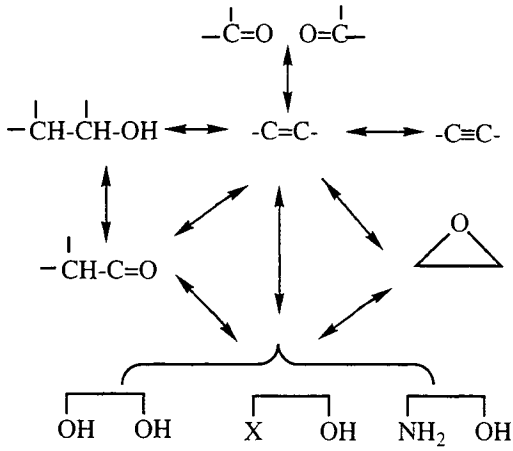
Sometimes, in the disconnection process, *it may be convenient to interconvert functional groups* (FGI) *with the aim of modifying either some highly reactive or*

unstable functional groups or to modify a double bond, or to perform a "reactivity inversion" (*Umpolung*) (see below) (HP-3).

The carbonyl group plays a very important role in organic synthesis, since it may act not only as a reactive functional group -activating the *ipso*-carbon atom-, but may also act as an activating group (at the α- and eventually at the β-position too). In fact, a great number of synthetic methods leading to carbon-carbon (or carbon-heteroatom) bonds involve such a group, and very often one of the most common FGI operations involves the substitution of a carbonyl group for some other functional group. Although as it has been stated by Corey, *any functional group may be in principle transformed into any other*, there are a series of equivalent *synthons*, in the sense that they can be mutually interconverted by means of one or more simple reactions familiar to any experienced organic chemist. Thus, in Schemes 4.8 and 4.8bis different *synthons* equivalent to the carbonyl group, as well as to the "-CO-CH_2-" grouping, are given. In this context it should be remembered here that, as Seebach has stated [21], "if carbonyl groups have been said to be 'virtually the backbone of organic synthesis', the epoxides correspond to at least 'one of the main muscles'" (see Sharpless [22]).



Scheme 4.8



Scheme 4.8bis

The usefulness of FGI operations is easily understood considering a very simple example. 1,3-Butanediol, notwithstanding being a 1,3-C system, does not offer a reasonable disconnection mechanism. However, if the primary hydroxyl group is converted to a carbonyl group, the resulting product can be then disconnected into two *stable* identical molecules of acetaldehyde, according to a *reasonable* retro-aldol mechanism, and the whole process represents a simple solution in accordance with the criterium of *maximum simplicity.*

$$CH_3\text{-}CH(OH)\text{-}CH_2\text{-}CH_2\text{-}OH \xrightarrow{\text{FGI}} CH_3\text{-}CH(OH)\text{-}CH_2\text{-}CH{=}O$$

$$CH_3\text{-}CH(OH)\text{-}CH_2\text{-}CH{=}O \xrightarrow{\text{retro-aldol}} 2\ CH_3\text{-}CHO$$

Alternatively, *it is possible to add a functional group (FGA), either to functionalise the carbon skeleton or to create new consonances (dissonances must be always avoided!) which can provide valid bond disconnection mechanisms* (HP-4). Of some special interest is the introduction of a double bond (in the α,β-position if a carbonyl group is already present in the target molecule) since it is a typical ambivalent group, of type A, which provides different valid bond disconnection mechanisms, either directly or after substitution by an equivalent *synthon*, such as a

hydroxyl group (in a 1,3-C relationship if the double bond is conjugated with the carbonyl group!). Very simple examples related to this heuristic principle are:

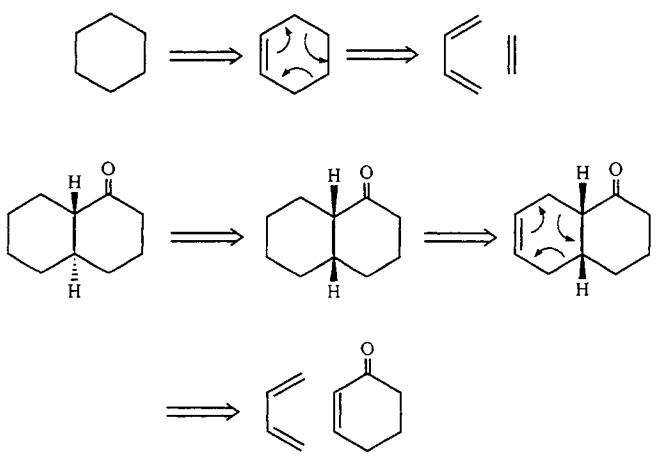
$$R\text{-}CH_2\text{-}CH_2\text{-}C(R')=O \xrightarrow{FGA} R\text{-}CH(OH)\text{-}CH_2\text{-}C(R')=O \Longrightarrow$$

$$R\text{-}CH=O + CH_3\text{-}C(R')=O$$

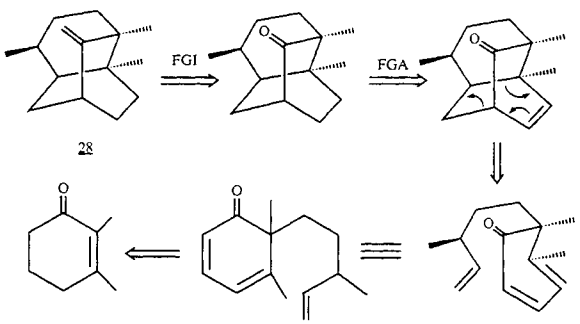
$$R\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3 \Longrightarrow R\text{-}CH=CH\text{-}CH_2\text{-}CH_3 \Longrightarrow$$

$$R\text{-}CH_2\text{-}CH(OH)\text{-}CH_2\text{-}CH_3 \Longrightarrow R\text{-}CH_2CHO + BrMgCH_2\text{-}CH_3$$

The possibility of introducing a double bond into a six-membered ring may sometimes be a requirement prior to a cycloelimination process, which may also require eventually a pertinent stereochemical correction. For instance:

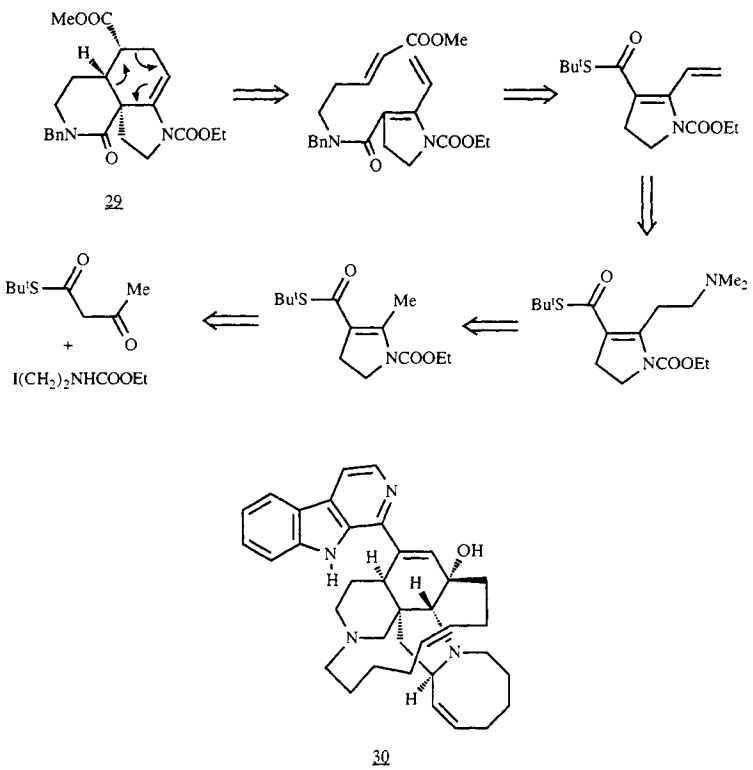


A possible synthetic pathway to seychellene (28) (Scheme 4.9) [23], for example, requires: a) the substitution (FGI) of the terminal methylene group by an equivalent *synthon*, such as a carbonyl group; b) introduction (FGA) of a double bond in one of the cyclohexane rings and c) a retro-Diels-Alder cycloelimination (equivalent to a *Diels-Alder transform*) (see *Heading 6.2*):



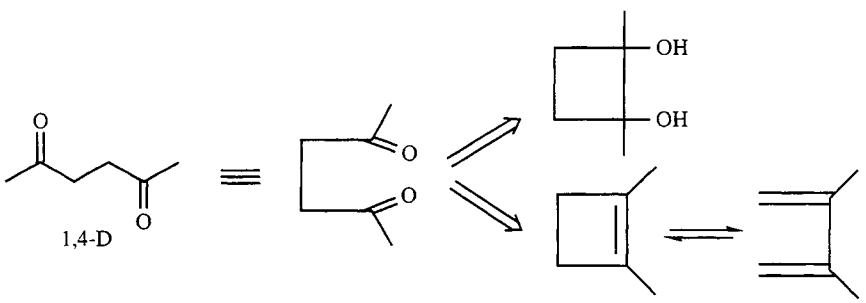
Scheme 4.9

A more recent example of an intramolecular Diels-Alder addition is the construction of the tricyclic ring system 29 [24] in an attempt to synthesise the complex pentacyclic system of the β-carboline 1-substituent in manzamine A (30). The retrosynthetic analysis proceeds as shown in Scheme 4.10.



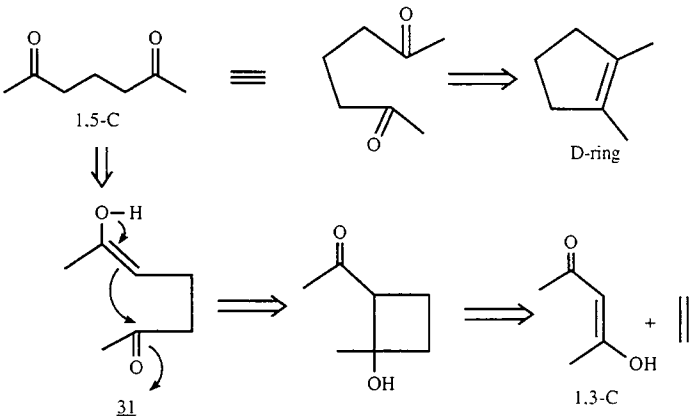
Scheme 4.10

Another "heuristic principle" concerning functional groups is *the possibility of proceeding, in some instances, to the reconnection of two functional groups to give a ring* (HP-5). In contrast with the previously stated heuristic principles, this new HP does not represent any simplification, but rather in creating new bonds introduces a greater complexity. However, the principle is heuristically justified since it is very efficient and *works* perfectly in most of the cases in which it has been applied. Althought different functional groups may in principle be reconnected, the reconnection of two carbonyl groups (to give either a double bond or a 1,2-diol system), which are separated by a chain of n + 2 carbon atoms, in which n is equal to 2, 3, 4 or 5 (i.e., the resulting ring is a 4, 5, 6 or 7-membered "normal-sized" ring), is especially useful because nowadays different and efficient methods for constructing them exist:



Notice that this HP is especially efficient in those cases in which n is equal to 2 and 4, since it means reducing 1,4-D and 1,6-D systems to 4- and 6-membered consonant rings, respectively (see Chapter 6).

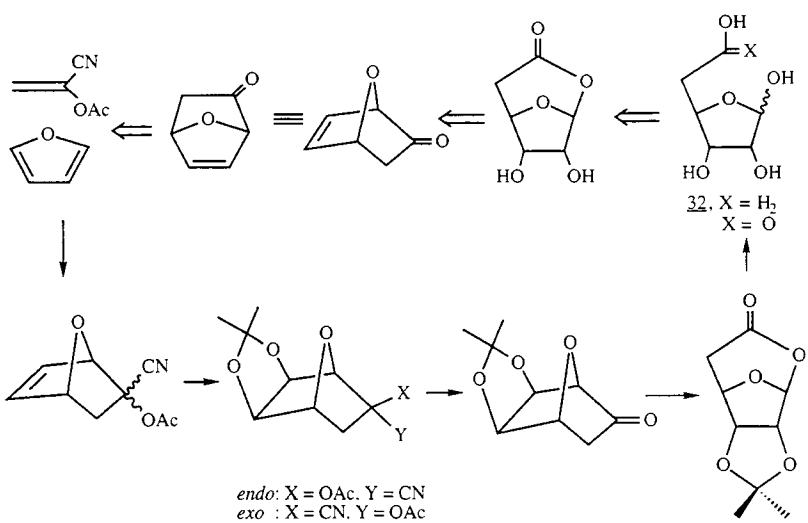
In the context of "functional group reconnections", an illustrative example is provided by the well known De Mayo photochemical reaction [25], which involves the cycloaddition of an alkene to a "photoenol" of a 1,3-dicarbonyl derivative to give a cyclobutanol which undergoes a spontaneous retroaldol reaction leading to a 1,5-C system (bis-homologation). The process (see Scheme 4.11), in the retrosynthetic direction, implies the "reconnection" of a carbonyl group with an activated methylene (31); i.e., implies a typical aldol condensation, a fact that illustrates not only the reversibility of aldol condensations, but the soundness of the "principle of microscopic reversibility". The driving force of the De Mayo photochemical reaction is obviously the strain of the cyclobutane ring.



Scheme 4.11

A rather unusual "reconnection" is found in the retrosynthetic analysis of hirsutic acid by Trost [26], in which two methyl groups are reconnected to an unsaturated six-membered ring.

By contrast, the reconnection of a carboxylic group with a hydroxy group to give a lactone is quite a normal operation since, in the synthetic direction, it represents a Baeyer-Villiger oxidation of a ketone, usually generated through a [2+2]- or a [4+2]-cycloaddition.

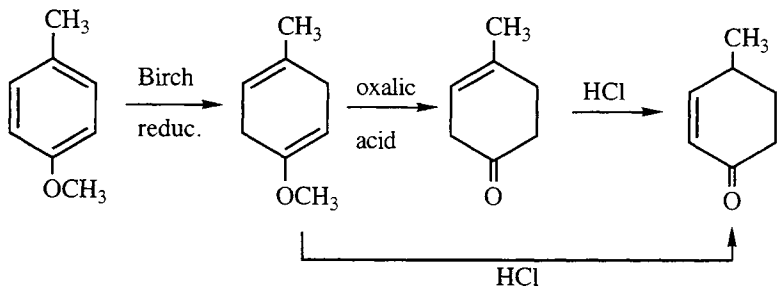


Scheme 4.12

Such is the case, for example, in the synthesis of semibullvalene [27] and some prostaglandin precursors [28], or in the synthesis of 5-deoxy-*ribo*-hexofuranose (32, X = H_2), or the corresponding uronate (32, X = O), shown in Scheme 4.12 [29].

Notice that the α-acetoxyacrylonitrile is in fact a "ketene equivalent" [30] in the Diels-Alder condensation with furan, since ketene itself undergoes [2 + 2]-cycloadditions rather than [4 + 2] cycloadditions.

Finally, also in connection with functional groups , there is a *set of "heuristic principles" which refer to the stability of aromatic and conjugated systems, as well as to the relationship between more or less unsaturated cyclohexane rings and benzene rings* ("HPs-6"). For instance, through a series of well known reactions, it is possible to establish a relationship between *p*-methylanisole and cyclohexane derivatives with different levels of unsaturation (Scheme 4.13):

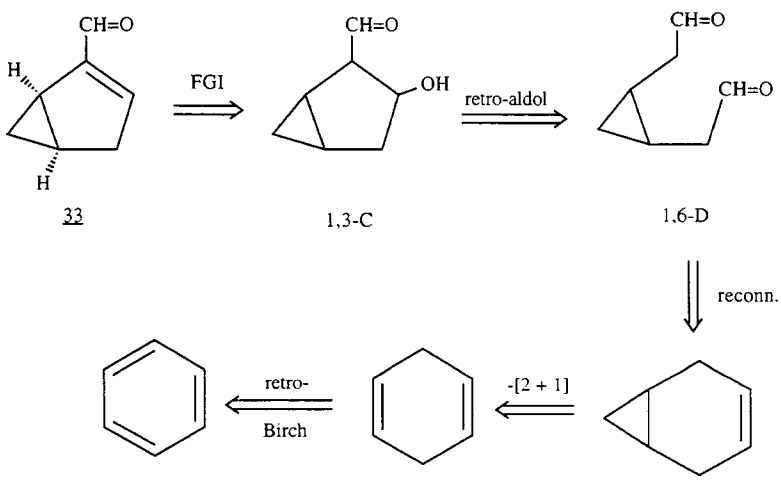


Scheme 4.13

An important advantage of using aromatic compounds as starting materials for the synthesis of organic molecules is the possibility of introducing different appendages and functional groups in a regioselective manner taking advantage of the "orientation rules", so familiar to organic chemists.

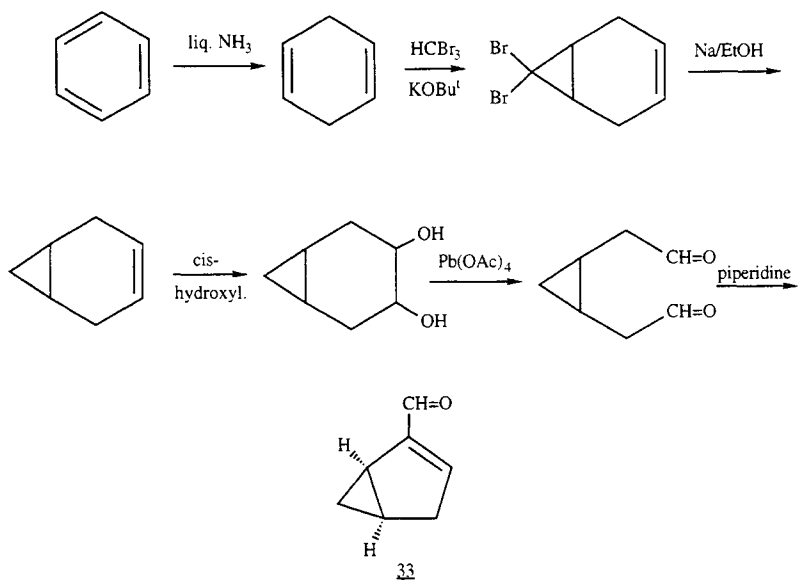
The great effectiveness of the heuristic principles so far enunciated can be realized considering a possible synthesis of bicyclo[3.1.0]hex-2-ene-2-carboxaldehyde (33). The pertinent structural analysis shows that the molecule has no real symmetry and has two fused dissonant rings (a 3- and a 5-membered ring), with a conjugated aldehyde group in the 5-membered ring. Proceeding retrosynthetically (see Scheme 4.14), the synthesis of compound 33 is reduced to

benzene as the exclusive starting material, according to a sequence of intermediate precursors, which implies: i) substitution (FGI) of the double bond by an equivalent *synthon* (an OH group in a 1,3-C relationship with respect to the carbonyl group); ii) retro-aldol disconnection of the resulting 1,3-C system to give a symmetrical 1,6-D system (which shows that the target molecule has in fact potential symmetry!); iii) reconnection of the 1,6-D system to a consonant 6-membered ring; iv) cycloelimination of the 3-membered ring by a cheletropic disconnection (i.e., a -[2 + 1] cycloaddition), to give a diene and a carbene ("methylene"); and v) "oxidation" of 1,4-dihydrobenzene to benzene itself according to a "retro-Birch" reduction.



Scheme 4.14

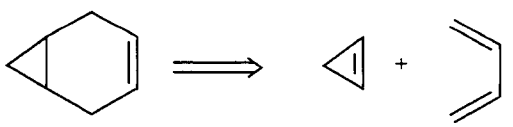
In practice, the synthesis of compound 33 was carried out according to Scheme 4.15, in which the "dibromocarbene" was substituted for "methylene" in order to exert better control of the reaction and thus giving the monoadduct as the predominant reaction product [31]. Although this meant an extra step in the synthetic sequence, the great selectivity and the excellent yields obtained compensated this "deviation" from the original retrosynthetic scheme.



33

Scheme 4.15

Since the norcarene intermediate 34 has a double bond in the 6-membered ring, a Diels-Alder cycloreversion leading to cyclopropene (35) and butadiene is also a possible disconnection. The corresponding synthetic sequence has been carried out in the laboratory in 37% yield [32]:

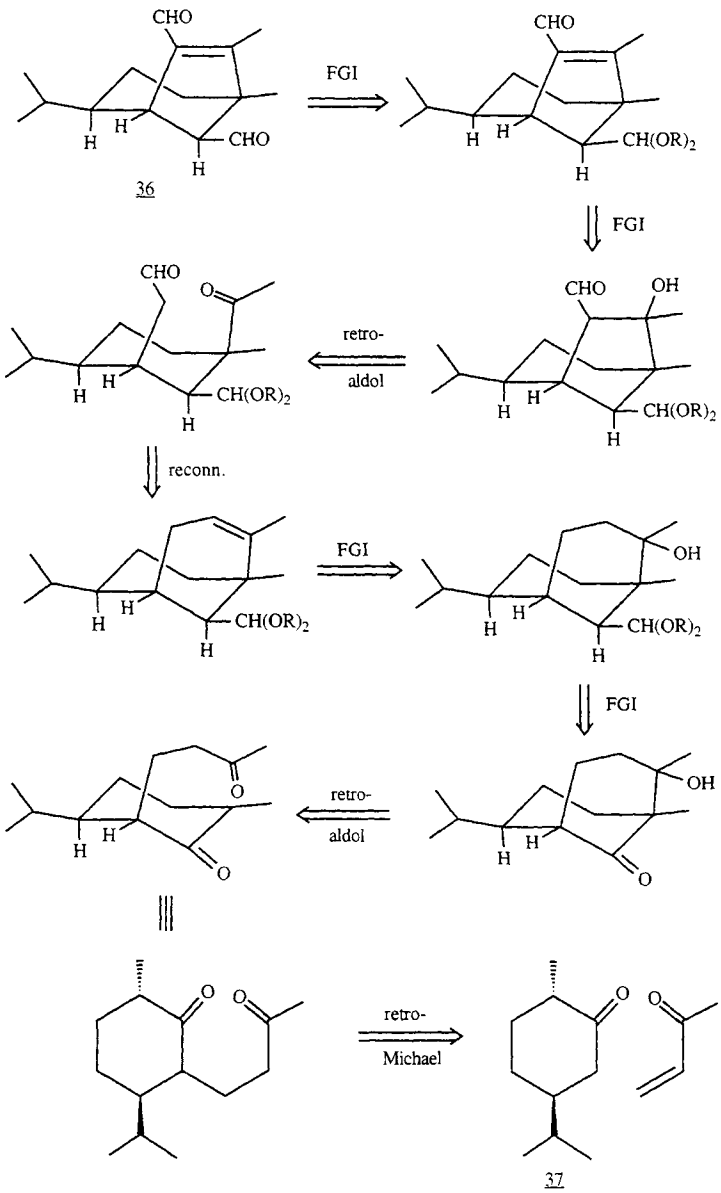


34 35

A practically identical retrosynthetic scheme was also worked out by Corey [33] for the synthesis of helminthosporal (36), a polycyclic natural product with somewhat greater structural complexity than compound 33.

As shown in Scheme 4.16, the retrosynthetic process proceeds as follows: i) FGI (substitution of the unconjugated aldehyde by an acetal group and the conjugated double bond by an OH group); ii) retro-aldol disconnection of the 1,3-C system; iii) "reconnection" of the resulting 1,6-D system to a 6-membered ring; iv) FGI (substitution of the double bond by an OH group and the acetal by a carbonyl

group); v) retro-aldol disconnection of the 1,3-C system to a 1,5-C system; vi) retro-Michael disconnection of the 1,5-C system to give, as starting materials, (-)-carvomenthone (37) and methyl vinyl ketone.

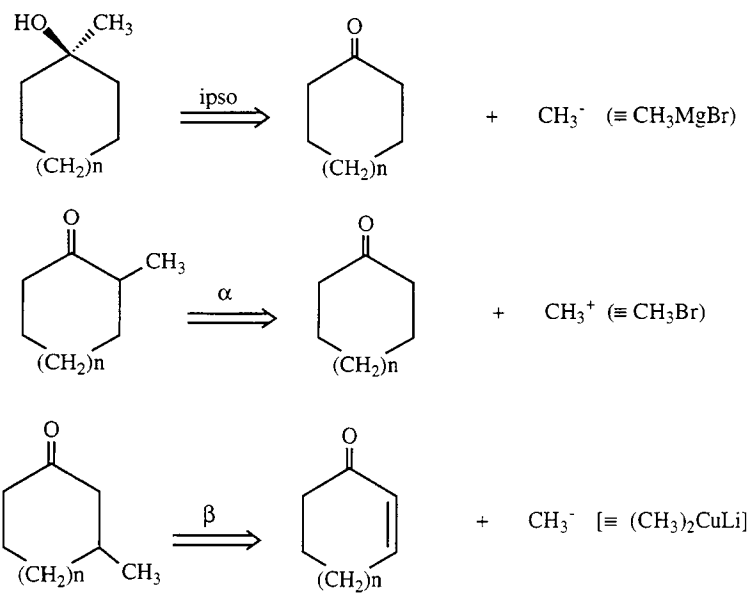


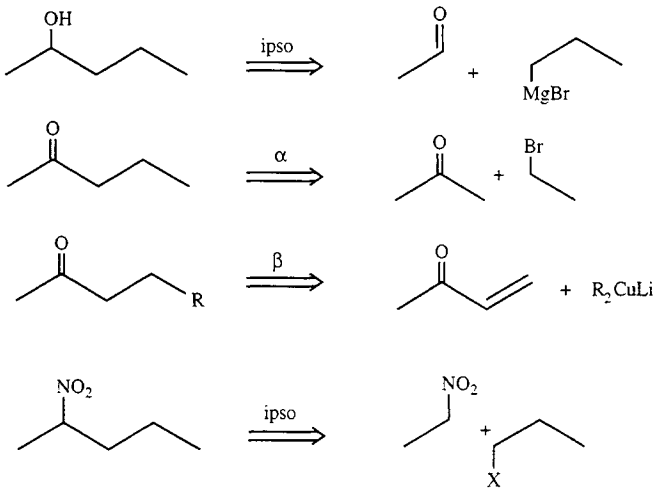
Scheme 4.16

In practice the derived retrosynthetic scheme must be modified and optimised in order to introduce the pertinent control elements (protecting groups, activating groups, etc.) and to direct the synthesis along the planned pathway.

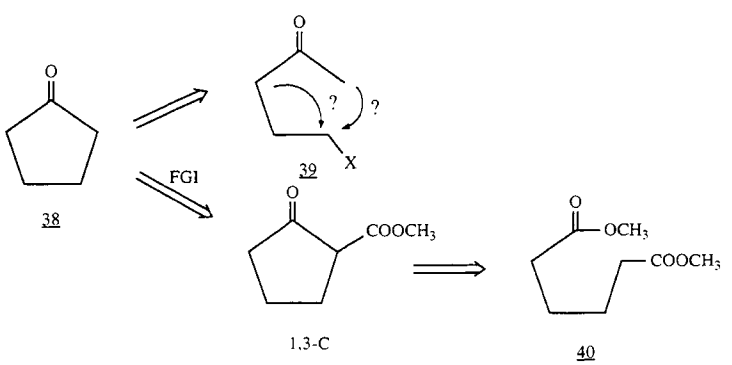
4.3. The carbon skeleton: chains, rings and appendages

1) Monofunctional systems: *With monofunctionalised chains and rings it may be advisable to proceed to the disconnection of those bonds which are near to functional groups of type* E, *or eventually of type* A (HP-7), either to eliminate appendages and simplify the synthetic problem, or to generate directly sequences of intermediate precursors. The introduction (FGA) or modification (FGI) of the functional groups may be necessary prior to such a disconnection. In principle, depending upon the oxidation level of the heteroatom, disconnections at *ipso*-, α- and β-positions are possible. The resulting fragments must be then properly functionalised in order to create the charge distribution generated by the disconnection (notice that whenever the anion of acetone is generated, it must be replaced by the more stable acetoacetic ester anion which does not undergo self-condensation; similarly, the anion of acetic esters may be replaced by the more stable malonic ester anion):

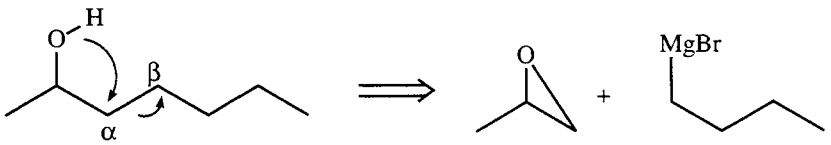




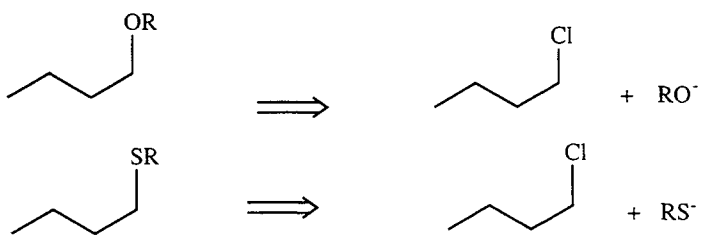
In the case of monofunctionalised rings, the direct disconnection of carbon-carbon (or carbon-heteroatom) bonds of the cyclic network at the *ipso*-, α- or β-positions leads to a single fragment in which some functional group incompatibilities may be present. In such a case, the disconnections are better performed if a functional group is first introduced (FGA) in such a manner that a new consonant relationship is created. The disconnection of the resulting bifunctional consonant relationship leads then to an intermediate precursor which is usually easily available. For example, the direct disconnection of cyclopentanone (38) at the α-position would lead to the "unusual" intermediate (39), but the introduction of a carboxylic ester group at the α-position affords a 1,3-consonant system which can then be disconnected by a retro-Dieckmann condensation leading to a diester of adipic acid (40).



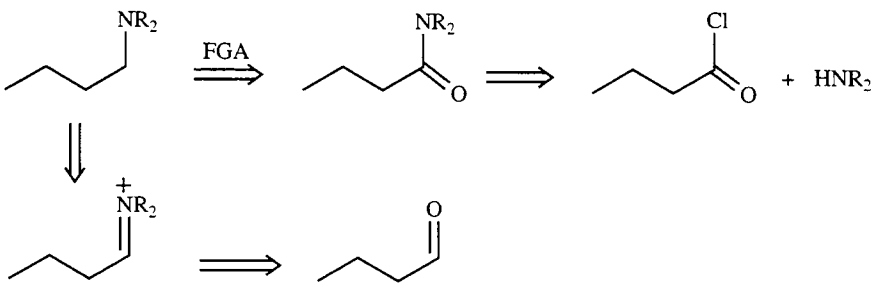
α-Disconnections may also be performed directly in alcohols by reconnecting the oxygen atom to the α-carbon atom, in which case an epoxide is formed as the intermediate precursor. Although this solution leads to a dissonant ring, it may be valid, provided that the resulting epoxide can easily be prepared by epoxidation of an alkene and that it is unsymmetrically substituted so that satisfactory regioselective control can be exerted (see below "plausible disconnections", *Heading 5.2*):



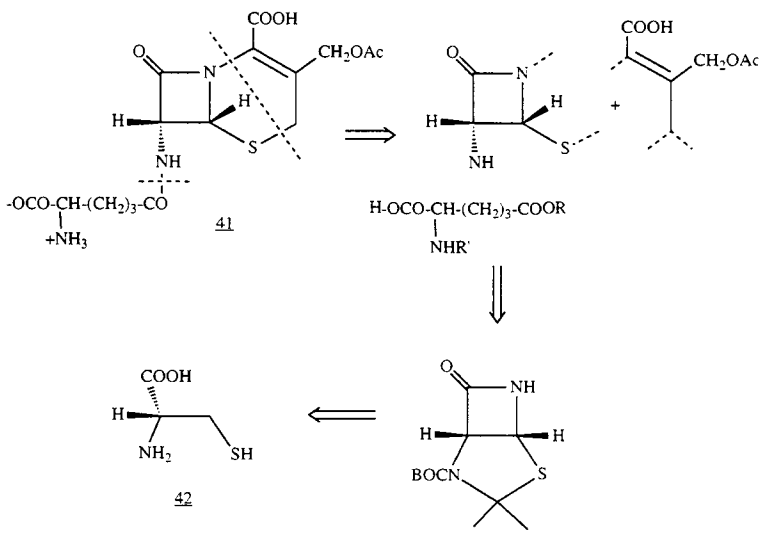
Finally, another important heuristic principle is *to carry out the systematic disconnection of substituted nucleophilic heteroatoms (O, N, S) directly attached to the carbon skeleton, especially if they are attached to a primary sp^3 carbon atom* (HP-8):



Such an operation represents, in the synthetic sense, the classical Williamson reaction (or its *thio*-equivalent in the case of sulphur). However, with amines, in order to avoid polyalkylations, a FGA must be carried out beforehand, introducing a carbonyl group (=O) at the *ipso*-position, and proceeding then to the *ipso*-disconnection to afford the amine and an acyl derivative -as an acid chloride, for instance-, since in the synthetic direction monoacylations can be easily controlled owing to the deactivation of the resulting amide, which prevents further acylations. In practice, the amide can then be reduced by $LiAlH_4$. As an alternative solution, a double bond between the N and C atoms may be introduced and then disconnection of the resulting imine to a carbonyl derivative can be carried out. In the synthetic direction, the method will also require a reduction in the last step ("reductive amination of aldehydes and ketones"):

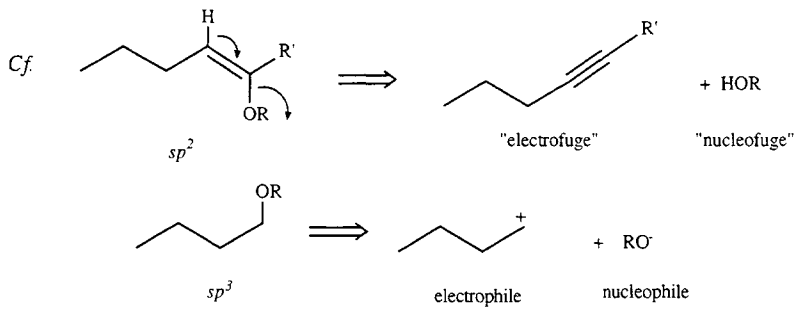


In the synthesis of cephalosporine C (41) by Woodward [34], the application of this simple heuristic principle allowed the direct establishment of a valid synthetic scheme which starts from L-(+)-cysteine (42) (Scheme 4.17):

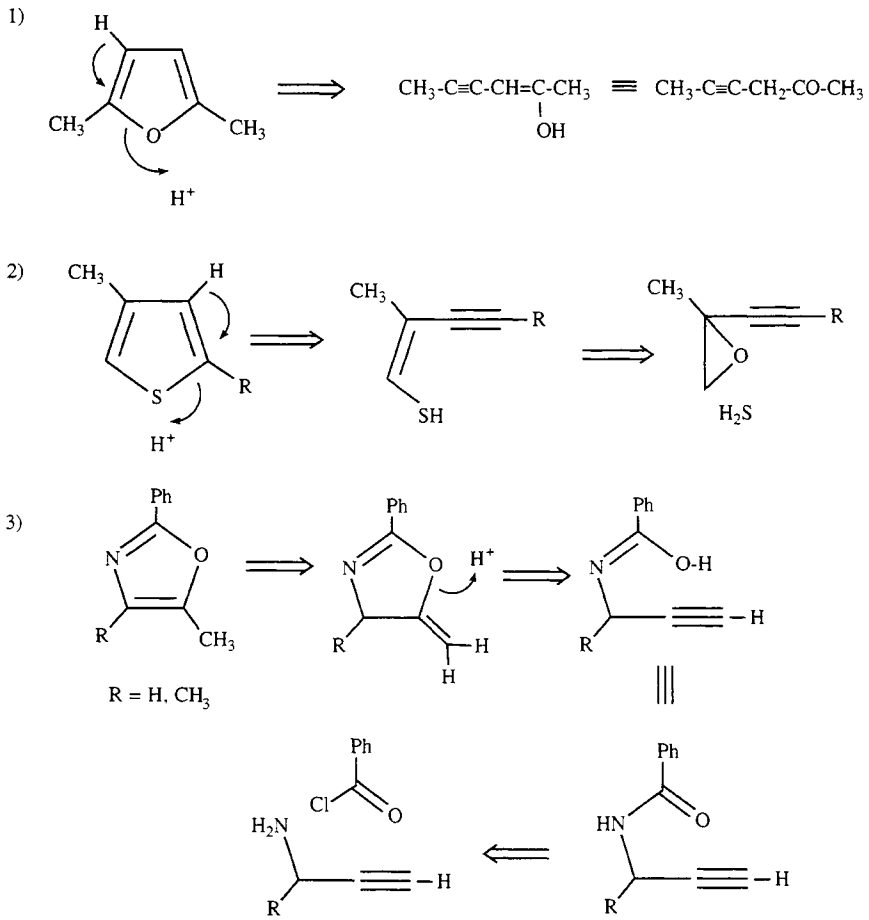


Scheme 4.17

In fact, this heuristic principle (HP-8), which refers to nucleophilic heteroatoms directly attached to sp^3 carbon atoms, may be also applied to nucleophilic heteroatoms directly attached to sp^2 olefinic carbon atoms. In such cases, however, rather than a "disconnection" we would have an "*anti*-elimination" which will afford the substituted heteroatom as the "nucleofuge" and a triple bond as the "electrofuge".



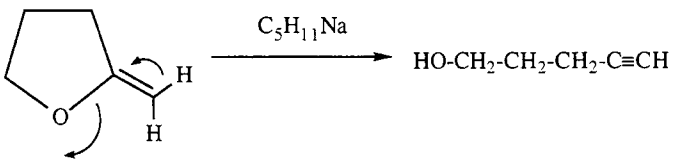
An example of such an elimination was already discussed in the synthesis of patulin (see *3.1*). Some other examples described in the chemical literature [35] are:



These retrosynthetic elimination processes, which are "purely mental", may have their equivalent in the laboratory and, in fact, they are related to the slow

decomposition observed in the ethereal solutions of organolithium compounds (as well as other alkaline reagents). Thus, as early as in 1910, Schorigin realised that vinyl alkyl ethers react with PhLi to give an alcohol and acetylene [36] and, apparently, the reaction is much faster with cyclic ethers (remember that even a saturated cyclic ether such as THF splits much more rapidly than an acyclic ether):

$$CH_2{=}CH\text{-}OR \xrightarrow{PhLi} HC{\equiv}CH + ROH \quad (R = Ph, Bu^i)$$



2) Bifunctional systems: In the case of bifunctional systems (or molecules) only two alternatives are possible: the bifunctional relationships are either "consonant" or "dissonant" (apart from molecules or systems with functional groups of type A to which we have referred to as "assonant"). In the first case, the synthetic problem will have been solved, in principle, in applying the "heuristic principle" HP-2; that is to say, the molecule will be disconnected according to a retro-Claisen, a retro-aldol or a retro-Mannich condensation, or a retro-Michael addition, proceeding if necessary by a prior adjustment of the heteroatom oxidation level (FGI).

On the contrary, if a "dissonant" bifunctional relationship is present in the system or molecule under consideration, then the synthetic problem may be much more complex and we will have to resort to some of the methods especially designed for such purposes, which will be discussed in the next Chapter.

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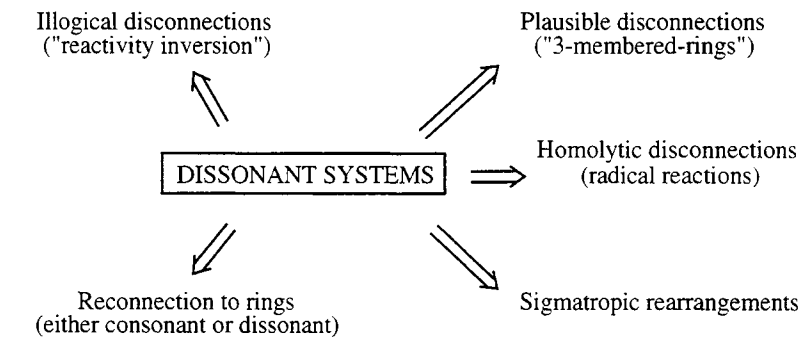
Chapter 5

5. SYNTHESIS OF DISSONANT SYSTEMS

The synthesis of dissonant systems is intrinsically more diffficult than the synthesis of consonant systems and because of this chemists have developed, in the past few years, more and more selective and efficient methods for performing it. Table 5.1 gives a summary of the most important methods developed so far, which have been classified into five main strategies:

TABLE 5.1. General strategies for the synthesis of dissonant systems

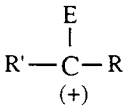


Although all these strategies imply, in some respect, a reactivity inversion of some of the starting reagents or synthons, the term "reactivity inversion" (or *Umpolung* as proposed by Seebach in 1979) [1] is commonly used in the context of the strategy known as "illogical disconnections" [2].

5.1. Illogical disconnections: reactivity inversion

In contrast with all the heterolytic disconnections considered so far, which have been called "logical" in the sense that they meet all the requirements already mentioned (see *Heading 3.5*), we will call "illogical disconnections" those disconnections which, although they do not fulfil some of these requirements, are still useful since they introduce an element of flexibility which is highly desirable in designing complex organic syntheses.

Let us consider, for example, a molecules such as



which may be disconnected in a "logical" fashion to give the E-functionalized fragment (E-C^+-R) as the electrophile and the R'^- fragment as the nucleophile (see Diagram 5.1). However, it may well happen that the radical R' is incompatible with a negative charge (because it can interact with other functional groups present in the fragment R', or because it can undergo an elimination to give a more stable anion and a carbene, for instance, etc.) in which case it may be necessary to disconnect the molecule in such a way that the E-functionalized fragment is now the nucleophile and the R' the electrophile. In such a case we will have performed an "illogical disconnection" since the first two requirements are not fulfilled; i.e., a reasonable mechanism for such a disconnection does not exist and the resulting fragments are not stable because the E-functionalized fragment now carries an "unnatural" negative charge.

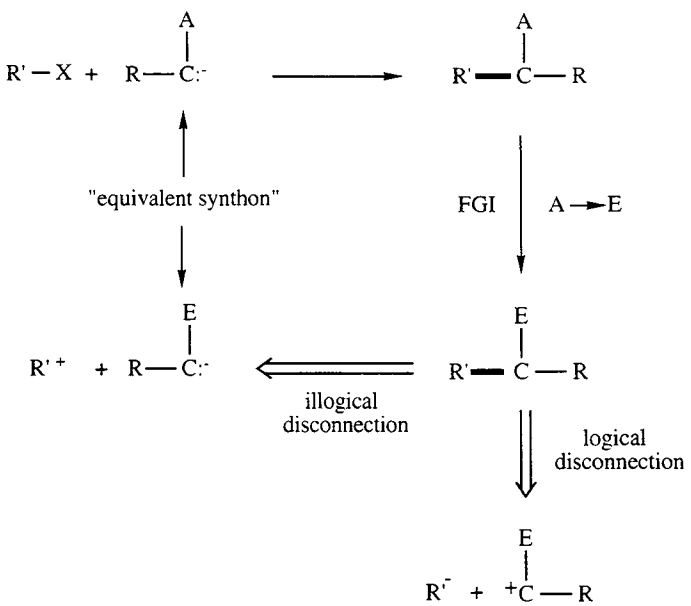
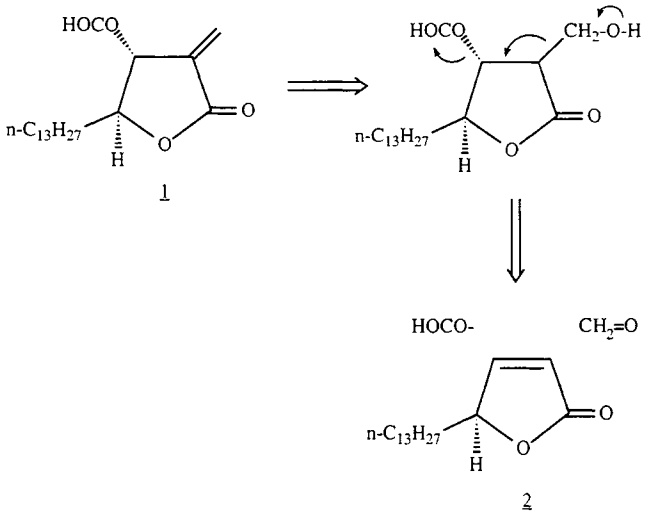


Diagram 5.1

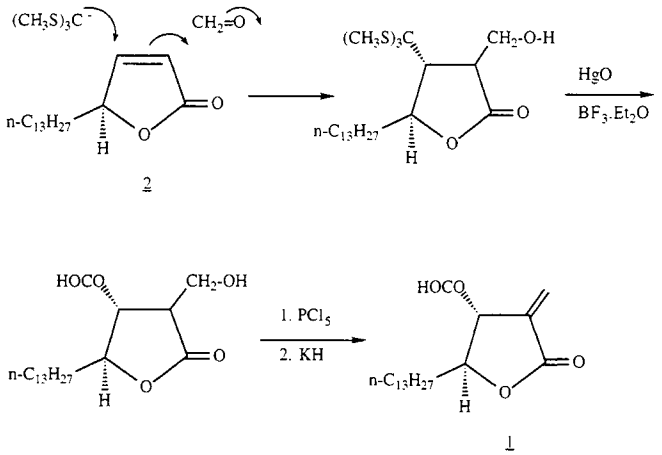
Nevertheless, the strategy may be quite useful if by means of a FGI operation the functional group of type E can be replaced by a functional group of type A which owing to its ambivalent character is highly versatile. In practice, it means having an *umpoled* synthon which is equivalent to a fragment with "unnatural" polarity. The *umpoled* synthon reacts with the electrophile (R'^{+}) to give an "assonant" system with a functional group of type A, which is then replaced (FGI) by the functional group of type E to afford finally the desired molecule through a pathway which involves an "illogical disconnection".

Although extensive lists of *umpoled* synthons may be found in the chemical literature [3], Table 5.2 gives a limited number of the most useful of them.

A highly illustrative example of "illogical disconnections" and the use of *umpoled* synthons is found in the synthesis of protochelisterinic acid (1) accomplished by Damon and Schlessinger in 1976 [4]. As shown in Scheme 5.1, proceeding retrosynthetically the terminal methylene group is substituted by the corresponding primary alcohol and the resulting 1,3-C and 1,4-D systems are disconnected according to a retro-aldol reaction and an "illogical" retro-Michael addition respectively to give formaldehyde and a butenolide, as two stable fragments, together with an "unnatural" nucleophilic carboxylic acid synthon, which because it does not exist must be substituted by an "equivalent *umpoled* synthon" such as methyl orthothioformate (see Table 5.2), which later on is transformed (FGI) into the carboxylic acid group present in the target molecule (Scheme 5.2).



Scheme 5.1

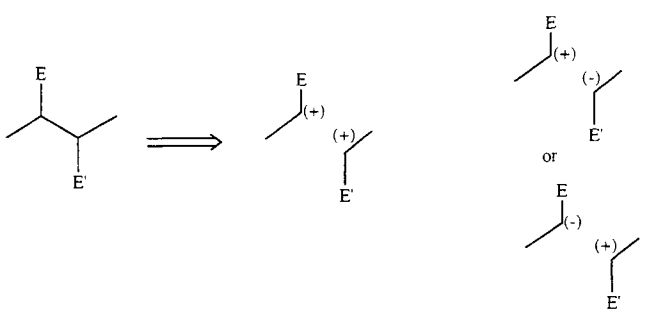


Scheme 5.2

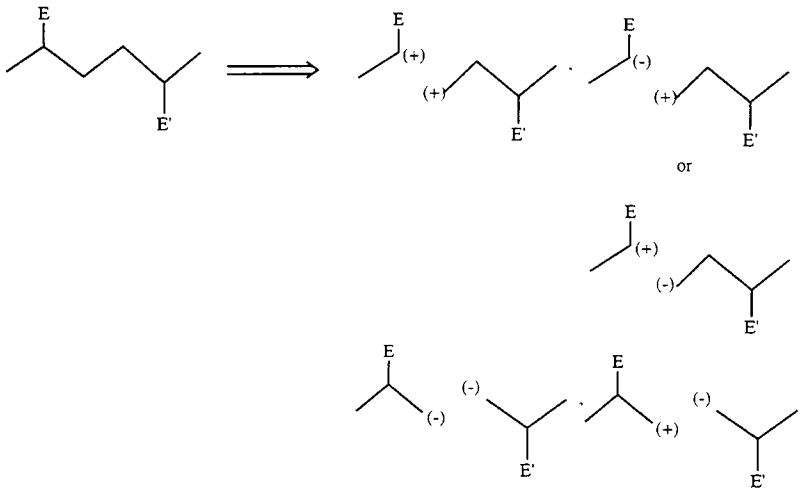
Because it is not possible to apply alternating polarities to dissonant molecules, the easiest method of dealing with them is to proceed as in the case of monofunctional molecules; i.e., the dissonant molecule is disconnected at the *ipso*-, α- or β-position with respect to one of the two functional groups and then alternating polarities, according to the Lapworth model, are assigned to the resulting fragments -which will indeed evince the "illogical" nature of the disconnection- and the polarity of either one of the two fragments is then inverted. Finally, referring to Table 5.2 or to a more complete list [3] we can see whether an *umpoled* synthon, equivalent to the non-existent fragment (or synthon) with inverted or "unnatural" charge actually exists or, at least, is easily accessible.

Let us consider the three possible dissonant systems: 1,2-D, 1,4-D and 1,6-D:

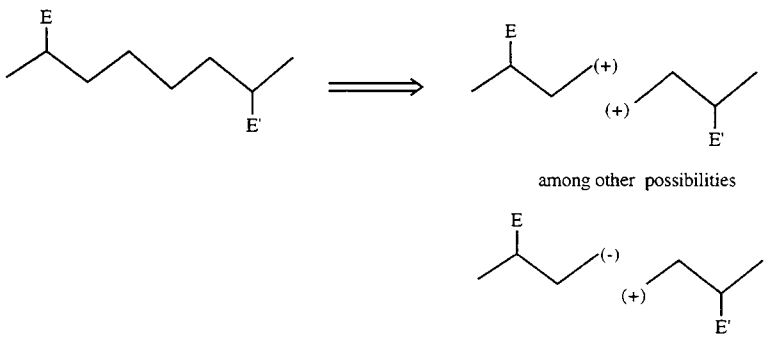
1,2-D system	Illogical disconn.	*Umpolung*



1,4-D system Illogical disconn. *Umpolung*



1,6-D system Illogical disconn. *Umpolung*



In using the "reactivity inversion" strategy, three different approaches may be considered: the simple, the reversible and the use of "inversion operators".

"Simple reactivity inversion" implies using an *umpoled* synthon whose origin has, in principle, nothing in common with the synthon with "unnatural" polarity. An example of this type of reactivity inversion is found in one of the possible synthesis of *cis*-jasmone (3) in which the nitroethane (4) is used as an equivalent of an "acetyl anion" and reacts with an α,β-unsaturated ketone to give the corresponding 1,4-bifunctional system which can then be transformed by a Nef-type reaction into the dissonant 1,4-dicarbonyl system [5]. An intramolecular aldol condensation finally affords the target molecule (Scheme 5.3).

TABLE 5.2. Umpoled synthons and their equivalent fragments with unnatural polarities

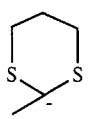
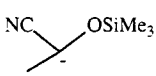
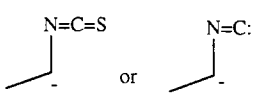
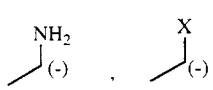
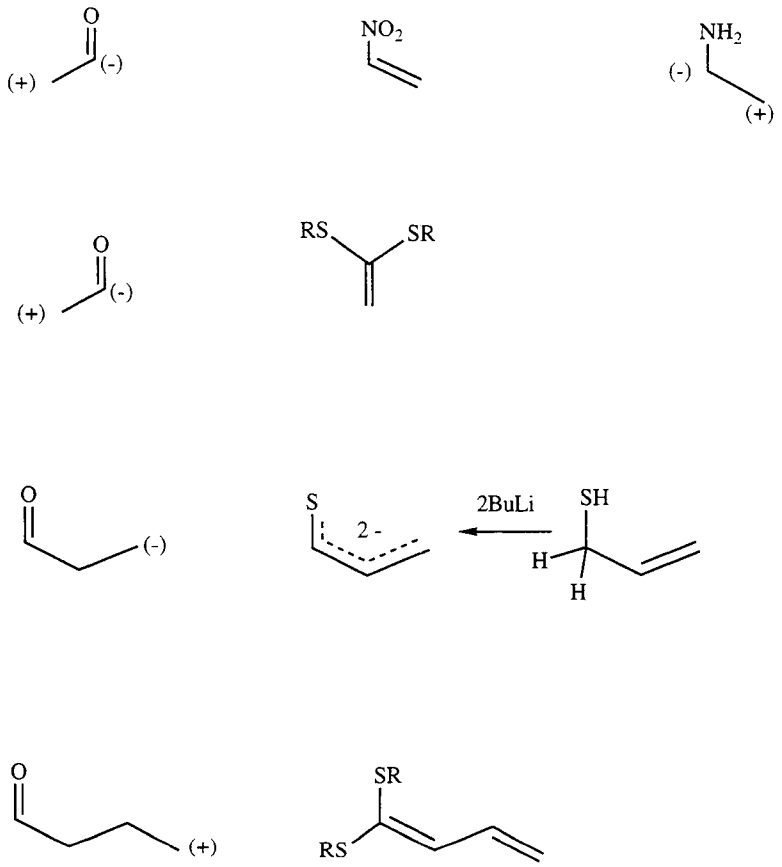
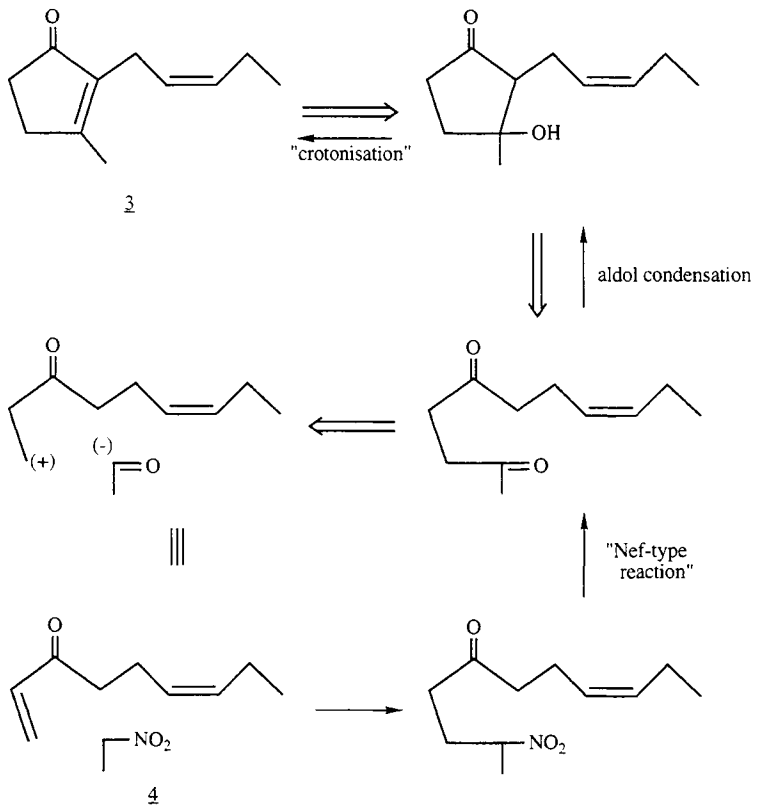
Umpoled synthon	Synthon equivalent to	Umpoled synthon
		
		
		
		
		
		
		
		

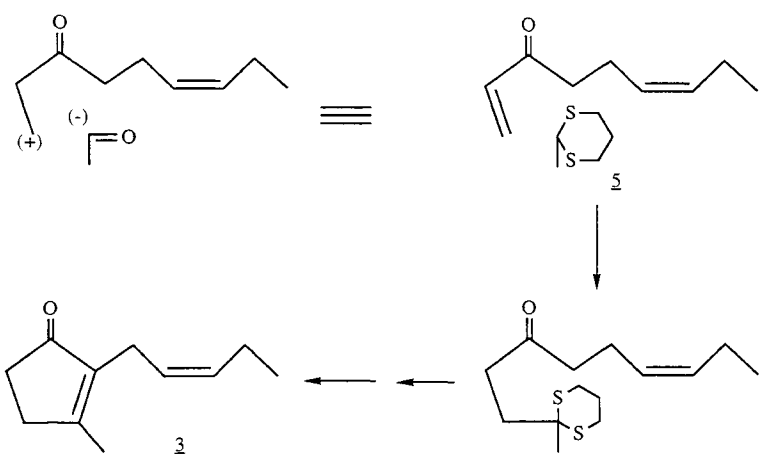
TABLE 5.2 (cont.)



By contrast, in "reversible reactivity inversion" the *umpoled* synthon is generated from the same synthon in which reactivity is to be inverted. For this, the functional group of type E is transformed into, or "masked" as, one of type A, then the resulting compound is coupled with the corresponding fragment to form a new carbon-carbon bond, and finally the functional group is "unmasked" to give the original one. For instance, for the synthesis of the dissonant 1,4-dicarbonyl system considered before (see Scheme 5.4), the acetaldehyde is transformed ("masked") into a thioacetal 5 which is treated with a strong base to generate the anion and condensed, under the appropriate conditions, with the α,β-unsaturated ketone and finally the thioacetal group is hydrolysed (or "unmasked") to give the same dissonant 1,4-dicarbonyl system.



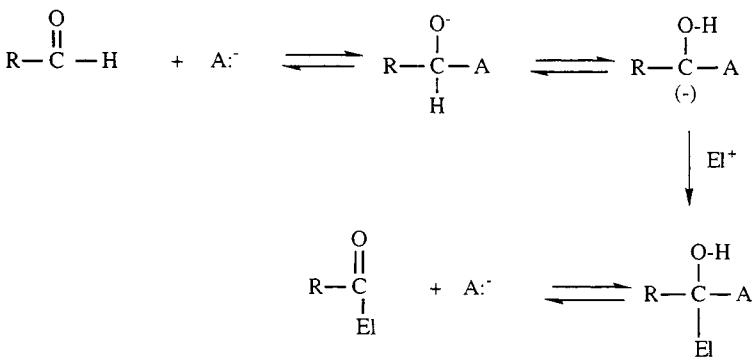
Scheme 5.3



Scheme 5.4

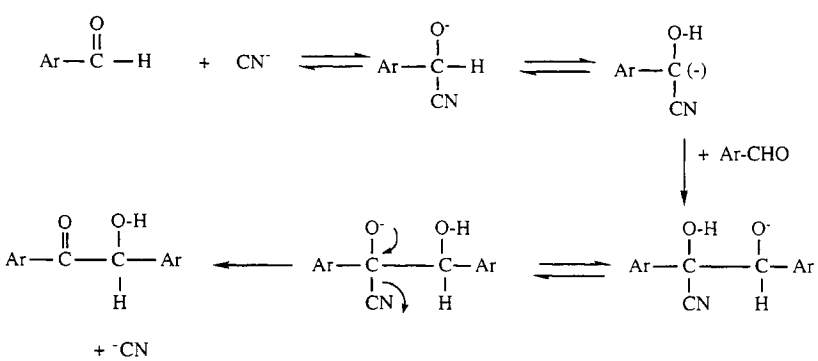
A variant of this last methodology, which constitutes the third type of approach, is the use of "inversion operators".

An "inversion operator", *in the most general sense, is any fragment, either organic or inorganic, which through a temporary binding with a functional group inverts temporarily the electrophilic or nucleophilic character of the corresponding* ipso-*carbon atom* (see Scheme 5.5). In fact, the "inversion operators" which are actually used in organic synthesis are nucleophiles, such as CN^-, R_3P:, and thiazolium salts, which readily react with carbonyl groups [6]:



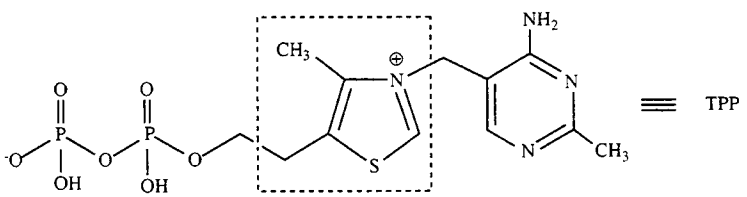
Scheme 5.5

Chemists were using cyanide ion for the synthesis of 1,2-D systems even before the concept of "reactivity inversion" was formally established. Thus, in the classical benzoin condensation, the cyanide-induced coupling of two aromatic aldehydes takes place according to the following mechanism [7] (Scheme 5.6):



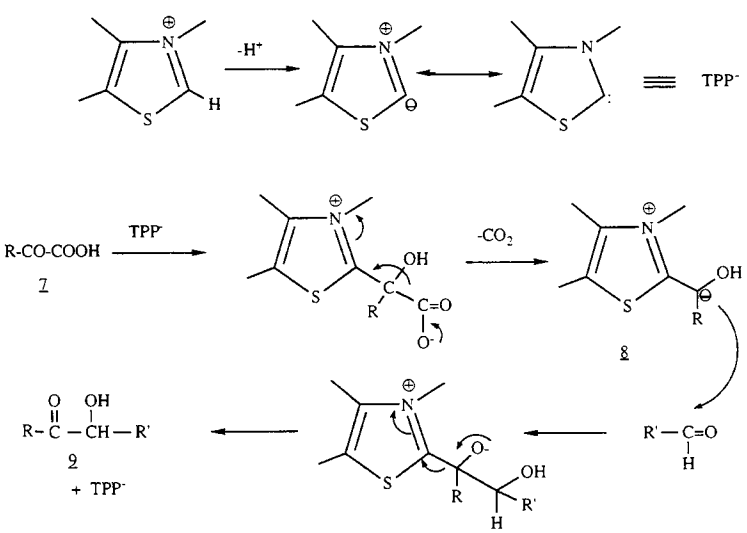
Scheme 5.6

However, cyanide ion is not suitable for inducing a benzoin-type condensation between two aliphatic aldehydes, since the basic character of this ion induces an aldol condensation between them. In Nature, nevertheless, condensations of this type take place easily. As Breslow proposed in 1958 [8], such condensations are catalysed by thiamine pyrophosphate 6 (or *cocarboxylase*), the active part of which is the conjugate base of the "thiazolium cation" present in it. According to Breslow [8a], the mechanism is, in fact, identical to that described for the cyanide ion (see Scheme 5.7); that is to say, the conjugate base of thiamine (TPP^-) reacts with an "aldehyde equivalent" -such as an α-ketoacid 7- to generate the corresponding "active aldehyde" 8 with *umpoled* reactivity, which then reacts with the electrophile to give finally, after elimination of "thiamine anion", a 1,2-D system (9).



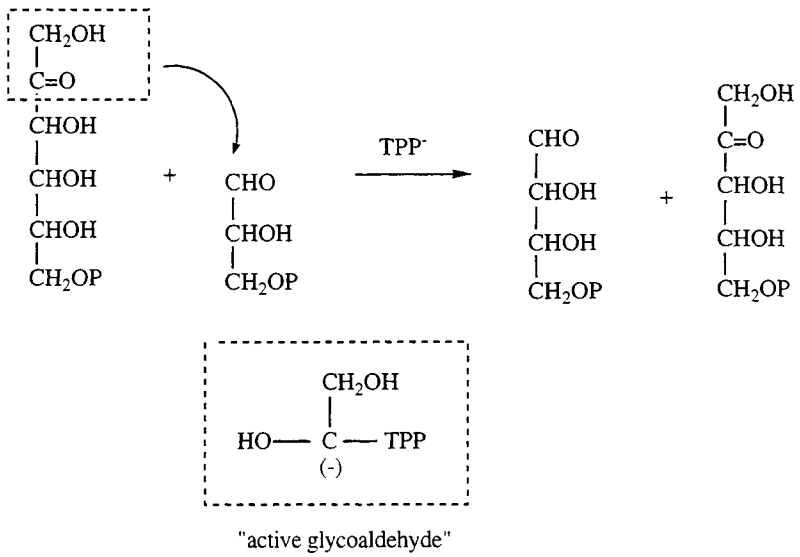
6

Thiamine pyrophosphate



Scheme 5.7

In the well known "transketolase reaction" [9] for instance, the transfer of the fragment $HOCH_2$-C=O from a hexose to a triose takes place via the "active glycoaldehyde" (Scheme 5.8):



Scheme 5.8

In fact, reactions of "active aldehydes" with *umpoled* reactivity are so common in Nature that some redundancy is observed [10].[12] Thus, the acetylation of CoA (12 ⟶ 13) takes place through the "active acetaldehyde" 10 which owing to its *umpoled* reactivity must react first with lipoic acid (11) -which plays the role of an "inversion operator"- in order to recover its natural electrophilic reactivity , as shown in Scheme 5.9.

In the past few years, thiazolium salts have also been used in the laboratory to induce benzoin condensations between aliphatic aldehydes [11].

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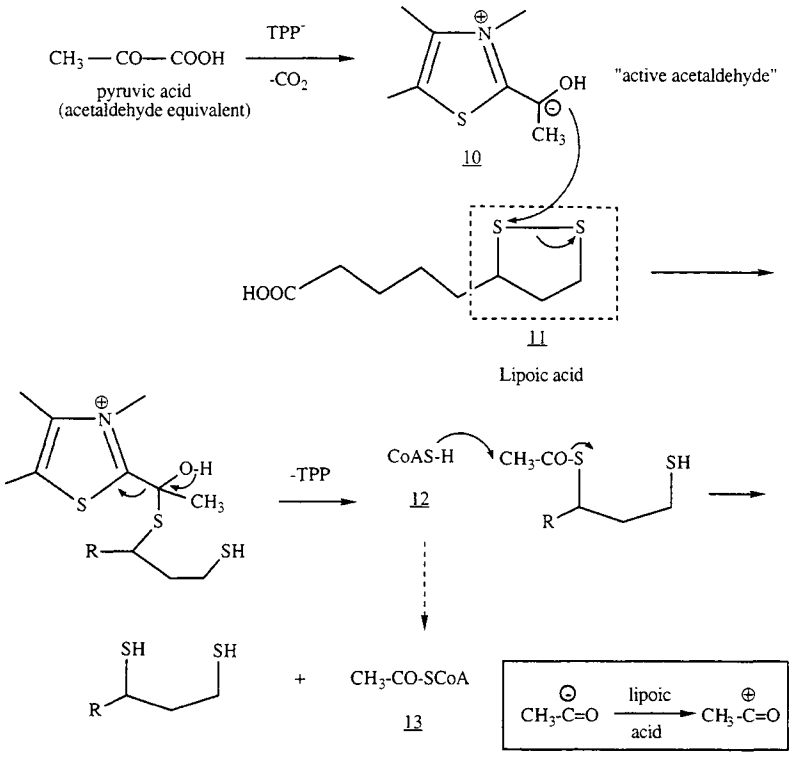
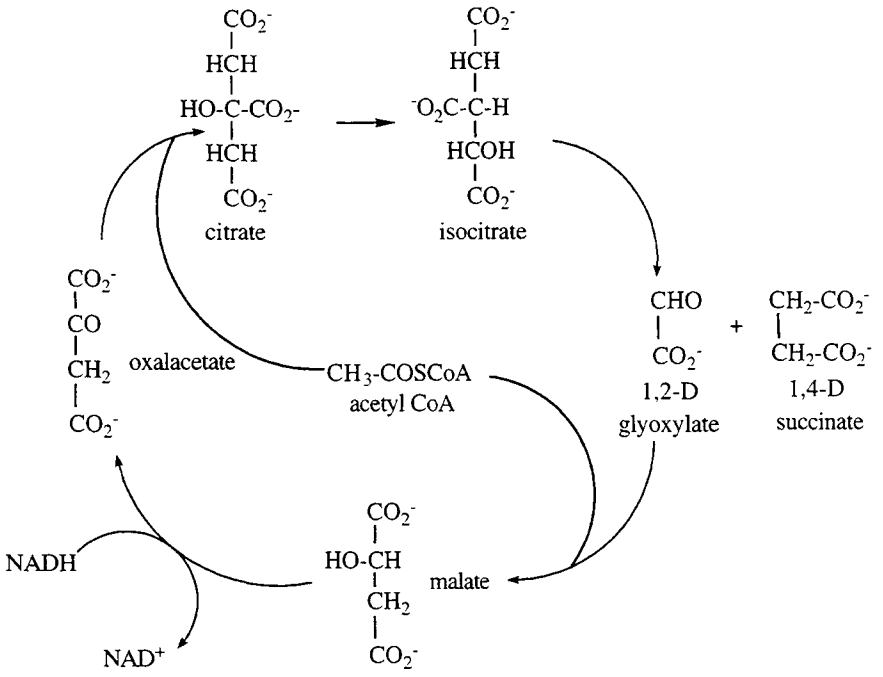
[12] In this context, the following statement by S. Turner could be mentioned: "Perhaps we shall eventually learn that Nature has its own difficulties".



Scheme 5.9

D.A. Evans [6] has also drawn attention to another strategy used in Nature for the synthesis of 1,4-D systems such as succinic acid. Succinic acid esters can be synthesised, for instance, by the oxidative coupling of two molecules of acetic acid ester, which requires the transfer of electrons (see below *5.5*). In Nature, however, the synthetic problem has been solved in a much more elegant manner by a process which does not involve high energy radical intermediates. Diagram 5.2 shows the "glyoxylate cycle", which is a modification of the "citric acid cycle". When acetate must be used not only as a source of energy but also as the basic building block for the synthesis of the main cellular components (which happens in some microorganisms, such as *E. choli*, *Pseudomonas* and algae, as well as in higher plants), then the citric acid cycle is modified giving rise to the "glyoxylate cycle" [9].



Reaction: $2CH_3COOH \longrightarrow HO_2C\text{-}CH_2CH_2\text{-}CO_2H$

Glyoxylate cycle
Diagram 5.2

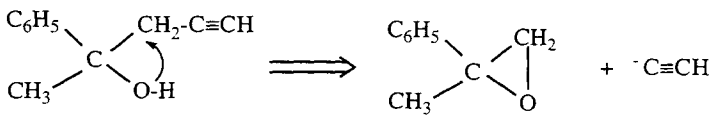
Acetyl-CoA is combined with oxaloacetate to give finally isocitrate. Degradation of isocitrate, however, does not occur through the usual *isocitratase-dehydrogenase* catalysed reaction leading to oxalosuccinate, but via an *isocitratase* catalysed retro-aldol reaction which gives a molecule of succinate and a molecule of glyoxylate. The glyoxylate enters the cycle again and is condensed with another molecule of acetyl-CoA to afford malate through a reaction catalysed by *malate-synthetase*. The malate is oxidised then to oxaloacetate which will condense again with another molecule of acetyl-CoA. Therefore, at every turn of the cycle two molecules of acetyl-CoA are incorporated, a molecule of succinate is formed -which will be then used for biosynthetic purposes-, and two hydrogen atoms are transferred from the malate to the oxygen through the respiratory chain which induces the oxidative phosphorylation of ADP to ATP. In this way, the "glyoxylate

cycle" supplies energy and a four-carbon atom intermediate for the synthetic transformations of the cell. The overall result is that Nature synthesises a 1,4-D system, such as succinate, using a 1,2-D system (glyoxylate) which plays the role of an "operator" or, even better, a "dissonant template".

5.2. Plausible disconnections: dissonant three-membered rings

In contrast to "illogical disconnections", in "plausible disconnections" a reasonable or, at least, plausible mechanism exists which involves the motion of electron pairs and leads to stable fragments, either ions or molecules. In any case, however, the "principle of maximum simplicity" does not hold here, since one of the resulting fragments is always a dissonant three-membered ring.

In connection with monofunctionalised molecules we have already referred to a "plausible disconnection" according to which an alcohol can be directly "disconnected" at the α-position, in such a manner that an epoxide rather than a carbonyl compound results, as for example in the case of the tertiary alcohol 14:

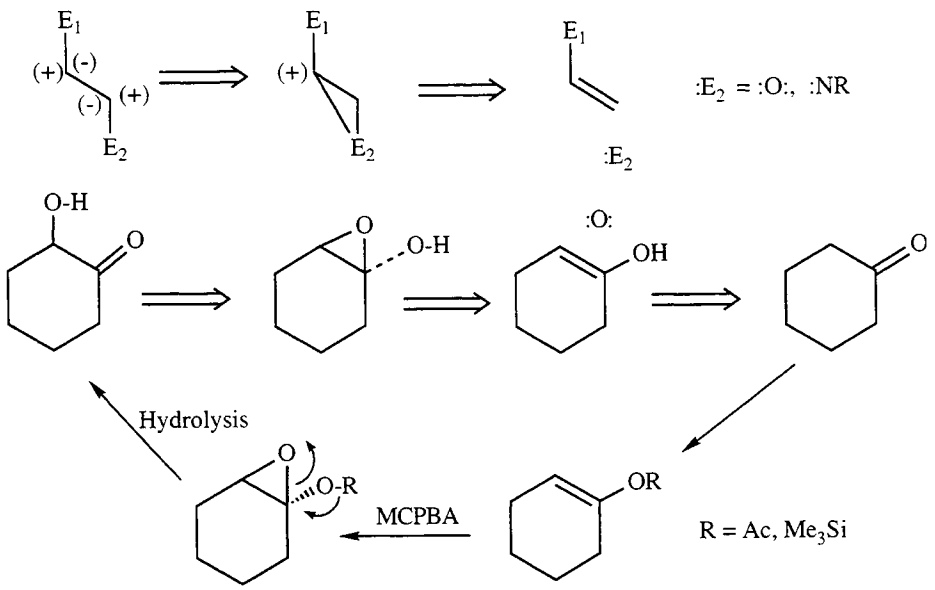


14

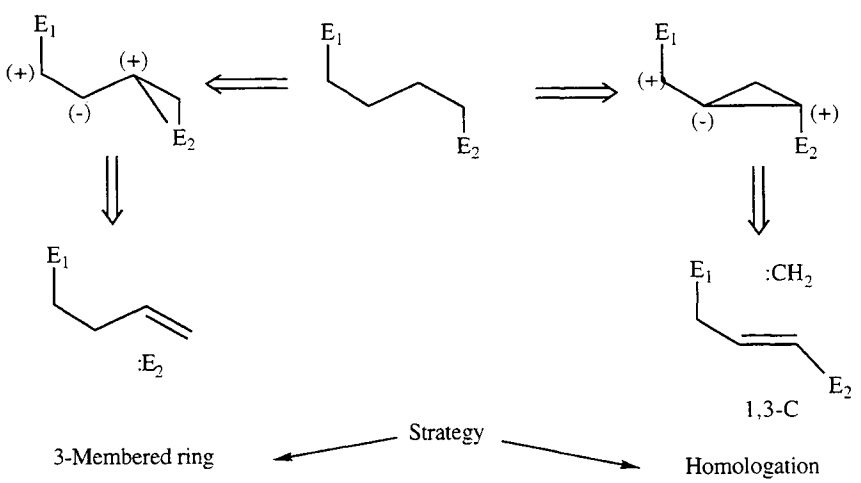
Since the difficulty in designing syntheses of dissonant molecules lies in the impossibility of assigning alternating polarities to the even number of carbon atoms present in the molecular skeleton, a way of solving the problem is to by-pass one of the carbon atoms [12] by creating a single bond between two atoms (whether carbon atoms or heteroatoms), which are in a 1,3-relationship, and proceeding then to a cheletropic cycloelimination [-(2 + 1)]. As usual in the context of synthesis design, the adjustment of the oxidation level of the heteroatom, or even of the carbon chain itself, may be a requirement prior to effecting the "plausible disconnection".

Let us consider separately the 1,2-D, 1,4-D and 1,6-D systems, though the methodology is of little interest for the 1,6-D systems which are more easily accesible either through sigmatropic rearrangements or by the cleavage of consonant 6-membered rings (see below *Headings 5.3* and *5.4*)

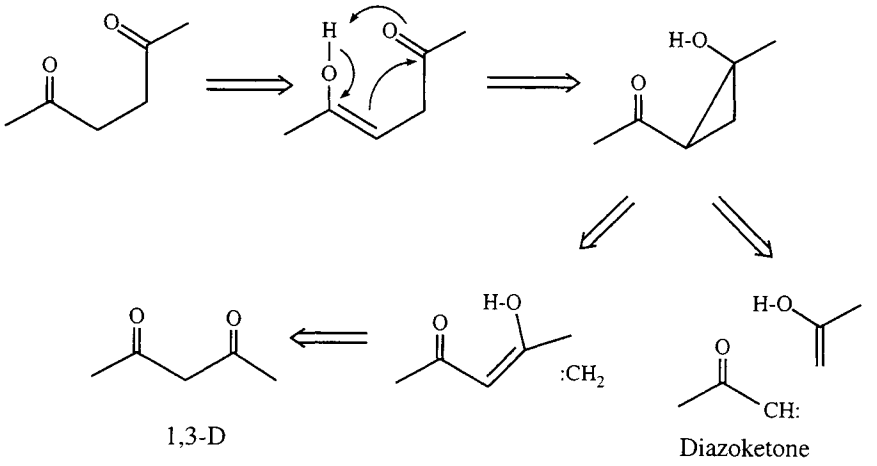
1,2-D:


E1
(+)
(-)
(-)
(+)
E2
:E2 = :O:, :NR
:E2
O-H
O
:O:
OH
Hydrolysis
O-R
MCPBA
OR
R = Ac, Me3Si

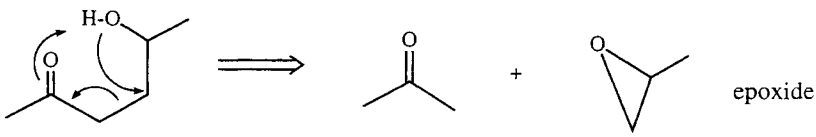
1,4-D:


E1
(+)
(+)
(-)
E2
:E2
:CH2
1,3-C
Strategy
3-Membered ring
Homologation

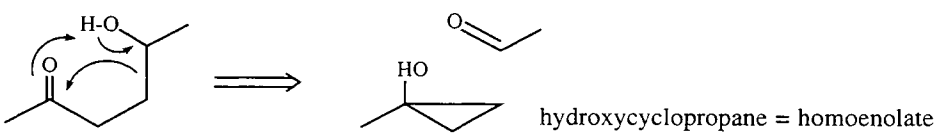
i)


O
O
H
O
O
H-O
O
H-O
O
:CH2
O
O
1,3-D
H-O
O
CH:
Diazoketone

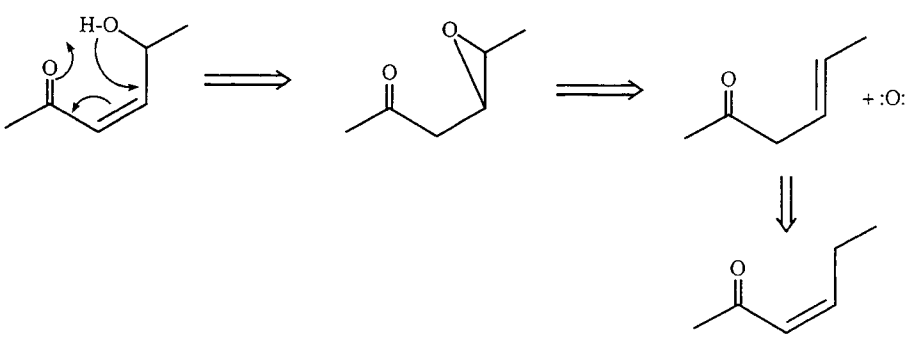
ii)


H-O
O
O
+
O
epoxide

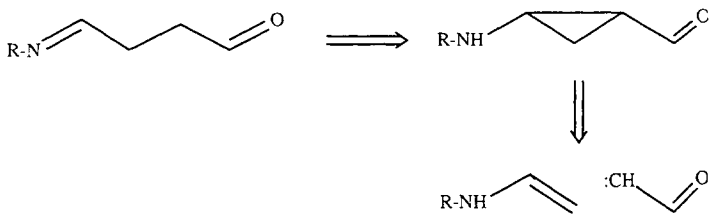
iii)


H-O
O
O
HO
hydroxycyclopropane = homoenolate

iv)

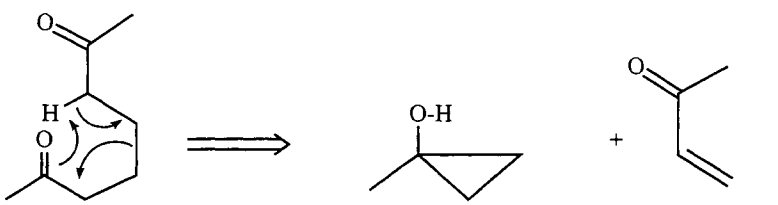

H-O
O
O
O
O
+ :O:
O

v) The same strategy, involving γ-imino carbonyl compounds, has also been applied by Wenkert [12b] to the synthesis of eburnamonine and dehydroaspidospermidine:



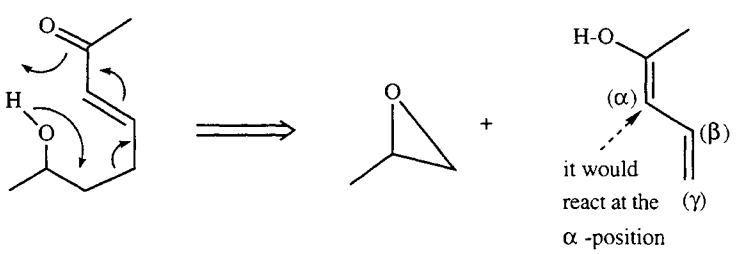
1,6-D: Similarly, examples related to 1,6-dissonant systems are,

i)

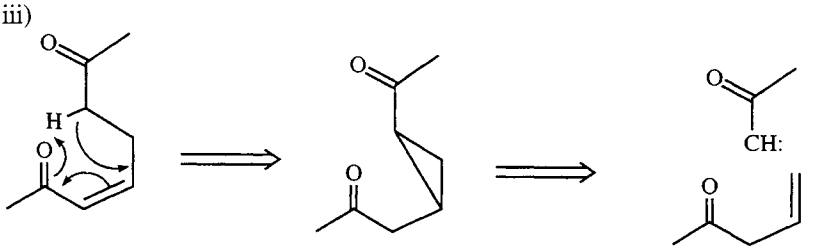


"hydroxycyclopropane ≡ homoenolate" (see text)

ii)



iii)



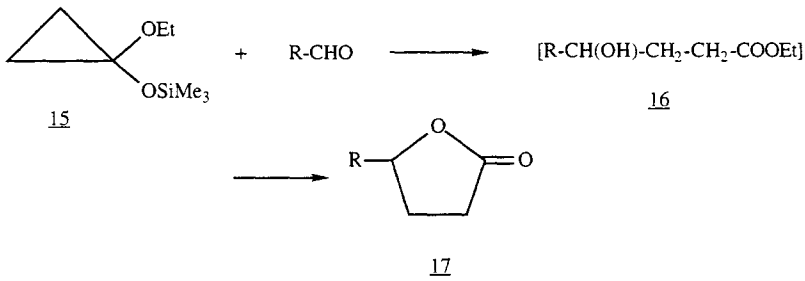
Notice that a 1,4-D system which contains a carbonyl group and a hydroxyl group can be considered, at least formally, as a "homoaldol", in such a way that its synthesis may be visualised as the reaction of a "homoenolate" (or the equivalent hydroxycyclopropane derivative) with a carbonyl compound (reaction iii) or, alternatively, as the reaction of an enolate with an epoxide (which might be considered, in a purely formal sense, as a "homocarbonyl" functional group) (reaction ii). Although the "homoenolate problem" affects all the methodologies which involve "reactivity inversion" [13], we will deal here only with "homoenolates" generated from hydroxycyclopropanes since it is, in principle, the most direct and elegant entry into them. All the other cases are in fact further examples of "equivalent" or *umpoled* synthons as have been dealt with in the section on "illogical disconnections" (see Table 5.2). However, hydroxycyclopropanes are useful precursors of "homoenolate" ions only:

i) if the alcohols are sufficiently stable to be easily prepared and handled, and

ii) if the "homoenolates" can be generated under strictly neutral conditions and also that electron-withdrawing groups which can stabilise the negative charge are present.

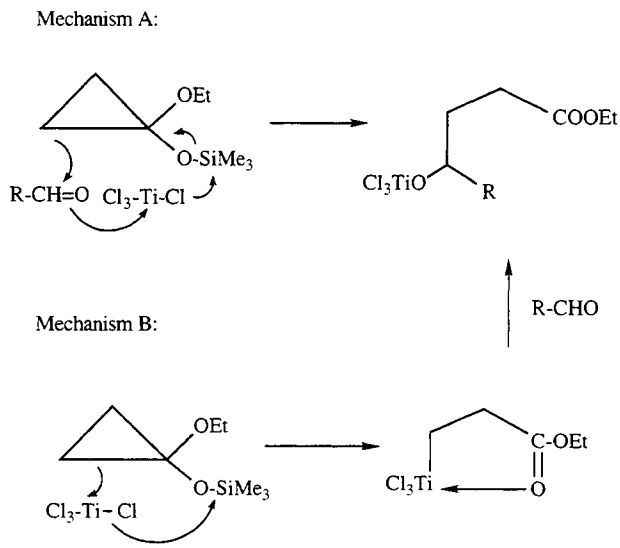
DePuy, as early as 1966 [14], reported that *cis*-1-methyl-2-phenylcyclopropanol gave exclusively deuterated 4-phenyl-2-butenone in 0.1 M $NaOD/D_2O$/dioxane. However, homoenolates derived from simple cyclopropanols by base-induced proton abstraction fail to react with electrophiles such as aldehydes and ketones, which would afford directly 1,4-D systems. Lack of a reasonably general preparative method was another factor which impeded the studies of homoenolate chemistry. For this reason, in the past twenty years more elaborated cyclopropanols, which might be suitable precursors of "homoenolates", have been prepared and studied.

For example, Nakamura and Kuwajima [15] have described 1-alkoxy-1-trimethylsilyloxycyclopropanes (15) -prepared by reductive silylation of alkoxy 3-chloropropanoates-, which react with aliphatic aldehydes, but not with ketones, in the presence of one equivalent of $TiCl_4$ to give good yields of γ-lactones 17 through the acyclic derivative ethyl 4-hydroxybutanoate (16) (Scheme 5.10). With aromatic aldehydes and their acetals the reaction leads directly to acyclic 1,4-D derivatives.



Scheme 5.10

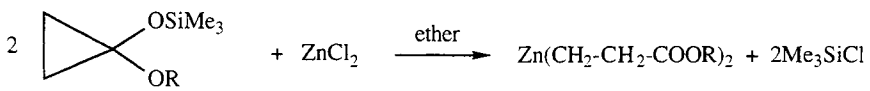
Although two possible mechanisms are conceivable (A and B) , the authors have been able to isolate trichlorotitanium homoenolates as intermediates, indicating that the second one is really operating (Scheme 5.11).



Scheme 5.11

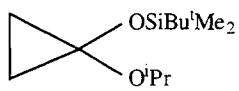
In practice, the original method had its limitations since one equivalent of $TiCl_4$ had to be used and usually led to the cyclic derivatives. Nonetheless, more recently it has been found that "homoenolate esters" actually exist if the appropriate metal, $ZnCl_2$ for example, is used [16], which reacts with carbonyl derivatives in the presence of one equivalent of Me_3SiCl to give 1,4-D systems by means of a "homo-

Reformatsky" reaction. Since $ZnCl_2$ is regenerated in the Me_3SiCl-mediated addition (see Scheme 5.12), a catalytic amount of $ZnCl_2$ makes possible the direct coupling of cyclopropanes 15 with aldehydes. ZnI_2 was then found to be even more effective than $ZnCl_2$, and as little as 1/1000 equivalent of ZnI_2 allowed direct coupling of cyclopropane 15 with aldehydes at room temperature (see Table 5.3). ZnI_2, but not $ZnCl_2$, promotes the addition of cyclopropane 15c to aldehydes, as well as to acetophenone and benzaldehyde dimethylacetal.



15

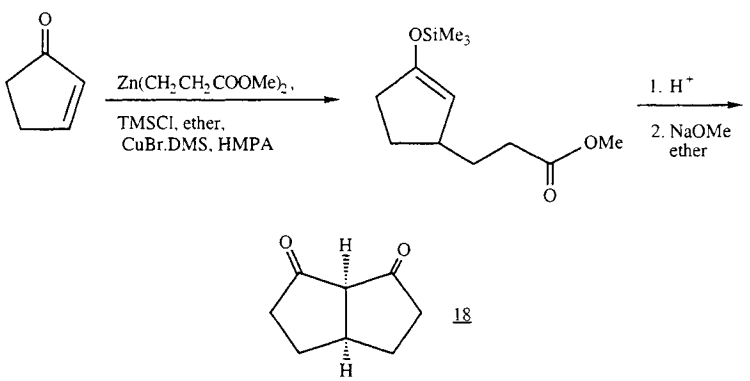
a: R = ^{i}Pr
b: R = Et
c:



Scheme 5.12

The zinc homoenolates from cyclopropanes 15 react in the presence of Me_3SiCl/HMPA with α,β-unsaturated ketones to give good yields of 1,6-D systems, by a copper-mediated (CuBr-Me_2S) Michael-type addition (Table 5.4).

The homoenolate conjugate addition has been used very recently by Paquette and Cheney [17] to synthesise the key diquinane intermediate 18 in their studies directed towards the total synthesis of trixikingolide (Scheme 5.13).



18

Scheme 5.13

TABLE 5.3. Catalytic homo-Reformatsky reaction

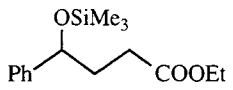
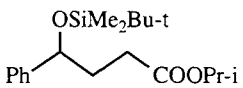
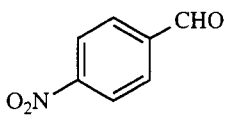
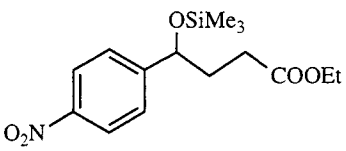
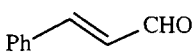
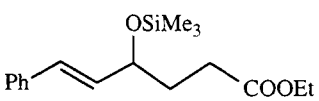
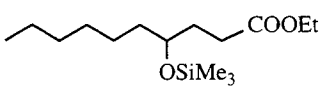
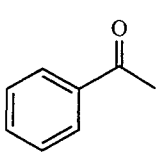
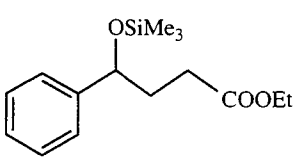
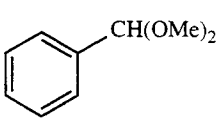
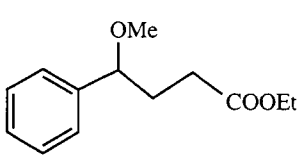
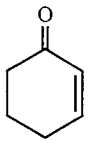
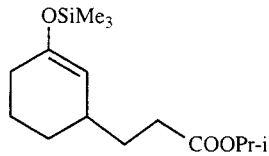
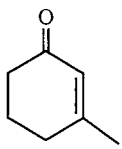
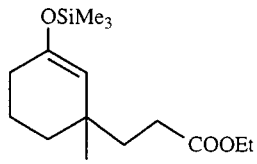
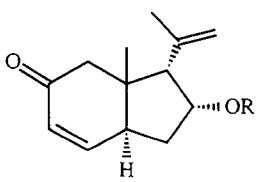
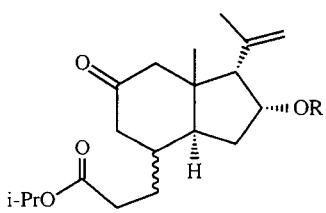
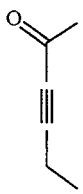
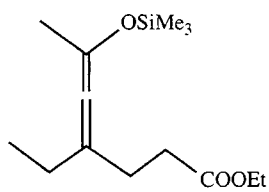
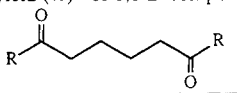
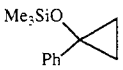
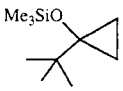
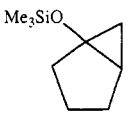
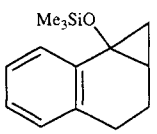
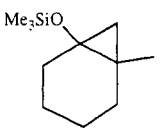
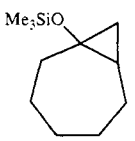
carbonyl compound	cyclopropane	product	catalyst, % yield $ZnCl_2$	ZnI_2
PhCHO	15b		84	89
PhCHO	15c		0	86
	15b		--	84
	15b		94	84
$CH_3(CH_2)_5CHO$	15b		51	44
	15b		0	77
	15b		0	91

TABLE 5.4. Conjugate addition of homoenolates

Enone	cyclopropane	product	% yield
	15a		93%
	15b		92%
 R = Me_3Si, Ac, MOM	15a		85-95%
	15b		73%

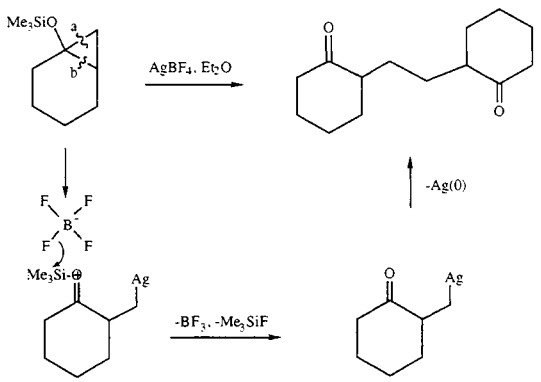
Symmetrical dissonant 1,6-dicarbonyl compounds (see Table 5.5) can also be prepared in good yields by either $Cu(BF_4)_2$ or $AgBF_4$-induced coupling of trimethylsilyloxycyclopropanes in ether solution at room temperature (Scheme 5.14)[18].

TABLE 5.5. 1,6-Dissonant dicarbonyl compounds from silyloxycyclopropanes

Siloxycyclo-propane	reagent	yield (%)* of 1,6-D compound 
	$AgBF_4$	42
	$Cu(BF_4)_2$	78
	$Cu(BF_4)_2$	68
	$AgBF_4$	68
	$Cu(BF_4)_2$	77
	$AgBF_4$	70
	$Cu(BF_4)_2$	87, <u>80</u>
	$AgBF_4$	<u>68</u>
	$Cu(BF_4)_2$	<u>74</u>
	$Cu(BF_4)_2$	69
	$Cu(BF_4)_2$	<u>70</u>

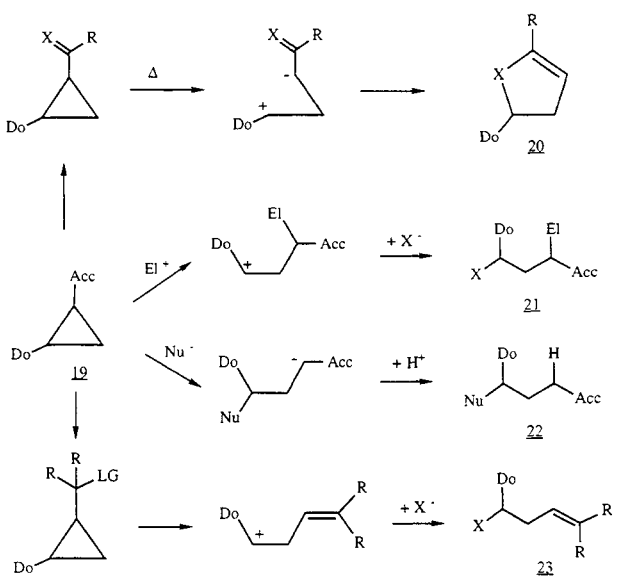
* Isolated yields are underlined

The cleavage of the cyclopropane ring takes place with siteselectivity at the less hindered bond *a* as shown in Scheme 5.14, and no product arising from cleavage of bond *b* is obtained.



Scheme 5.14

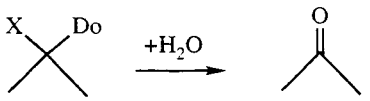
Of great interest are the "donor-acceptor-substituted cyclopropanes" 19, such as 2-silyloxycyclopropanecarboxylic esters (19a), first reported by Reissig [19b] and then also studied independently by Marino [20]. The general reactivity pattern of cyclopropanes 19 is outlined in Scheme 5.15 [19a].



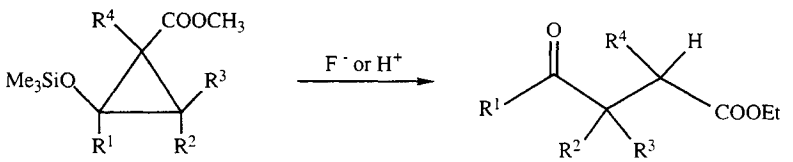
Do = Donor = RO, RS, R_2N....
Acc = Acceptor = COOR....
LG = Leaving group

Scheme 5.15

However, the isolated compounds usually do not have the structures 20-23, since the structure of the product depends upon the experimental conditions. Thus, in protic media very often carbonyl compounds are obtained according to the hydrolytic cleavage:



From the point of view of the synthesis of dissonant systems the most important finding reported by Reissig [19c] is the opening of cyclopropanes 19a by fluoride ion-induced desilylation to give carboxylic ester stabilised "homoenolate" anions, from which a series of 4-oxoalkanoic esters (21a), with a 1,4-D relationship, were prepared (Table 5.6):



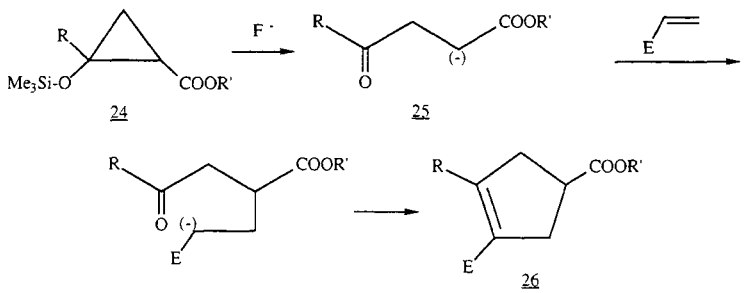
19a 21a

TABLE 5.6. Synthesis of 4-oxoalkanoic esters 21a via homoenolate (with NEt_3. 2HF)

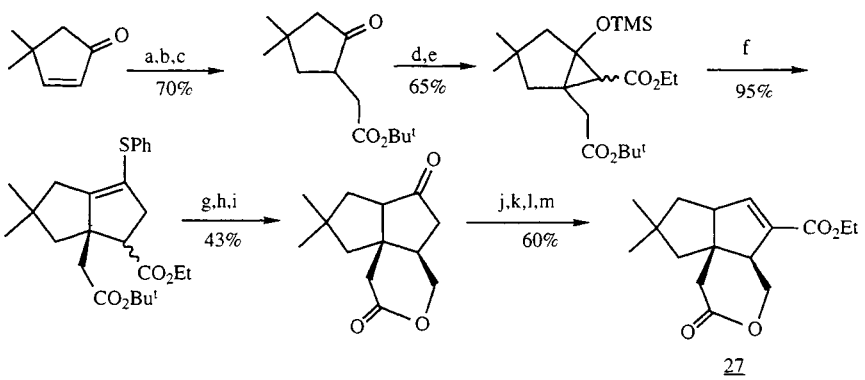
R^1	R^2	R^3	R^4	%Yield
H	H	H	H	63
Me	H	H	Me	81
Me	H	H	n-Bu	98
i-Pr	H	H	H	89
t-Bu	H	H	Me	90
CH_2=CH	H	H	Me	70
Ph	H	H	Me	99
-[CH_2]$_{3-5}$-		H	H	84-97
-[CH_2]$_4$-		$OSiMe_3$	H	(98)

It is worthwhile remembering here that the fluoride ion-induced desilylation fails in the cases of simple silyloxycyclopropanes.

Marino and his coworkers [20a], on the other hand, studied the fluoride ion-induced desilylation of ethyl 2-silyloxycyclopanecarboxylates 24; and the resulting "homoenolate" anion 25 was allowed to react with different electrophiles, such as Michael acceptors, to give dissonant cyclopentene rings (26) via a [3 + 2] annulation strategy (Scheme 5.16).



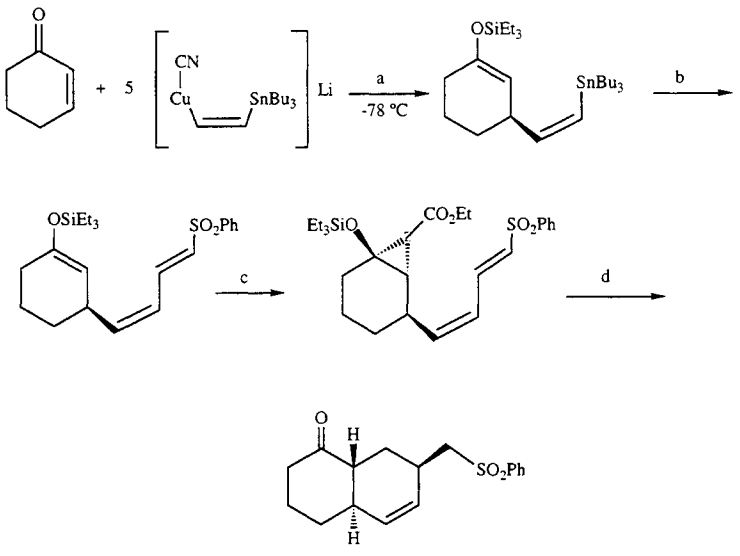
Scheme 5.16.



a) Et_3SiH, $RhCl(PPh_3)_3$, PhH (regiospecific reductive enol silylation); b) (2.5 equiv.) $N_2CHCO_2Bu^t$, $CuSO_4$, PhH; c) Et_3NHF, THF, 25 °C; d) Me_3SiCl, Et_3N, DMF, 135 °C; e) 4 equiv. of N_2CHCO_2Et, $CuSO_4$, PhH; f) (2 equiv.) [α-(phenylthio)vinyl]triphenylphosphonium tetrafluoroborate, (5 equiv.) KF, (0.1 equiv.) 18-crown-6, CH_3CN, 82 °C; g) $NaOH/H_2O$, MeOH, THF, 60 °C; h) $ClCO_2Me$, THF; $NaBH_4$, THF/H_2O, r. t.; i) TFA, $CHCl_3$; j) C_4H_9N, *p*-TsOH, PhH, 80 °C; k) (10 equiv.) $ClCO_2Me$, PhH, 80 °C; l) (3 equiv.) $NaCNBH_3$, MeOH, HCl, r. t.; m) (1.1 equiv.) MCPBA, CH_2Cl_2, K_2CO_3, THF, r. t.

Scheme 5.17

This strategy [20b] has been applied, for instance, in a total synthesis of pentalenolactone E methyl ester (27) (Scheme 5.17), and more recently Marino and Long [20c] have described the intramolecular version of this annulation procedure to synthesise an octahydronaphthalene derivative (28) which is a key intermediate for a new synthesis of dihydrocompactin (Scheme 5.18). However, the reaction with aldehydes affords only very low yields of a mixture of lactones.

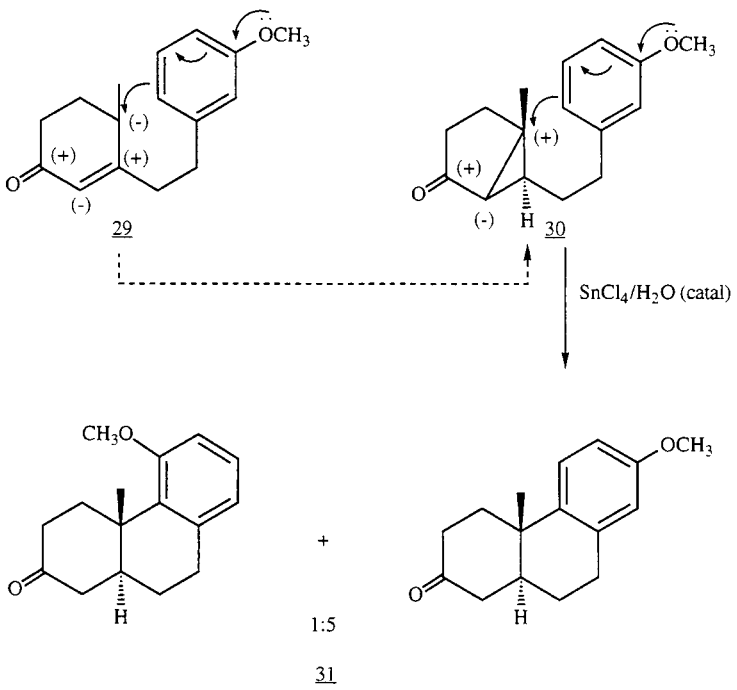


28

a) 5 equiv. of Et_3SiCl, 6 equiv. Et_3N, THF, -78 °C to 0 °C; b) 1 equiv. of *trans*-$PhSO_2CH{=}CHOTs$, 2-3 mol% $PdCl_2(PPh_3)_3$, 6-10 mol% CuI, 3 equiv. LiCl, THF, 67 °C; c) N_2CHCO_2Et, 2M soln. in PhH, 0.5 mol% bis(*N*-benzylsalicylaldiminato)copper(II), 85 °C; d) 5 equiv. of CsF, CH_3CN, 80 °C.

Scheme 5.18

A classical application of cyclopropane rings in "reactivity inversion", in which a previously negatively polarised γ-carbon atom (see 29) to a carbonyl group is inverted by formation of a cyclopropane ring (30) and is then intramolecularly attacked by a nucleophilic aromatic ring, is found in the synthesis of hydrophenanthrene system 31 (Scheme 5.19) developed by Stork in 1969 [21].



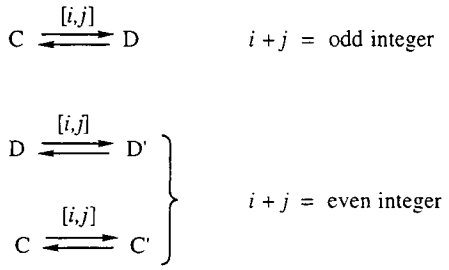
Scheme 5.19

5.3. Sigmatropic rearrangements

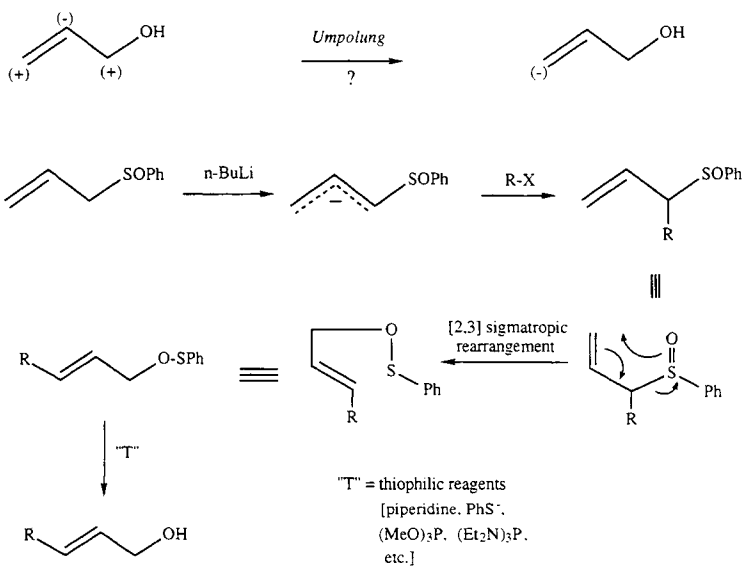
The synthetic applications of sigmatropic rearrangements to the synthesis of dissonant molecules (mainly 1,6-D) were extensively studied by Evans [22]. Although such a methodology meets the first two requirements of "logical disconnections", it does not meet the third one since it lacks simplicity.

A sigmatropic rearrangement "is said to be of order [*i,j*] when a σ bond, flanked by one or more π electron systems, migrates to a new position whose termini are *i*-1 and *j*-1 removed from the original bonded loci, in an uncatalysed intramolecular process" [23]. Thus the well known Claisen and Cope rearrangements, for example, are sigmatropic rearrangements of the order [3,3].

Besides the selection rules, which are based on the conservation of orbital symmetry, for sigmatropic rearrangements of order [*i,j*] it is possible to demonstrate that the following correlations will always apply:

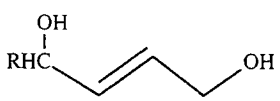


An example of a [2,3]-sigmatropic rearrangement involving an allyl sulphoxide was studied by Evans and Andrews in 1974 [22] (Scheme 5.20):



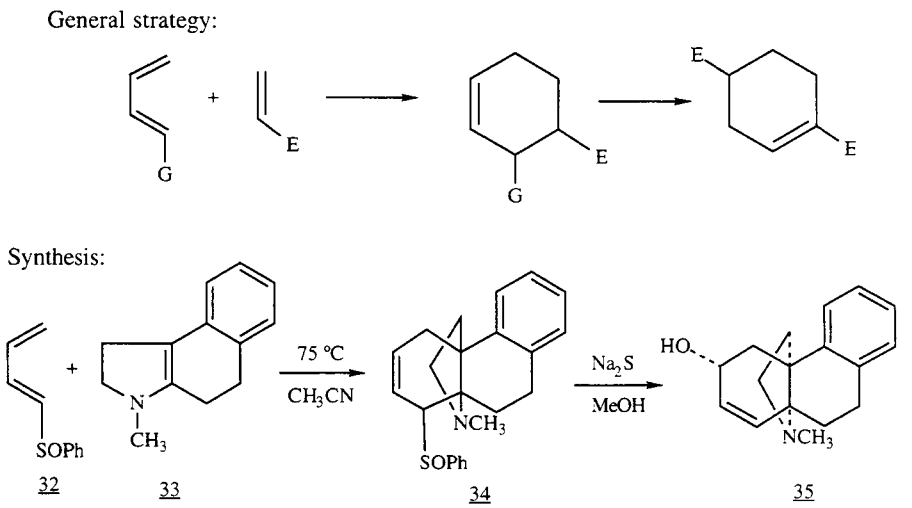
Scheme 5.20

Notice that the final result is a 1,3 charge affinity inversion (*Umpolung*) of an allylic derivative via a FGI of a functional group of type E by a group of type A, followed by a [2,3]-sigmatropic rearrangement. If the intermediate allyl anion reacts with a carbonyl compound as the electrophile the result is then a 1,4-D system, such as:



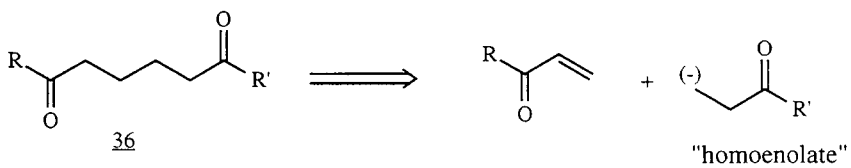
1,4-D

Another application of this strategy is the construction of cyclic systems bearing 1,4-dissonant relationships. For example, the synthesis of the hasubanan alkaloid ring system 35, reported in 1972 by Evans [24], involves the Diels-Alder cycloaddition of a dienyl sulphoxide 32 with an endocyclic enamine 33, followed by a [2,3]-sigmatropic rearrangement of the resulting cycloadduct 34 (Scheme 5.21).

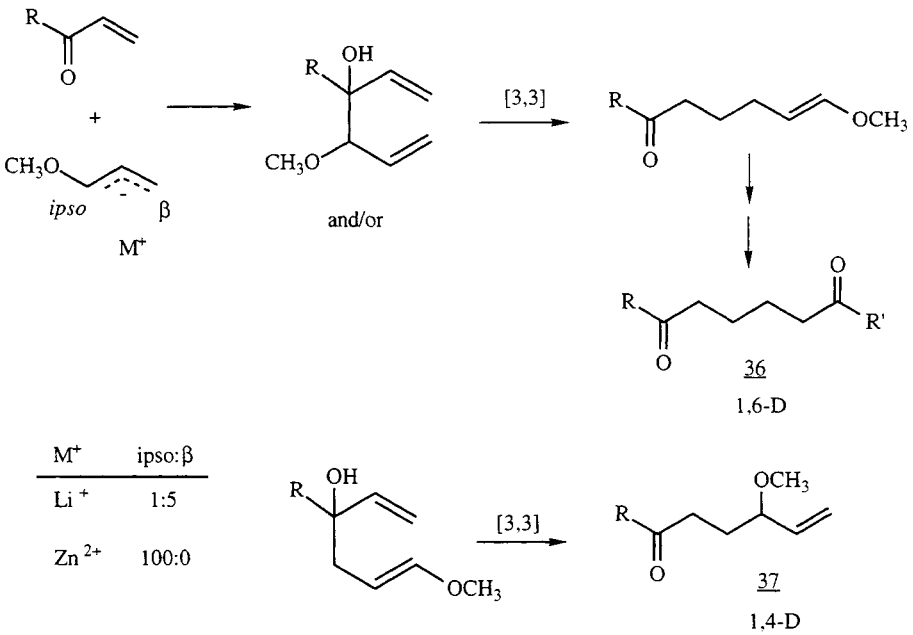


Scheme 5.21

Let us now consider a dissonant 1,6-dicarbonyl system, which provides a good example of a [3,3]-sigmatropic rearrangement. The "illogical disconnection" would lead to an α,β-unsaturated ketone and a "homoenolate" anion:

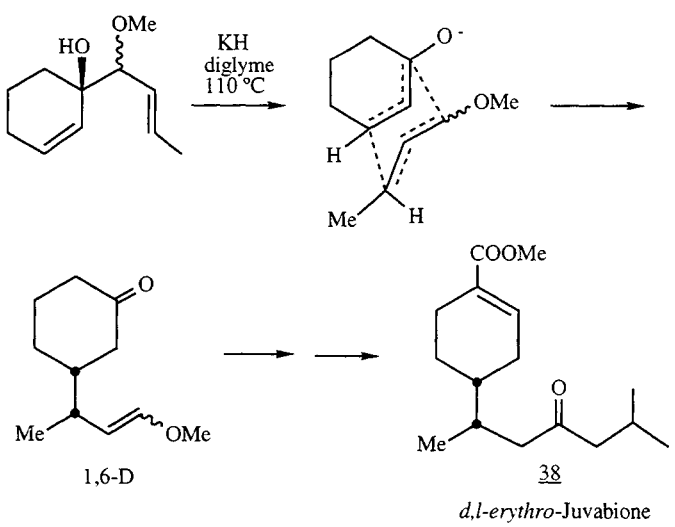


In the solution proposed by Evans [25], however, the unsaturated ketone is condensed with the anion of an alkyl allyl ether, followed by a [3,3]-sigmatropic oxy-Cope type rearrangement (Scheme 5.22). In the retrosynthetic sense this means a [3,3]-sigmatropic rearrangement of the bis-enol form of the 1,6-dicarbonyl system.



Scheme 5.22

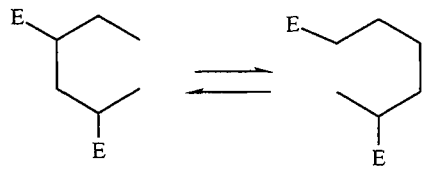
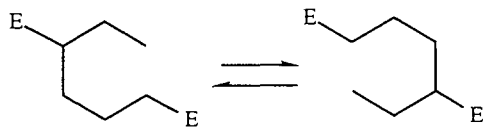
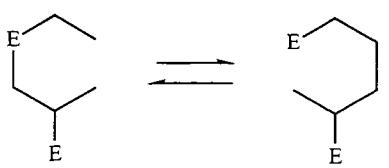
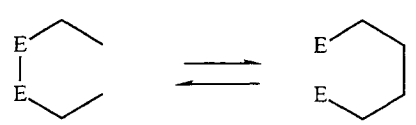
Another example of a synthesis of a 1,6-D system is found in the key step of the synthesis of juvabione (38), also by Evans [26], which proceeds through a base catalysed [3,3]-sigmatropic oxy-Cope rearrangement (Scheme 5.23).



Scheme 5.23

Table 5.7 summarises the different possibilities for [3,3]-sigmatropic rearrangements [25].

TABLE 5.7. [3,3]-Sigmatropic rearrangements

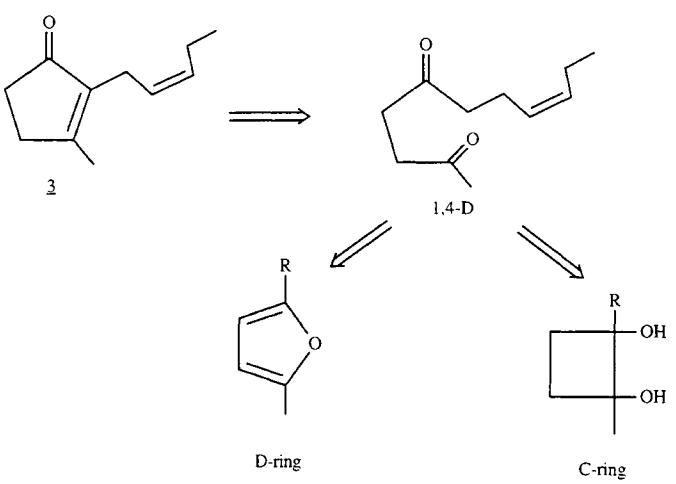
1,2-D		1,6-D
1,3-C		1,5-C
1,4-D		1,4-D
1,2-D		1,4-D
1,3-C		1,3-C
0,0-D		1,4-D

5.4. Reconnection of bifunctional dissonant systems to rings

A highly efficient strategy for designing synthesis of dissonant systems is related to HP-5, which refers to the reconnection of dissonant molecules to either consonant rings or dissonant heterocycles. As already mentioned in *Heading 4.2*, functional groups in 1,4- and 1,6-relationships can be reconnected to give 4-membered and 6-membered consonant rings, which in turn can be disconnected -either directly or after introducing a double bond- according to a conrotatory electrocyclic cyclobutane ring opening or to concerted pericyclic cycloeliminations of the type -[2+2] and -[4+2]. In the synthetic sense these processes correspond to the electrocyclic ring closure of a butadiene precursor (usually a not very favorable process), to the photochemical addition of two olefins and to the classical Diels-Alder cycloaddition, respectively, which are allowed by orbital symmetry, either in the excited or in the ground state.

This methodology, as in the cases of rearrangements and of plausible disconnections, does not meet the criterium of maximum simplicity, since the reconnection represents an increase of the "cyclic order" and therefore of the complexity of the molecule.

In fact a 1,4-dissonant system may be also reconnected to a dissonant 5-membered heterocycle. This solution is also valid when the heterocycle is an easily available starting material such as furan or furfural. For instance, syntheses of *cis*-jasmone (3) have been reported which follow retrosynthetic schemes shown in Scheme 5.24 [27]:



Scheme 5.24

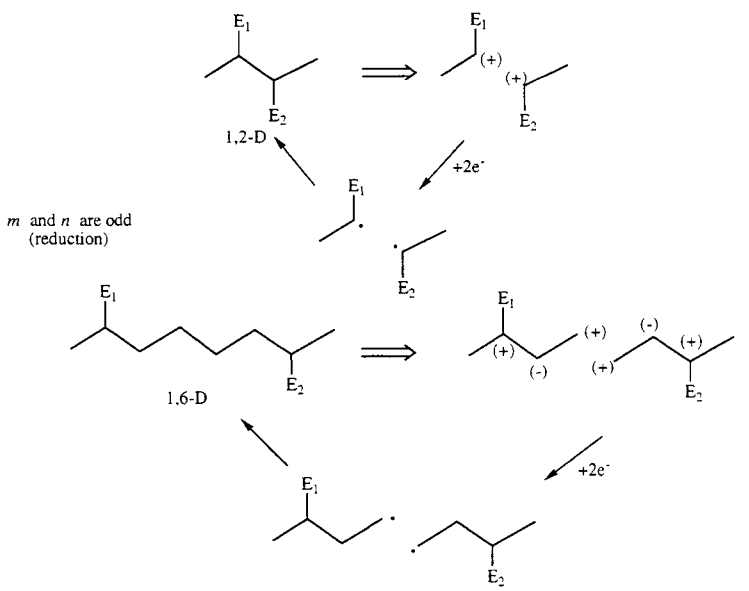
5.5 Homolytic disconnections: couplings involving electron-transfer

Since disconnection of any of the C-C bonds of a dissonant system leads to two fragments of identical reactivity (either nucleophilic or electrophilic), in the synthetic direction the reactivity of one of the two fragments must be inverted (see *5.1*, "illogical disconnections"). Another possibility, however, is to oxidise or to reduce the resulting fragments to radical species.

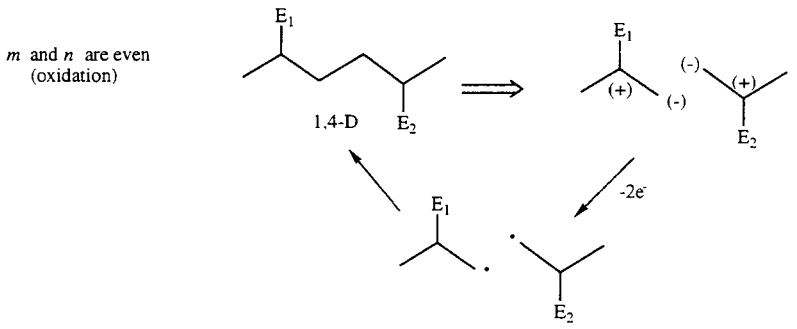
Let us suppose a dissonant molecule such as E_1-$(C)_q$-E_2 (where q is an even number) which is disconnected into two fragments

$$E_1\text{-}(C)_q\text{-}E_2 \Longrightarrow E_1\text{-}C_m + E_2\text{-}C_n$$

(where $m + n = q$). If m and n are both even, or alternatively if both are odd, then the removal (oxidation) or the addition (reduction), respectively, of two electrons will afford two radical fragments which may then dimerise to give the dissonant relationship. In such a case we are actually dealing with "homolytic disconnections". For example, considering the 1,2-, 1,4- and 1,6-D systems we will have:[13]



[13] We consider only symmetrical homolytic cleavages.

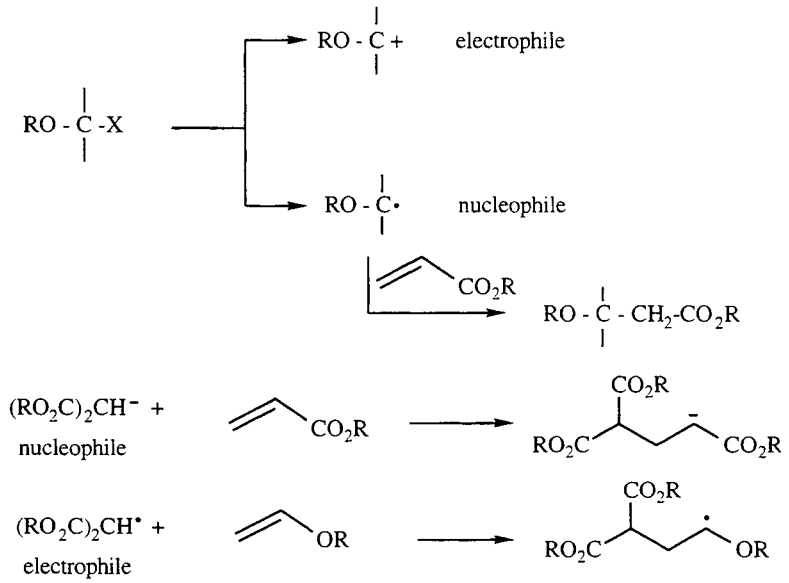


As classical examples we will consider the pinacol and acyloin condensations, the electrochemical reductive dimerisation of acrylonitrile and the oxidative coupling of enolates. However, the "homolytic disconnection" is nowadays a strategy which can be chosen provided that it meets the three abovementioned criteria required by "logical disconnections", that is to say: i) a reasonable mechanism exists (either a radical chain reaction or some other controlled radical generation method); ii) stabilised radicals which undergo highly selective reactions are generated and iii) the overall process represents a great simplification.[14]

On the other hand, radicals frequently behave as *umpoled* synthons of ionic species which lead to dissonant systems (Scheme 5.25). The generation of ions from α-haloethers, for instance, leads to cations because they are stabilised by the alkoxy substituents. These cations are, of course, electrophiles which add easily to electron rich alkenes like enolethers. The corresponding alkoxy alkyl radicals, however, are nucleophilic species which, because of their high lying SOMO, attack preferentially electron-poor alkenes like acrylonitrile or acrylic esters. Carbanions generated from malonates are nucleophiles which undergo Michael addition with electron-poor alkenes, and the corresponding radicals are, in contrast, electrophilic species which, because of their low lying SOMO, easily attack enolethers. The result is that, whereas the ionic species lead to 1,5-diheterosubstituted products, the radicals lead to the 1,4-diheterosubstituted analogues [28].

---

[14] A concise collection of some modern methods of radical formation via rupture of C-E, C-G and C-A bonds, as well as from alkenes and cyclopropanes, by metals, organometallic hydrides, and photochemical and electrochemical means, are given in the last Chapter of Giese's book [28]. For some examples of radical generation and reactions leading to cyclic and polycyclic compounds see next Chapter (*Heading 6.1.3*).



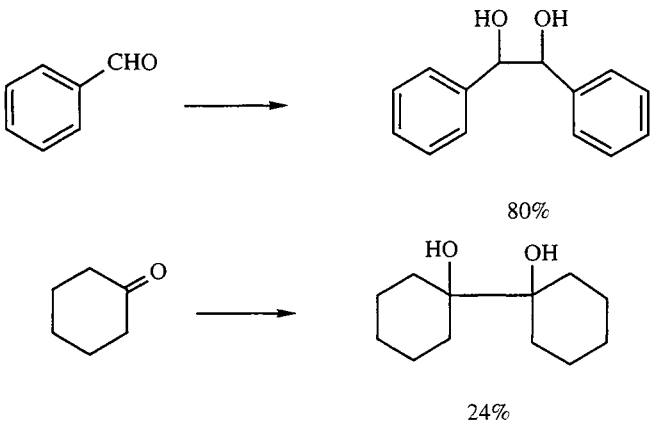
Scheme 5.25

5.5.1. Pinacol-type condensations

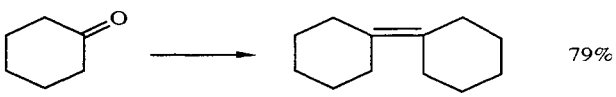
Probably the most familiar radical reactions leading to 1,2-D systems are the so-called "acyloin condensation" and the different variants of the "pinacol condensation". Both types of condensation involve an electron-transfer from a metal atom to a carbonyl compound (whether an ester or an aldehyde or a ketone) to give a "radical anion" which either dimerises directly, if the concentration of the species is very high, or more generally it reacts with the starting neutral carbonyl compound and then a second electron is transferred from the metal to the radical dimer species (for an alternative mechanism of the acyloin condensation, see Bloomfield, 1975 [29]).

Although in the classical "pinacol condensation" the metal usually used has been magnesium, in the last decade a great variety of alternative methods have been developed which use other reducing agents and which offer the advantage of being suitable for the condensation of ketones as well as aldehydes, either between themselves or in mixed or unsymmetrical couplings.

Thus, Mukaiyama [30] introduced the $TiCl_4$-Zn couple, which gives good results with aromatic aldehydes and ketones, but not with the corresponding aliphatic derivatives:



McMurry, in 1974, introduced as the reducing agent the $LiAlH_4$-$TiCl_3$ couple, in which the active species is probably Ti(II) and which allows the coupling of ketones to afford directly the corresponding olefin in good yields [31].



Corey, in 1976, obtained the diols in higher yields using species of Ti(II) generated either from the Mg(Hg)-$TiCl_4$ couple (reagent A) or from Cp-$TiCl_3$-$LiAlH_4$ (reagent B, Cp = cyclopentadienide anion) [32]. Some examples of unsymmetrical and intramolecular couplings are shown in Table 5.8. Unsymmetrical couplings afford good yields of the cross-coupling product only if one of the components (usually a cheap and volatile compound) is used in excess, otherwise a statistical mixture of all possible symmmetrical and unsymmetrical products is obtained which may be very difficult to separate (see below *5.5.5*).

At the same time, McMurry with species of Ti(0) prepared by reduction of $TiCl_3$ with potassium or lithium in liquid ammonia, obtained excellent yields of alkenes in unsymmetrical couplings as well as in intramolecular reactions [33] (Table 5.9).

TABLE 5.8. Corey's reductive coupling of carbonyl compounds

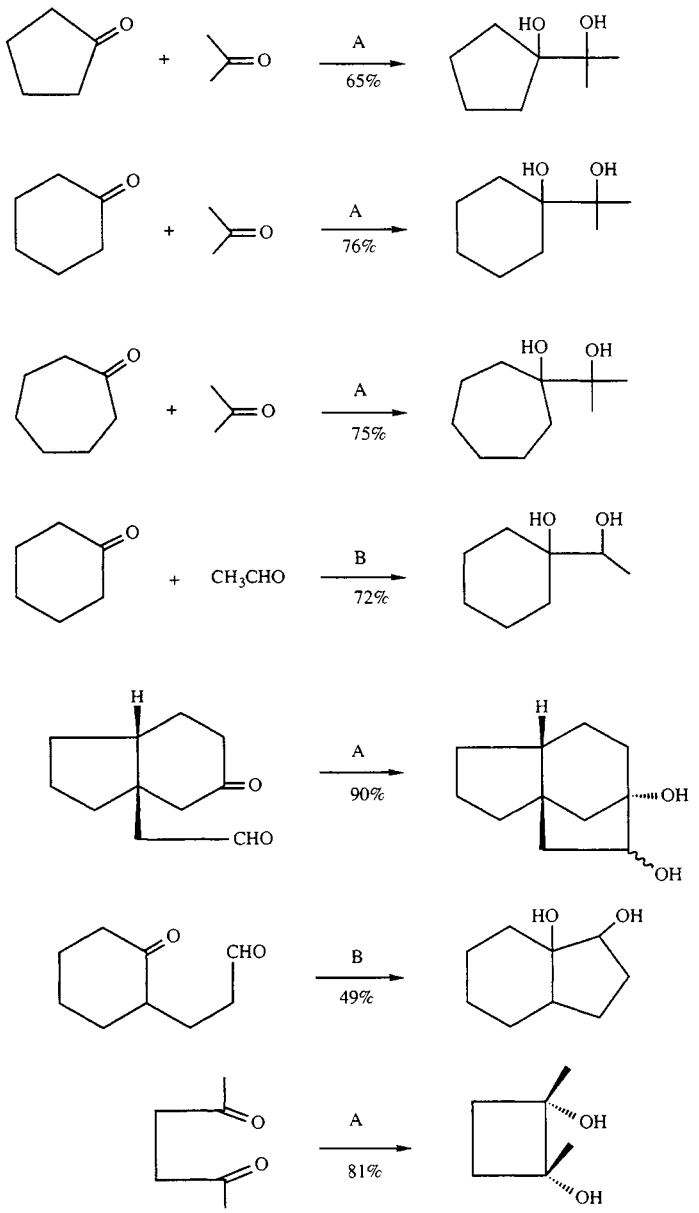
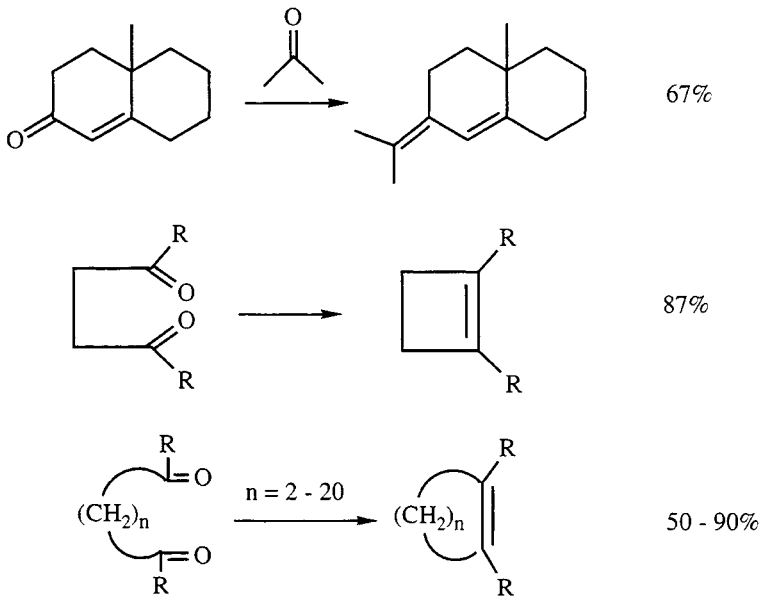


TABLE 5.9. McMurry's reductive coupling of carbonyl compounds

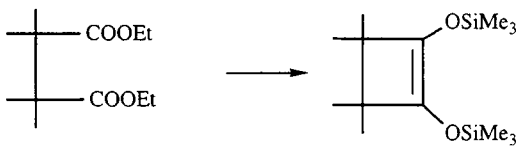


5.5.2. Acyloin condensation

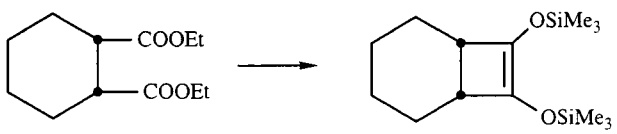
The classical "acyloin condensation" occurs between two carboxylic esters in the presence of sodium in boiling toluene. Of special interest are the intramolecular condensations of esters of dicarboxylic acids, which proceed with variable yields depending upon the size of the resulting ring, being practically zero in the case of small and medium-size rings. However, Rühlman in 1967 introduced a modification which gives excellent yields (80-90%), even in the case of small and medium-size rings [34]. Rühlman's modification consists in carrying out the reaction in the presence of trimethylsilyl chloride which acts not only as a base scavenger, but stabilises the intermediate enediolate species, thus preventing secondary aldol-type reactions (Claisen, Dieckmann) which are responsible for the low yields in the classical "acyloin condensations". For instance, under these conditions yields from 81 to 90% are obtained in the intramolecular condensations of methyl esters of dicarboxylic acids (Table 5.10).

TABLE 5.10. Acyloin condensations according to Rühlmann's procedure

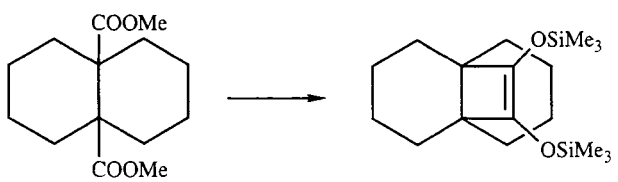
81%



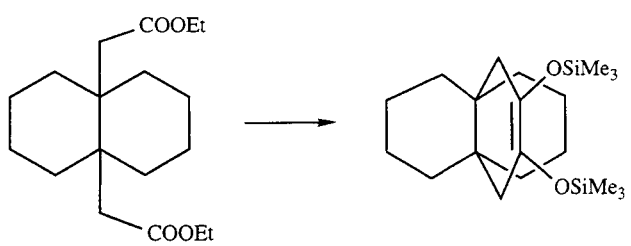
84%



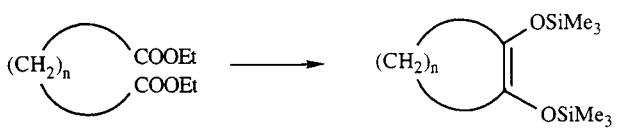
89%



90%



88%

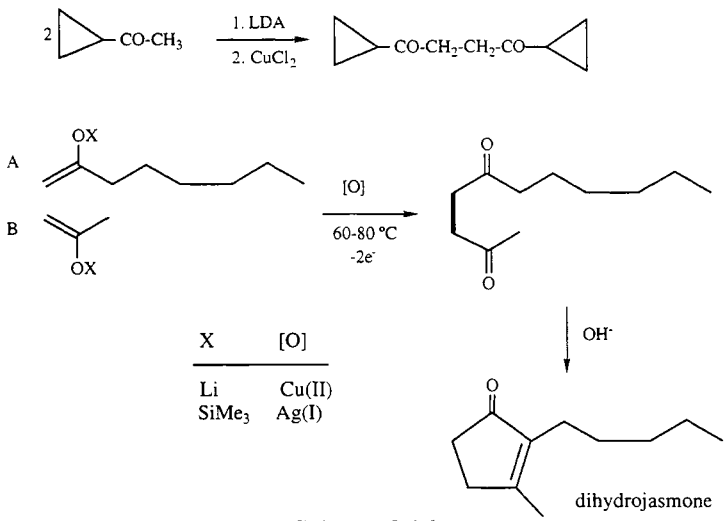


n = 5 , 81%
n = 7, 22%
n = 8, 22-54%

The resulting silylated endiols are easily hydrolysed in acid medium to give the corresponding acyloins in good yields.

5.5.3. Oxidative coupling of enolates

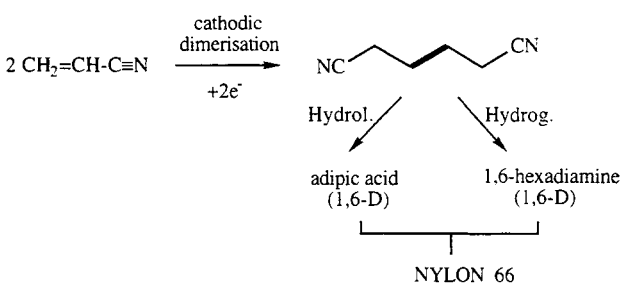
Examples of the synthesis of dissonant 1,4-dicarbonyl systems by oxidative coupling of the corresponding enolates have been described by Saegusa [35] (Scheme 5.26):



Scheme 5.26

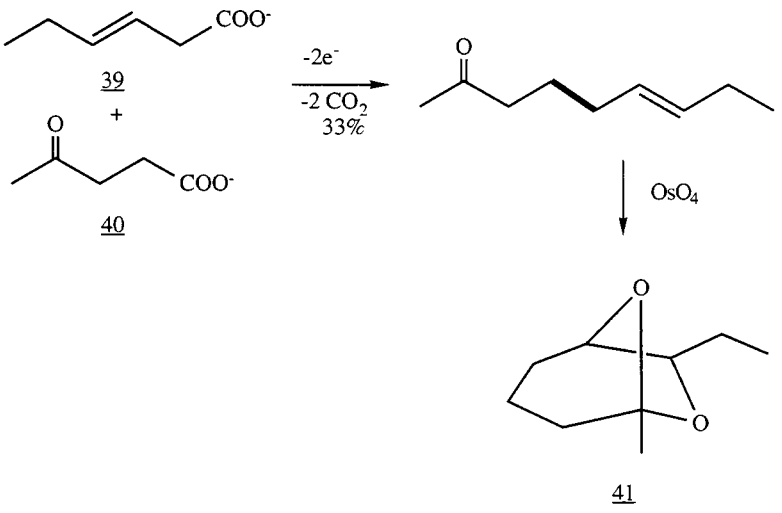
5.5.4. Electrochemical couplings

A synthesis of great industrial interest is the electrochemical anodic reductive dimerisation of two molecules of acrylonitrile to give adiponitrile, from which adipic acid and 1,6-hexanediamine are prepared by hydrolysis and reduction, respectively, of the two nitrile groups. Polycondensation of the resulting products leads to Nylon 66 (Scheme 5.27).



Scheme 5.27

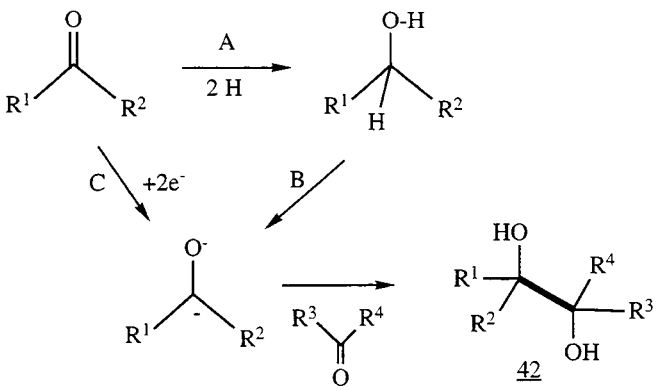
A very simple synthesis of the pheromone *exo*-brevicomin (41) proceeds via an electrochemical Kolbe condensation between the unsaturated carboxylic acid 39 and the ketoacid 40, followed by hydroxylation of the double bond with OsO_4, as shown in Scheme 5.28 [36]:



Scheme 5.28

5.5.5. Double deprotonation ("LUMO-filled" π-systems)

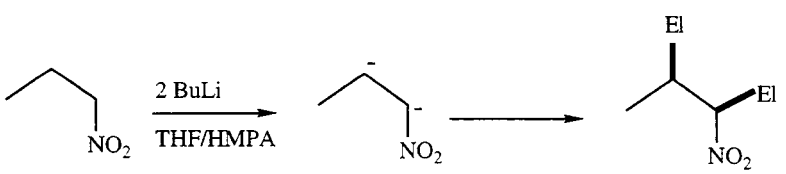
In order to solve the problems arising from scrambling (self-condensation) in unsymmetrical couplings involving electron transfer (see above *5.5.4*), Seebach and his associates [1][37] have studied the double deprotonation of π-systems. The principle is summarised in Scheme 5.29. Instead of dealing with radical intermediates -which can undergo self-condensation-, the π-system is reduced (A) and the resulting dihydro derivative is then doubly deprotonated (B) to give a dianion with reactivity *umpolung*. Notice that the overall result is equivalent to adding two electrons (C) to the π-system. The doubly reduced species (to which Seebach refers to as "LUMO-filled") thus obtained can be added to a different electrophilic π-system to give a "crosslinked dimer" as 42.



Scheme 5.29

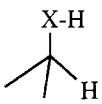
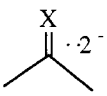
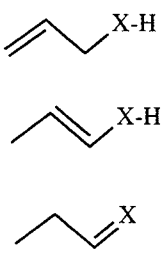
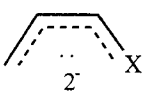
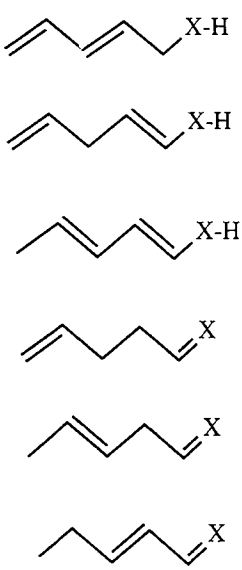
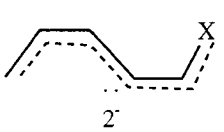
Several hydrogenated precursors of the desired dianion are possible for more extended π-systems (see Table 5.11).

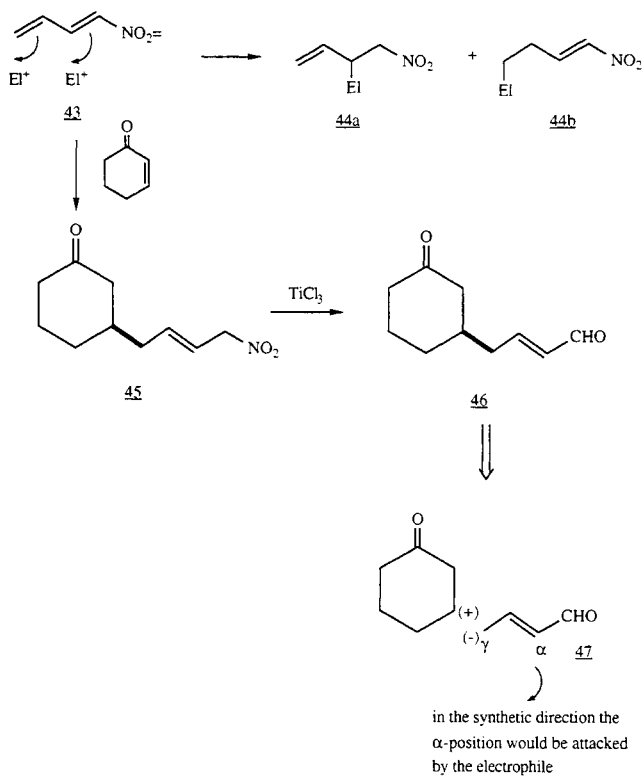
As we have seen in Chapter 2 (Scheme 2.3, equation 3), the doubly deprotonated nitroalkanes are nitroalkenes with reactivity inversion which violate the Lapworth model of alternating polarities and react with electrophiles at the *ipso*- and α-positions:



On the other hand, doubly deprotonated nitroalkenes are reagents with a double reactivity inversion (Scheme 5.30) provided they are used to prepare normal *O*-, *N*-derivatives [1]. For instance, the 1-nitrobutadiene dianion 43 reacts with electrophiles to give a mixture of α- and γ-isomers, 44a and 44b. Addition of the dianion 43 to 2-cyclohexenone gives only the γ-adduct 45 which was transfomed into the 1,7-ketoaldehyde 46 by a Nef-type reaction with $TiCl_3$ [38]. As shown in Scheme 5.30, although the resulting product is a "consonant system" (1,7-C), the double reactivity inversion assures the regioselectivity of the reaction 47 ⟶ 46.

TABLE 5.11. Doubly reduced π-systems from hydrogenated precursors

Precursors	"LUMO-filled" π-system	
		2 atoms 4 electrons
		4 atoms 6 electrons
		6 atoms 8 electrons



Scheme 5.30

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Chapter 6

6. MONOCYCLIC AND POLYCYCLIC SYSTEMS

In principle, cyclic systems can be created either a) from acyclic precursors or b) by modification of previously existing rings. In the first case, two different routes are possible, either: i) by an intramolecular ring closure of a single acyclic precursor, or ii) by an intermolecular ring closure involving two (or more) acyclic precursors. Kocovsky [1] has referred to these as "monotopic" and "ditopic" cyclisations respectively. On the other hand, modification of a previously existing ring may require either a ring contraction (as in the Favorskii or Wolff rearrangement) or a ring expansion (as in the Tiffeneau-Demyanov ring expansion, Beckmann rearrangement, Baeyer-Villiger reaction or the vinylcyclopropyl rearrangements).

In the present chapter, however, because the problem is considered from a retrosynthetic point of view, we will distinguish only between heterolytic and homolytic disconnections -to which we will refer to as "retro-annulations"- and concerted or "pericyclic (or cheletropic) cycloreversions". In the same way that Woodward-Hoffmann rules [2] apply to pericyclic reactions, the Baldwin rules [3] may be said to apply to heterolytic as well as to homolytic "monotopic" annulations (see Table 6.1). Although in the preceding Chapter (see *5.5*) we have already described some radical "monotopic" annulations, later on in this Chapter (see *6.1.3*) and mainly in Chapter 7 we will refer to some new methods, syntheses and strategies which have been developed recently.

As we have seen in some of the examples already commented on in the preceding Chapters, the same "heuristic principles" which apply to acyclic compounds may also be applied, in principle, to cyclic compounds. The bond disconnections lead to acyclic systems or, at least, to a reduction in the cyclic order.

The "cyclic order" C_n of a molecule -or of the corresponding *graph*- is equal to the number of bonds less the number of atoms, plus one:

$$C_n = \text{number bonds} - \text{number atoms} + 1$$

TABLE 6.1. The Baldwin rules

Hybridisation	Breaking bond	Ring Size 3	4	5	6	7
Tet (sp^3)	*exo*	+	+	+	+	+
	endo	-	-	-	-	-
Trig (sp^2)	*exo*	+	+	+	+	+
	endo	-	-	-	+	+
Dig (*sp*)	*exo*	-	-	+	+	+
	endo	+	+	+	+	+

+ means that the cyclisation is favoured; - means that it is not favoured; *endo* and *exo* refers to whether the bond to be broken is *endo-* or *exo-* cyclic to the smallest ring to be formed (in the synthetic direction) (see Fig. 6.1).

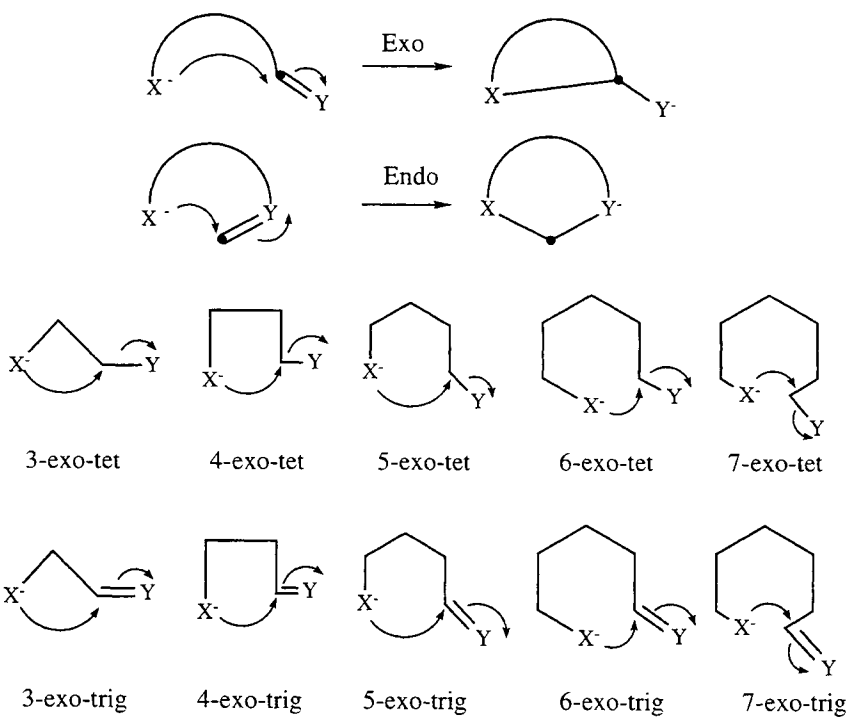


Fig. 6.1

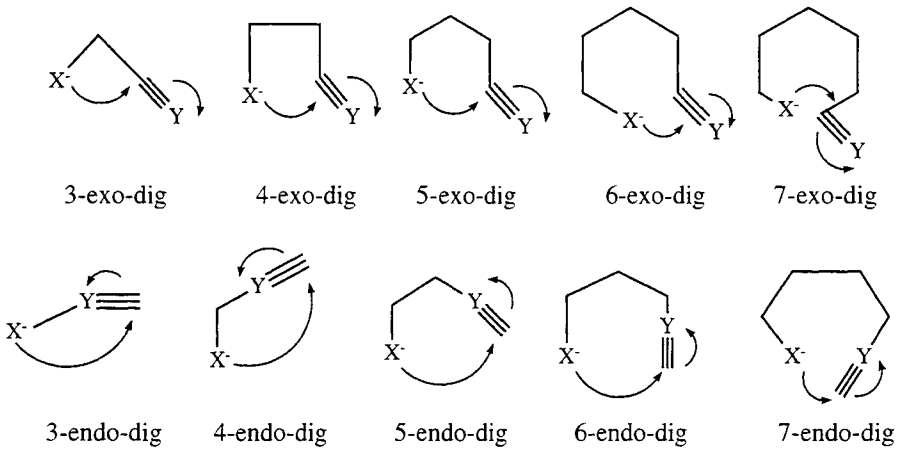


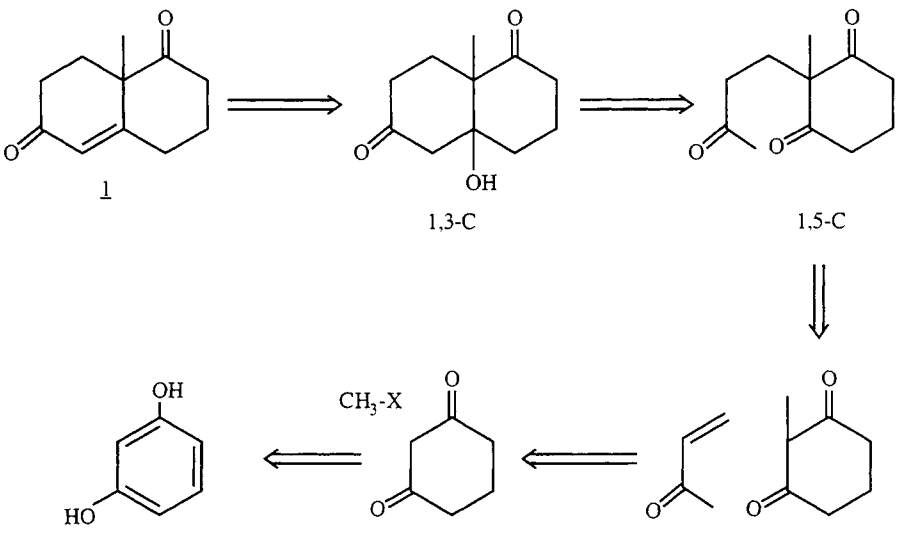
Fig. 6.1 (cont.)

As in the case of acyclic compounds, the level of difficulty of the synthesis of a cyclic compound depends upon whether the molecule is a consonant or a dissonant system. However, some additional difficulties may be encountered in molecules with medium-sized rings as well as in polycyclic bridged compounds, which are treated in the next Chapter. On the other hand, as we have seen in *Heading 4.3*, even simple monofunctionalised cyclic molecules may require a FGA operation before bond disconnection of the cyclic network at the *ipso*-, α- or β-positions can be effected.

6.1. *Retro-annulations*

6.1.1. Heterolytic disconnections

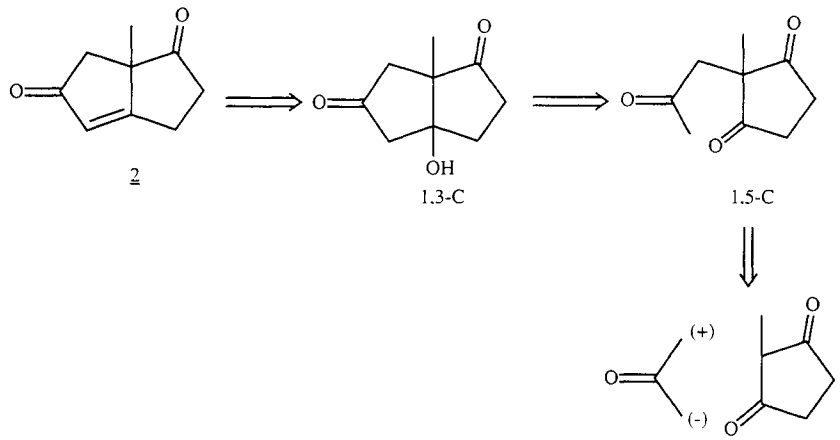
An example of a consonant cyclic molecule is the Wieland-Miescher ketone (1) [4], whose synthesis was reported in 1950 and can be reduced to methyl vinyl ketone and resorcinol as starting materials. The retrosynthetic process (Scheme 6.1) presupposes: i) a FGI operation which involves substitution of the conjugated double bond by the corresponding alcohol; ii) retro-aldol disconnection of the resulting 1,3-C system; iii) retro-Michael disconnection of the 1,5-C monocyclic intermediate to give methyl vinyl ketone and 2-methylcyclohexane-1,3-dione; iv) disconnection of the methyl group at the α-position according to a nucleophilic dealkylation, and v) "oxidation" of cyclohexane-1,3-dione to the corresponding aromatic compound (resorcinol).



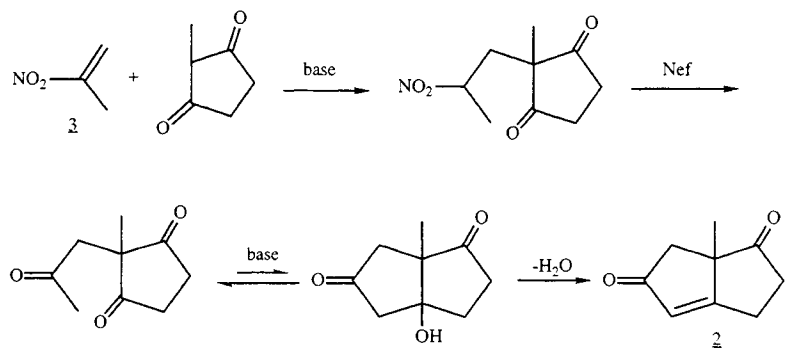
Scheme 6.1

In contrast, the so-called bis-nor-Wieland-Miescher ketone (2) is a more complex synthetic problem, since the molecule is a multidissonant system with two dissonant bifunctional group relationships (1,4-D and 1,6-D) and two dissonant cyclopentane rings, besides a 1,5-consonant bifunctional group relationship. Its synthesis was only accomplished 30 years after the synthesis of its consonant homologue [5].

The retrosynthetic process (Scheme 6.2) involves the following operations: i) substitution of the conjugated double bond by an OH group; ii) retro-aldol disconnection of the 1,3-C system, and iii) disconnection at the α-position of the resulting 1,4-D system which leads to 2-methylcyclopentane-1,3-dione and an *umpoled* three-carbon atom fragment. This retrosynthetic process offers, however, only a theoretical scheme which, in practice, presents some difficulties. For example, Table 5.1 gives 2-nitropropene (3) as a possible equivalent of the *umpoled* C_3 fragment, in which case the process in the synthetic direction would be as shown in Scheme 6.3.

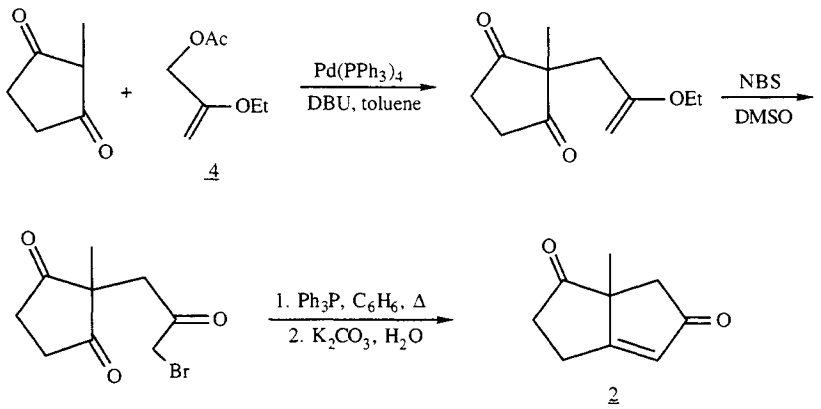


Scheme 6.2



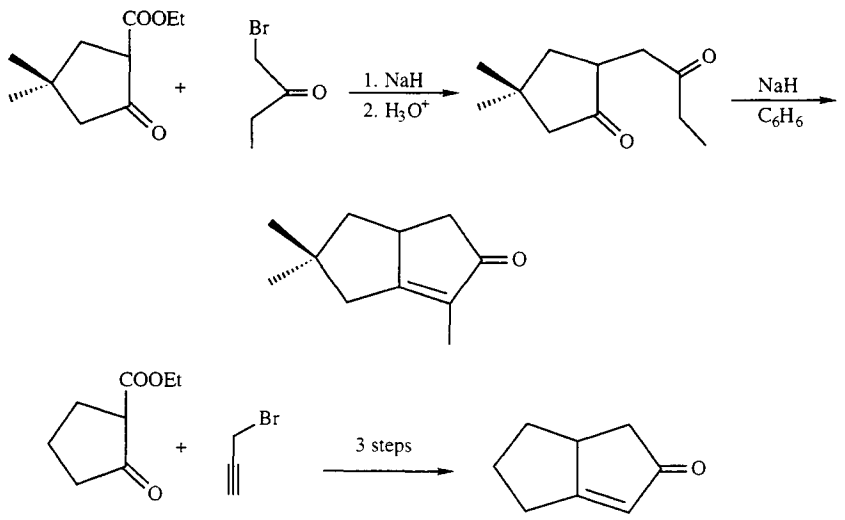
Scheme 6.3

In practice, however, the annulation does not take place because the aldol condensation is essentially a reversible reaction and strain between the two cyclopentane rings shifts the equilibrium towards the reactants rather than towards the products. In order to overcome this difficulty, the synthetic scheme was substantially modified and 3-acetoxy-2-ethoxypropene (4) was used as the *umpoled* C_3 fragment and the aldol condensation was substituted by a Wittig reaction, as shown in Scheme 6.4.



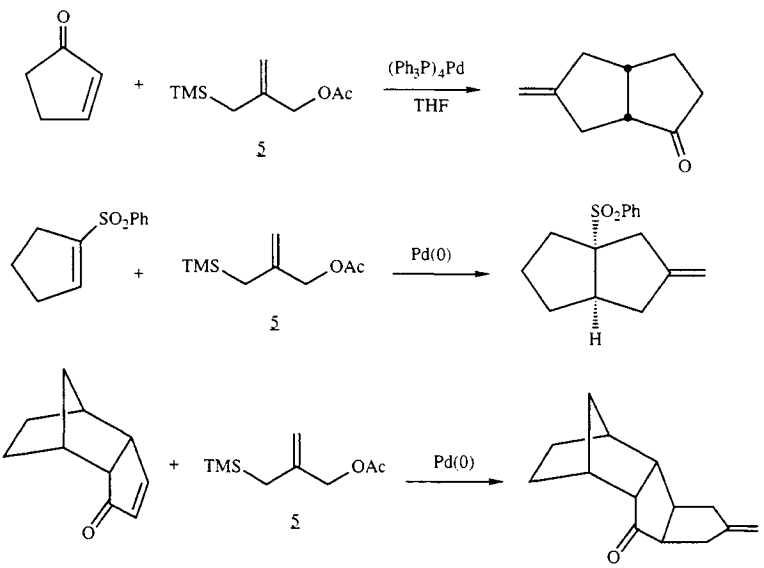
Scheme 6.4

Umpoled C_3 fragments other than 4 have been used for the synthesis of related compounds following the [3 + 2] cycloaddition methodology [6] (Scheme 6.5).



Scheme 6.5

[2-(Acetoxymethyl)allyl]trimethylsilane (5) in the presence of a Pd(0) reagent, for instance, acts as an equivalent of trimethylenemethane in cycloadditions to electron-deficient alkenes such as α,β-unsaturated ketones, esters, nitriles, sulphones and lactones [7] (Scheme 6.6).

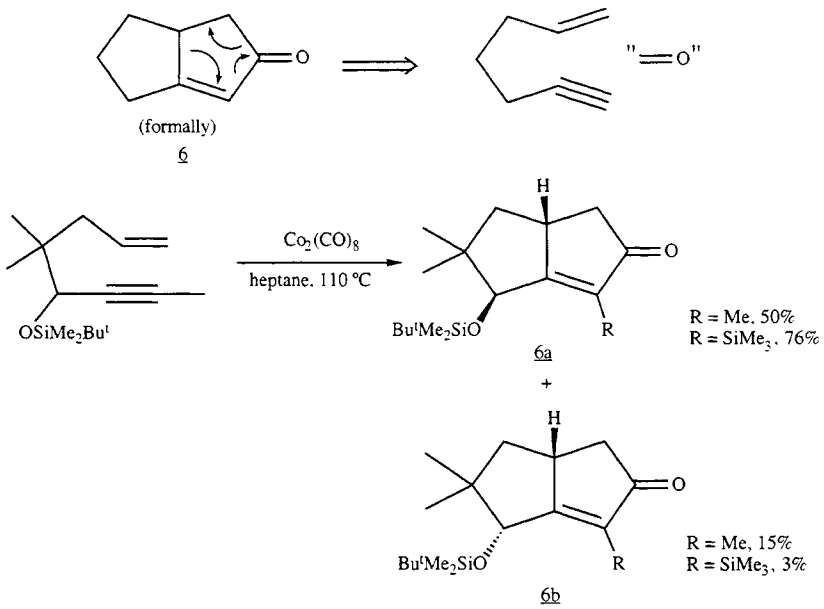


Scheme 6.6

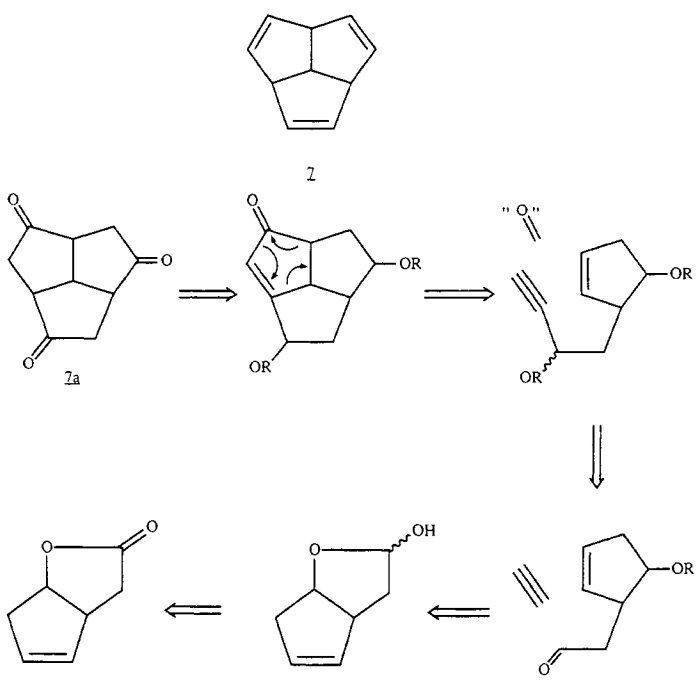
In fact, in the last decade, owing to the great number of new natural products which have been isolated bearing cyclopentane rings and the increasing interest in "polyquinanes", very efficient syntheses of five-membered rings have been developed (for reviews of these new methods, see [8] to [11]).

6.1.2. "Transition metal-mediated" cycloeliminations

Since there are many useful transition metal-mediated cycloadditions -as for example, the coupling of dicobalt hexacarbonyl alkyne complexes with alkenes to give cyclopentenones in a formal [2+2+1] cycloaddition (see Scheme 6.7) (Pauson-Khand reaction) [10][11]- they must be also taken into account, mainly because very simple retrosynthetic schemes can be derived which lead to easily available starting materials. Such cycloadditions are usually compatible with a wide range of functionality, the presence of aromatic and heteroaromatic rings, as well as with substitution of the alkynes, the alkenes and the carbon chain linking them. This is especially significant when considering "monotopic" cycloadditions [12], in which case the benefits of the rarely invoked "Thorpe-Ingold effect" [13] must be kept in mind, provided that substitution does not introduce excessive steric interactions in the intermediates leading to the transition states [14].



Scheme 6.7



Scheme 6.7bis

Some illustrative examples from the field of polyquinanes are the synthesis of some derivatives of bicyclo[3.3.0]octane 6 (Scheme 6.7) [12] [15] -which have been used in the total syntheses of coriolin, hirsutic acid and quadrone- and the synthesis of triquinacene 7 and some of its derivatives. The retrosynthetic analysis of perhydrotriquinacene-1,4,7-trione (7a) is shown in Scheme 6.7bis. In the actual synthesis the hydroxy groups must be protected either as trialkylsilyl ethers or more conveniently as benzyl ethers [16] [17].

An enantioselective intramolecular Pauson-Khand reaction based on chiral auxiliary-directed π-face discrimination in acetylenic *O*-alkyl enol ether-dicobalt hexacarbonyl complexes, which proceeds with good yields and high facial diastereoselectivity, has recently been developed by M.A. Pericàs, A. Moyano, A.E. Greene and their associates. The method has been applied to an enantioselective formal synthesis of hirsutene. Moreover, the process is stereodivergent and the chiral auxiliary -*trans*-2-phenylcyclohexanol- is recovered in a yield as high as 92% [18].

6.1.3. Homolytic disconnections: radicals in the synthesis of cyclic systems

In the preceding Chapter we have already referred to some classical synthetic methods which proceed via radicals and which are usually used for the synthesis of dissonant molecules, including some cyclic and polycyclic systems.

In the past few years, however, very efficient new methods of cyclisation proceeding via radical intermediates have been developed and several reviews [19a] and a comprehensive book by Giese [19b] have been published. Rather than reactions involving the dimerisation of two radicals -as in the Kolbe electrochemical synthesis [20] or the radical induced dehydrodimerisation developed by Viehe [21]- more important are the reactions between a radical with a non-radical species. The advantage of this type of reaction is that the radical character is not destroyed during the reaction and a chain-reaction may be induced by working with catalytic amounts of a radical initiator. However, in order to be successful two conditions must be met: i) The selectivities of the radicals involved in the chain-reaction must differ from each other, and ii) the reaction between radicals and non-radicals must be faster than radical combination reactions.

These methods are usually highly regio- and stereoselective and represent a breakthrough for synthetic chemistry using radicals. Giese quotes, as an example, that the cyclisation of the 5-hexenyl radical 8 affords the primary cyclopentylmethyl

radical 9 rather than the more stable secondary cyclohexenyl radical 10. The ratio is 98:2 and the cyclisation has a rate constant of about 10^6 (s^{-1}) at 20 °C, which is increased by electron-withdrawing substituents at the double bond. Although radicals 8 and 9 have the same nucleophilicity, they show a quite different selectivity. Thus, whereas radical 8, generated from bromide 12, reacts intramolecularly with the double bond, radical 9 reacts intermolecularly, for instance with Bu_3SnH to give methylcyclopropane (11). Since both the reactivity and the selectivity requirements for chain reactions are fulfilled, intramolecular radical cyclisations are synthetically useful (Diagram 6.1).

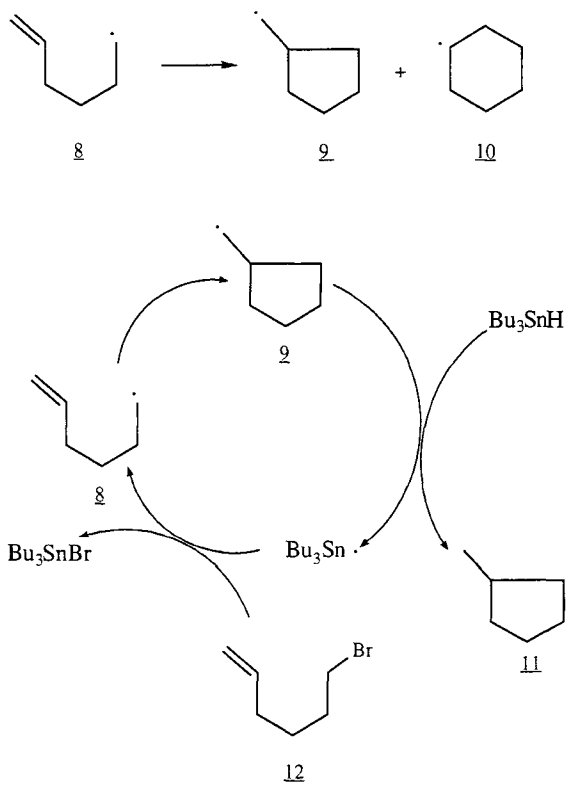
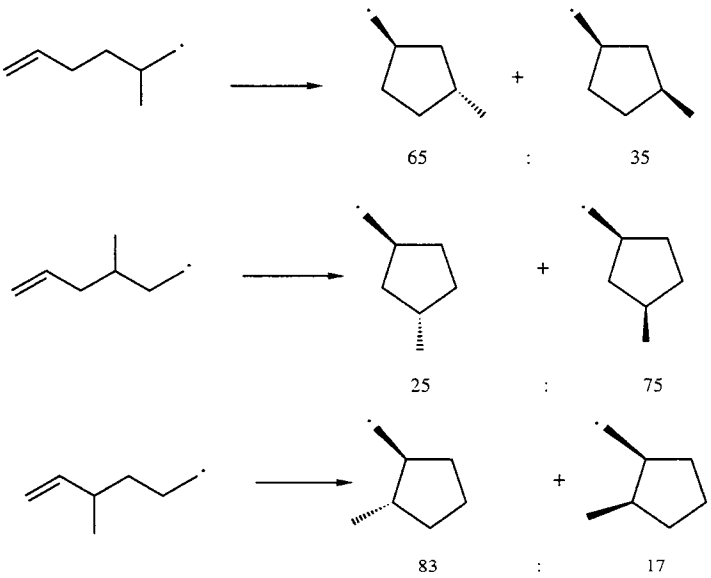


Diagram 6.1

According to the Baldwin rules (see Table 6.1), the *exo*-cyclisation leading to the primary radical (9) is favoured over the *endo*-cyclisation which would lead to the more stable secondary radical (10), the stereoelectronic factors playing a fundamental role in the observed selectivity.

On the other hand, Beckwith rules [22] are useful guidelines for predicting the stereoselectivity in the cyclisation of substituted hexenyl radicals: i) 1- or 3-substituted radicals give preferentially *cis*-disubstituted cyclopentane derivatives and ii) 2- or 4-substituted radicals give mainly *trans*-disubstituted derivatives. These rules can be explained in terms of 1,3-diaxial interactions present in a chair-like transition state. Some examples which demonstrate such an effect are [19b]:

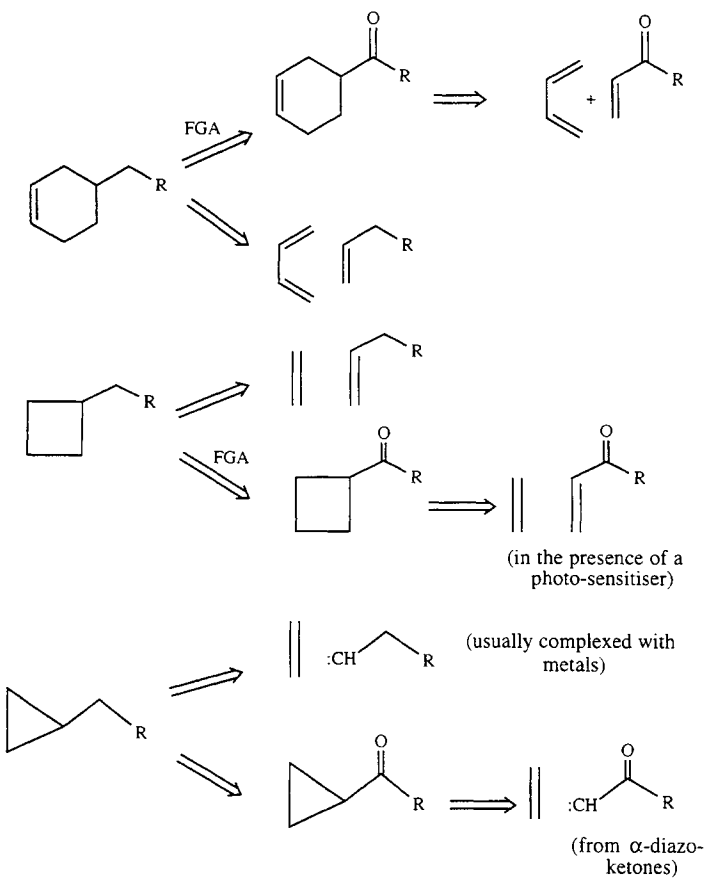


Since cyclisations via radicals lead frequently to compounds with little or no functionality, the "heuristic principles" guiding the homolytic retro-annulations lie basically in the concept of the "strategic bond" which will be introduced in Chapter 7 in connection with polycyclic bridged systems, together with "Corey's rules" and the concept of the "dual graph" [23] which applies in the special case of polycyclic fused systems. Some general principles which may be useful for designing syntheses of polycyclic compounds, either fused or bridged, via radical reactions will be discussed there.

6.2. *Cycloreversions: pericyclic and cheletropic disconnections. The Woodward-Hoffmann rules*

In addition to being treated in a similar manner to acyclic systems, cyclic systems can also be disconnected according to concerted *pericyclic* or *cheletropic* cycloreversions. In this context, the Woodward-Hoffmann rules [2] are of

paramount importance, not only for determining which processes are symmetry allowed, but also for determining the stereochemistry of the compounds involved in the cycloadditions, since they are stereospecific reactions. Notice that whereas the consonant four- and six-membered rings offer valid disconnection mechanisms, either directly [-(2+2)] or after introducing a double bond [-(4+2) or retro-Diels-Alder], according to pericyclic cycloreversions, the dissonant three- and five-membered rings must be disconnected according to cheletropic processes, [-(2+1) and -(3+2)]. A FGA prior to bond disconnections may be a necessary operation in order to "activate" the *retron* properly (see Scheme 6.8). However, it should be remembered that intramolecular (or "monotopic") Diels-Alder condensations proceed easily without any kind of activation. Moreover, transition metal-mediated cyclisations, either intra- or intermolecular ("ditopic"), take also place readily.



Scheme 6.8

On the other hand, Table 6.2 predicts the regioselectivity considering the frontier orbital contributions, [24] and is very useful in designing syntheses in which the key step involves a Diels-Alder addition.[15]

TABLE 6.2. Regioselectivity in Diels-Alder cycloaddions*

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	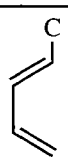	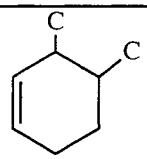
		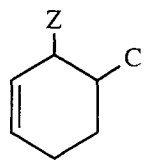
	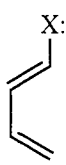	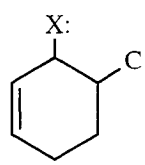
	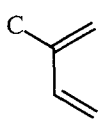	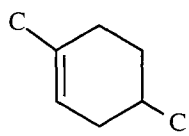
	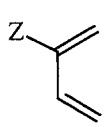	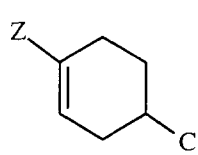
	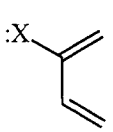	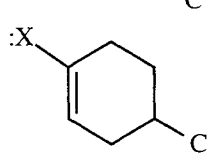

[15] For highly functionalised dienes and their equivalents, also very useful for designing organic syntheses involving cycloaddition and cyclocondensation reactions, see S. Danishefsky, *CHEMTRACTS Organic Chemistry*, **1989**, 2, 273-297.

TABLE 6.2 (cont.)

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	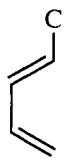	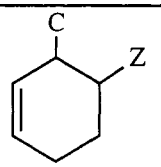
	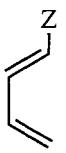	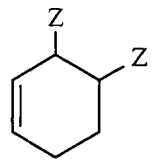
	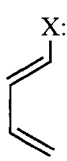	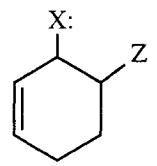
	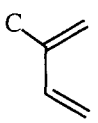	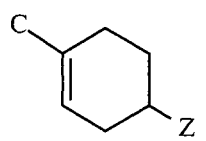
	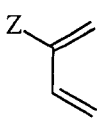	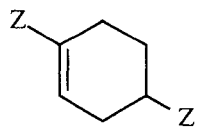
	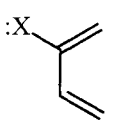	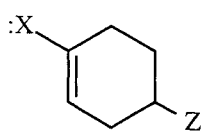

TABLE 6.2 (cont.)

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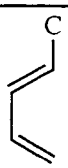
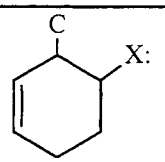
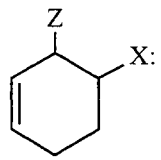
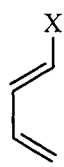
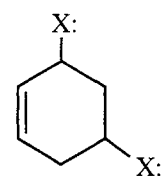
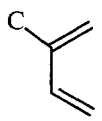
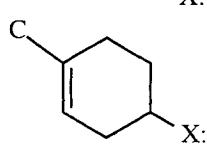
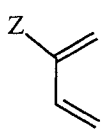
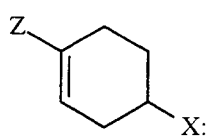
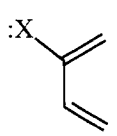
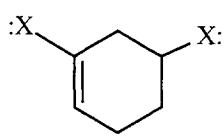
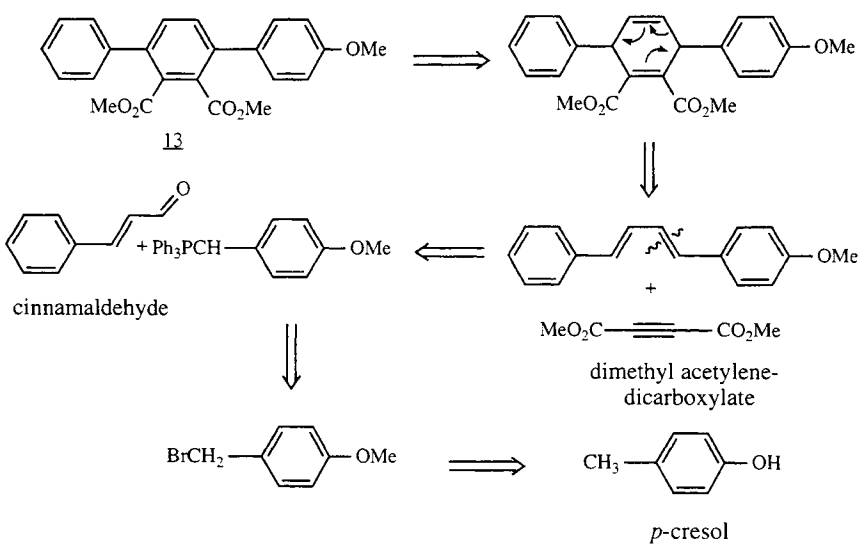
		
		
		
		
		
		

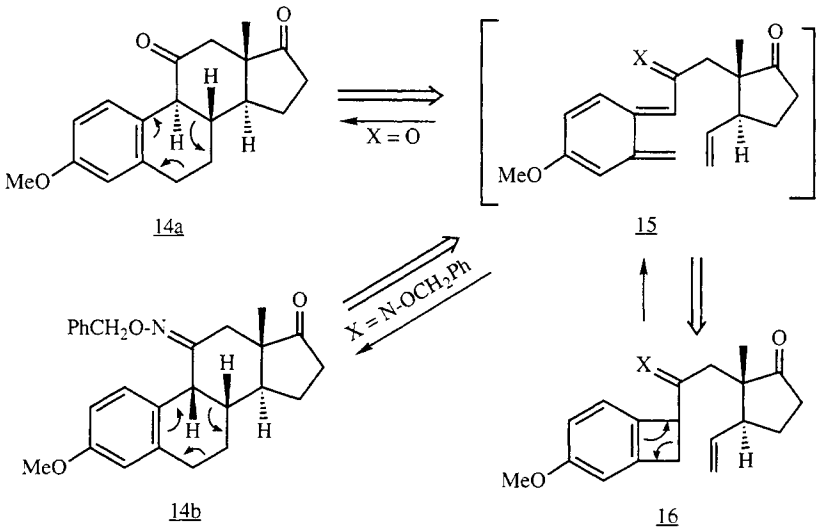
*The symbols C, Z and :X refer to "extra conjugation", "electron-withdrawing" and "electron-donating" groups, respectively.

Somewhat unusual examples, which illustrate the usefulness of cycloadditions in the synthesis of polycyclic compounds, are the controlled synthesis of an unsymmetrically substituted aromatic compound (13) from very simple commercially available compounds (Scheme 6.9), and the one-step thermal cyclisation of compound 16 to the aromatic steroid 14 (Scheme 6.10).

The first example illustrates how a 1,4-dehydroaromatic system with cyclohexane ring having two double bonds may be also disconnected according to a retro-Diels-Alder to give a diene and an acetylene as the dienophile [25]. The second example makes clear that even an aromatic double bond may be -in some instances- involved in a retrosynthetic pericyclic disconnection [26]. In the synthetic direction, the polycyclisation involves a conrotatory electrocyclic cyclobutene ring opening, (16 ⟶ 15) followed by an intramolecular Diels-Alder addition (see Scheme 6.10). Notice that the substituents present in the precursor play a crucial role in the choice of the transition state (*exo* or *endo* approach) and, ultimately, in determining the stereochemistry of the resulting cyclisation product, either 14a or 14b.



Scheme 6.9



Scheme 6.10

The most important cheletropic reactions are those that involve the reaction of an electro-defficient species -as a carbene, nitrene or "atomic oxygen"- with an olefinic double bond and lead to three-membered rings.

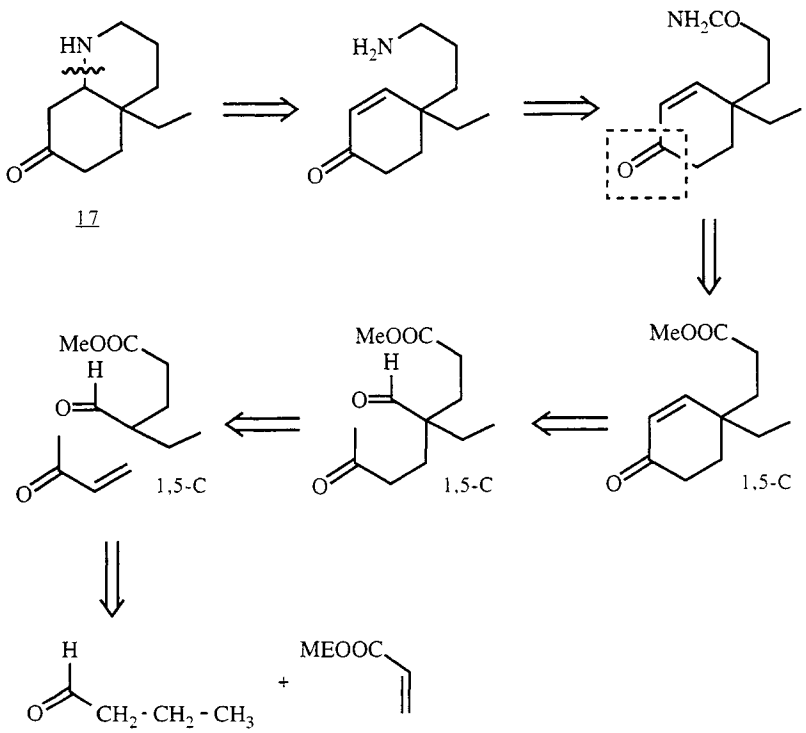
Finally, it should be mentioned that from a purely synthetic point of view the reactions involving "transfer" of methylene groups -like the Simmons-Smith reaction [27] or Seyferth's reagents [28]- may be considered formally as *cheletropic* additions of a [2 + 1] type.

6.3. Heterocyclic compounds

In principle, the same "heuristic principles" which apply to carbocyclic compounds are also applicable to heterocyclic systems [29]. However, it must be kept in mind that:

1) Since in the synthesis of heterocyclic compounds the ring closure usually involves the formation of the carbon-heteroatom bond, in the retrosynthetic analysis *the first bond to be disconnected is the carbon-heteroatom bond (Cf.* heuristic principle HP-8), either directly or after the pertinent (FGI or FGA) functional group manipulation. For instance, compound 17 -which is the starting material for Stork's synthesis of *Aspidosperma* alkaloids [30]- may be disconnected as shown in Scheme 6.11.

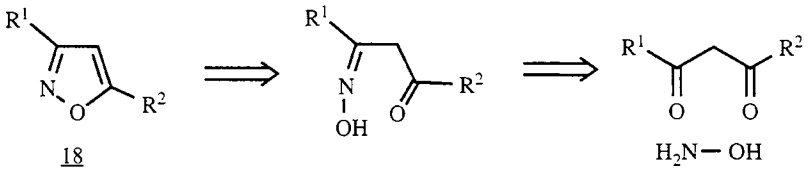
2) Since in the systems containing two adjacent heteroatoms it is not usual that the ring clorure involves the formation of the bond between them (exceptions may be found in the cases of functional groups such as nitro, nitroso or diazonium), in the retrosynthetic analysis *the bond between the two adjacent heteroatoms should not be disconnected.*



Scheme 6.11

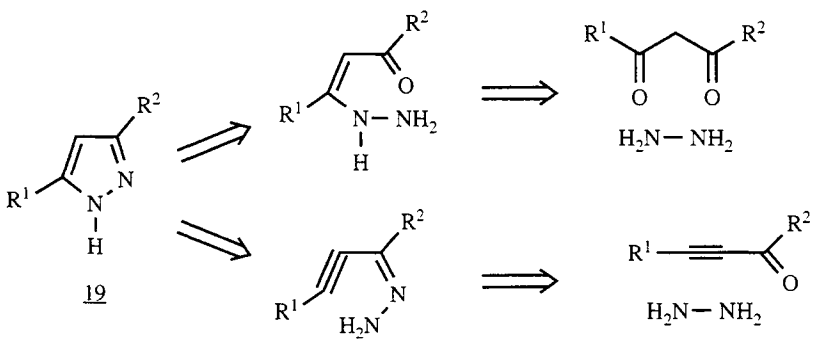
In fact, in systems containing two (or more) heteroatoms, wheter they are adjacent or not, the best strategy is to recognise the substructure or retron containing the heteroatoms and to proceed then to the systematic disconnection (remember again HP-8) of the carbon-heteroatom bonds linking the "inorganic" fragment with the organic moiety. Further elaboration of the resulting synthons will lead to readily available starting materials. Thus, among many other possible disconnections, we may consider for example the disconnection of:

i) an isoxazole (18) to give hydroxylamine and a 1,3-dicarbonyl compound (or some related precursor),



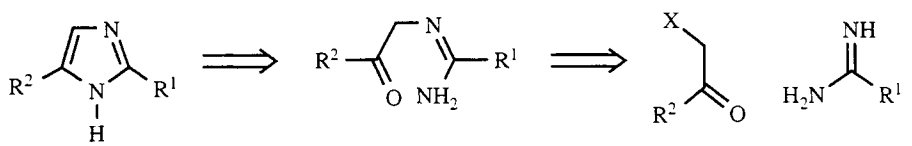
18

ii) a pyrazole (19) to afford hydrazine and a 1,3-dicarbonyl compound (or some related precursor),



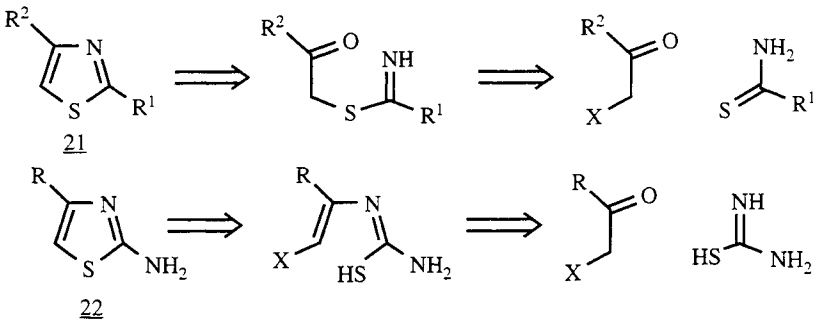
19

iii) an imidazole (20) to yield an amidine and an α-halocarbonyl compound,



20

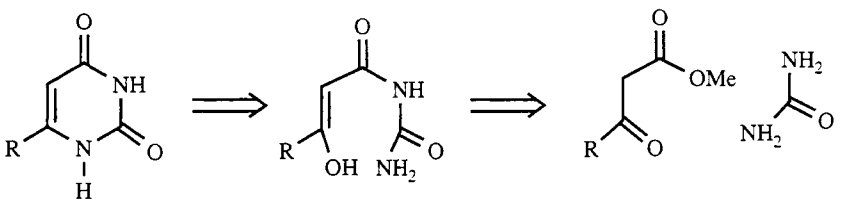
iv) a thiazole (21 or 22) leading to a thioamide (or thiourea or some derivative) and an α-halocarbonyl compound,



21

22

v) a pyrimidine (23-25), which may afford urea (or thiourea or some derivative) and, for instance, a β-keto ester, a cyanoacetic ester or an acrylic ester.



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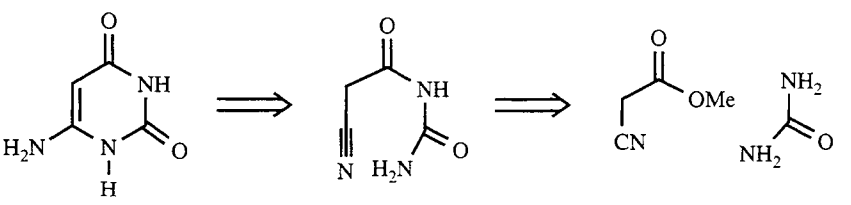

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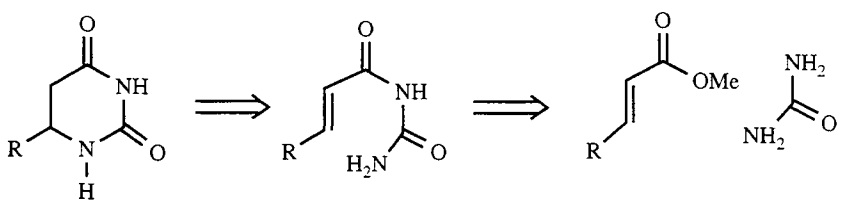
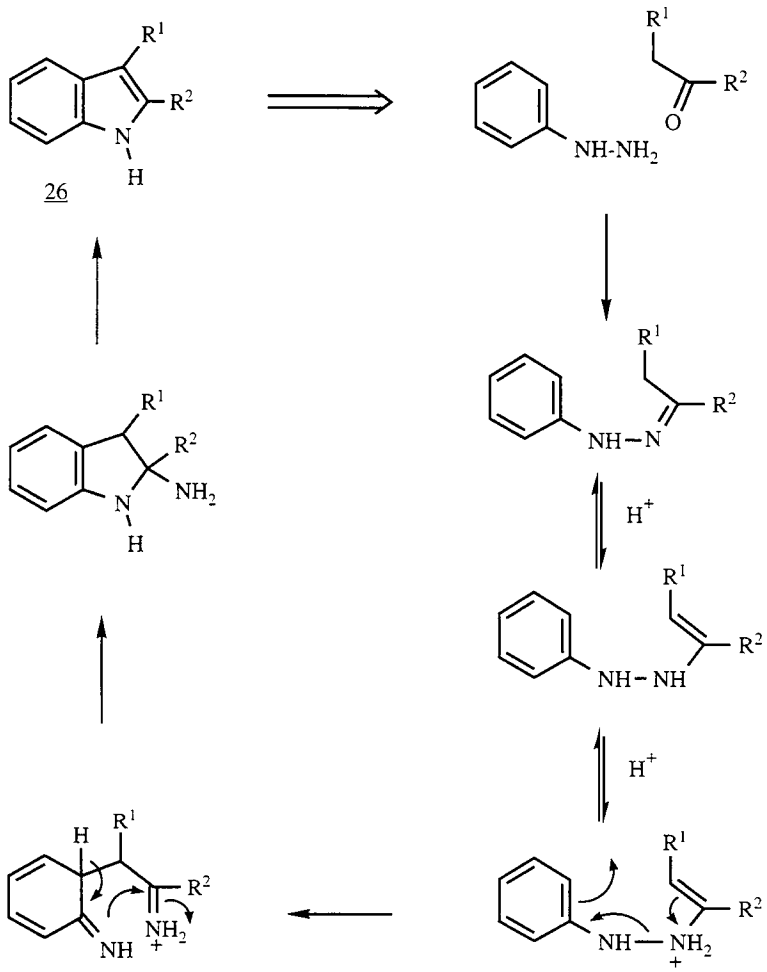


3) Wherever the heterocyclic ring is fused to an aromatic system the starting material must always be a preformed aromatic derivative. In this context the Fischer indole synthesis (Scheme 6.12) provides a good example:



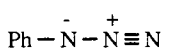
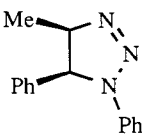
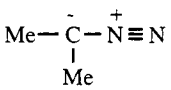
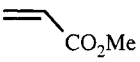
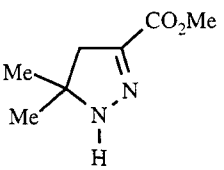
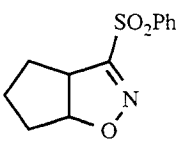
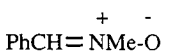
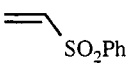
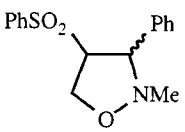
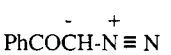
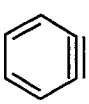
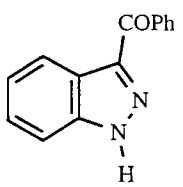
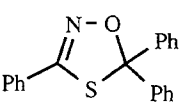
Scheme 6.12

Other general principles applicable to the synthesis of heterocycles refer to cycloreversions (either pericyclic and cheletropic or 1,3-dipolar), valence-bond isomerisations and retro-annulations leading to enamines.

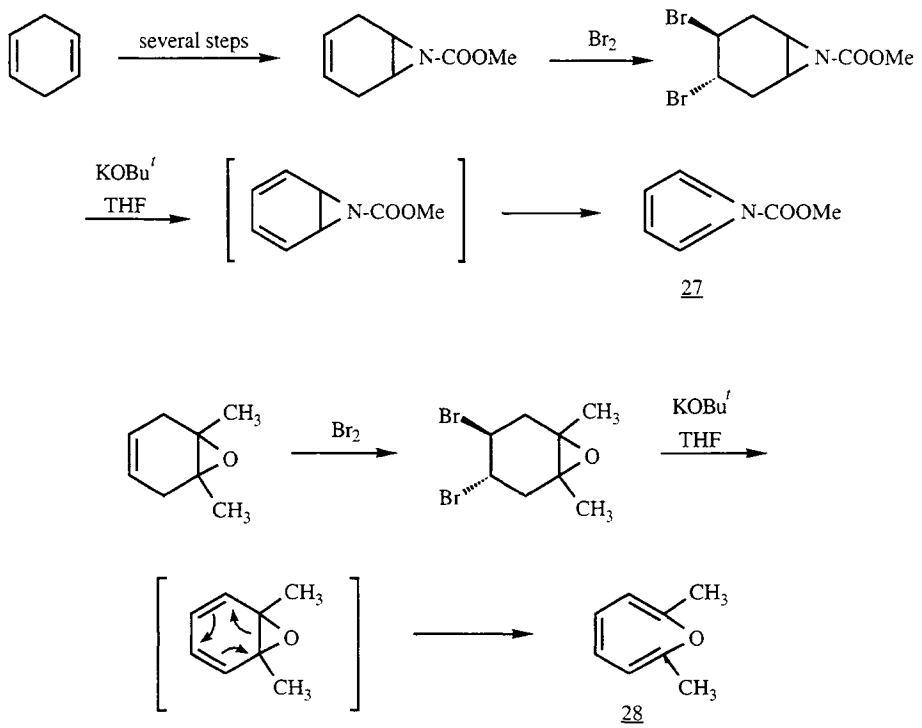
Besides the bond-pair cheletropic disconnection of oxiranes and aziridines to an alkene and "atomic oxygen" (from a carboxylic peracid) or a nitrene, respectively, and the hetero-Diels-Alder cycloreversion, of special interest are the 1,3-dipolar cycloeliminations of five-membered rings [-(3+2)] leading to 1,3-dipoles and an unsaturated acceptor or dipolarophile. So large is the number of different five-membered heterocyclic systems resulting from 1,3-dipolar

cycloadditions that only a few examples can be mentioned here. Some of the most representative 1,3 dipoles are nitrile ylides, nitrile imines, nitrile oxides, diazoalkanes, azides, azomethine ylides, azomethine imines and nitrones. The scope and the synthetic possibilities of 1,3-dipolar additions is really enormous (see Table 6.3) [31].

TABLE 6.3. Examples of 1,3-dipolar cycloaddition leading to heterocyclic compounds

Dipole/precursor	Dipolarophile	Products
		
		
$PhSO_2CBr{=}NOH$, base		
		
		
$PhCCl{=}NOH, Et_3N$	$Ph_2C{=}S$	

Among the valence-bond isomerisations leading to heterocyclic systems, the synthesis of derivatives of azepine (27) and oxepin (28) have been specially successful (Scheme 6.13) [32].



Scheme 6.13

Finally, bridged polycyclic systems containing heteroatoms should be menctioned and they are treated in the next chapter, as an appendix to Corey´s rules for the selection of "strategic bonds" (see 7.2.2).

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31. R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565; see also ref. 29a, pp. 88-102.

32. E. Vogel and H. Günther, *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385.

Chapter 7

7. SYSTEMS WITH UNUSUAL STRUCTURAL FEATURES: QUATERNARY CARBON ATOMS, MEDIUM-SIZED RINGS AND BRIDGED SYSTEMS

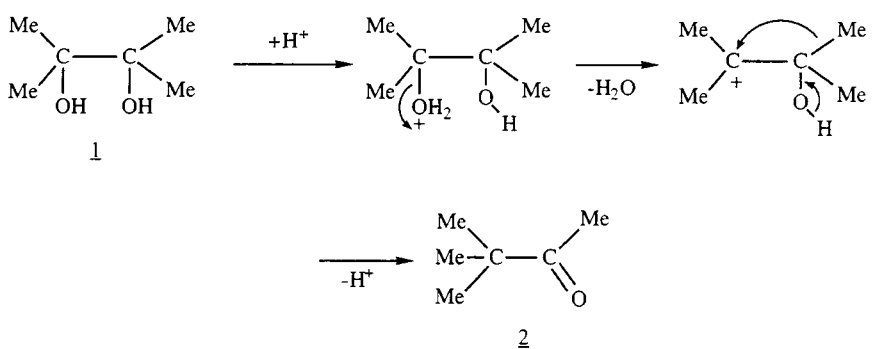
Up to now, we have seen how the "heuristic principles" can be applied to both linear and cyclic systems which we could call "normal systems". When some unusual structural features -such as quaternary carbon atoms, medium-sized rings or bridged systems- are found in the molecular structure under consideration, one may assume that they are derived either from a rearrangement or from an internal fragmentation [1].

Although we have already referred to some rearrangements in connection with the synthesis of dissonant bifunctional relationships, in the present Chapter we will consider those rearrangements which affect mainly the molecular skeleton.

7.1. Rearrangements and internal fragmentations

7.1.1 Pinacol rearrangement and Grob fragmentation

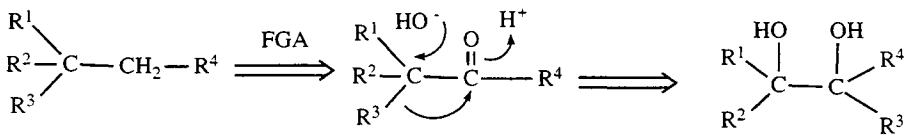
The presence of a quaternary atom, for instance, may be traced back to either a "pinacol" or a "Wagner-Meerwein-type" rearrangement. In the classical "pinacol rearrangement", pinacol 1 (a 1,2-diol) under strong acid conditions rearranges to pinacolone 2 which bears a quaternary atom at the α-position of the carbonyl group:



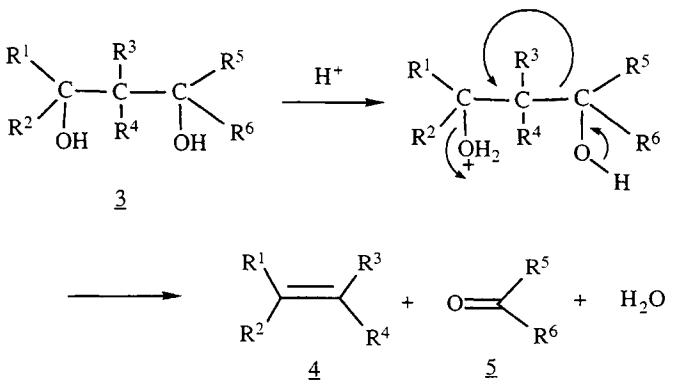
1

2

In the retrosynthetic direction this means that wherever we have a quaternary carbon atom at the α-position to a keto group -either because it already existed in the target molecule or because it has been introduced by a FGI or a FGA- the molecule can be "disconnected" as shown in the following sequence:



If we now consider a 1,3-diol (3), accepting a similar mechanism to the abovementioned for 1,2-diols, in acid conditions the fragmentation of the molecule will take place according to a process known as "Grob fragmentation" [2] to give water as the "nucleofuge", an alkene (4) and a carbonyl compound (5) as the "electrofuge":[16]



From a synthetic point of view, however, the processes which are really useful are the "pinacol rearrangements" which proceed in practically neutral conditions -induced either by a Lewis acid such as $LiClO_4$ in THF solution, in the presence of $CaCO_3$, or by a weak base such as a suspension of activated Al_2O_3 in $CHCl_3$- and the "Grob fragmentations" which proceed in strong basic conditions. In both cases, one of the two OH groups must be activated as a leaving group (either a mesylate or tosylate, or by substitution by a chlorine or bromine atom). In the simpler case of a "pinacol rearrangement" we would have:

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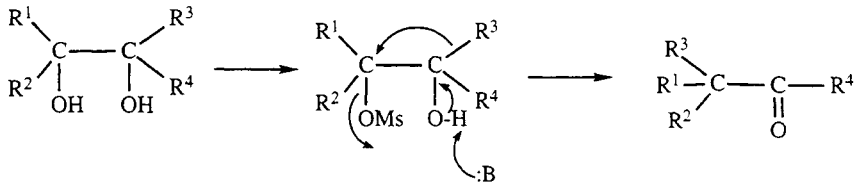
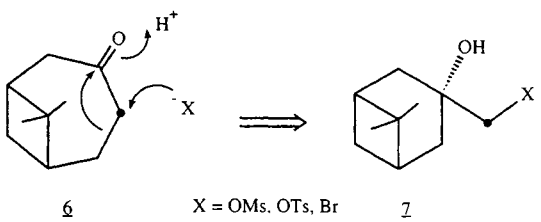
[16] Whereas the terms nucleophile and electrofile refer to bond-formation reactions, the terms "nucleofuge" and "electrofuge" refer to bond-cleavage processes (see footnote 3 of ref. 2b).



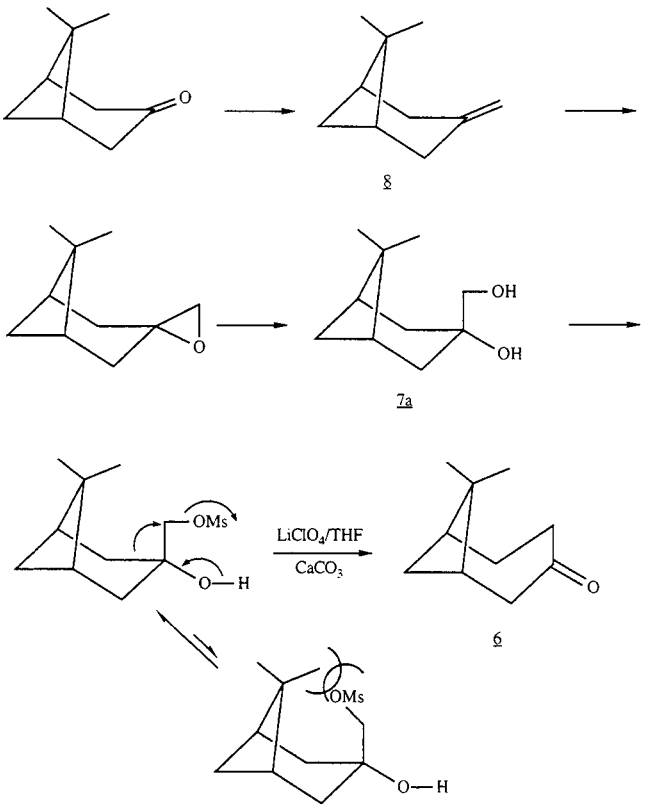
Such a scheme is, however, a purely hypothetical one, since in practice it would be difficult to exert a *chemoselective* control which could allow the two similar tertiary OH groups to be distinguished. For this reason, pinacol rearrangements are only really synthetically useful in rigid molecules, in which the two OH groups not only have a clearly differentiated reactivity, but the molecule can adopt a conformation which may facilitate the rearrangement. In such cases the method is mainly useful as an entry into medium-size rings. With respect to these rings a very useful "heuristic principle" is *to reduce medium-sized rings of 7 to 10 carbon atoms to "common-sized" rings of 5 or 6 carbon atoms* (HP-9). For instance, in the bicyclic cycloheptanone 6 we will proceed as shown in Scheme 7.1 [3] in which the 7-membered ring is reduced to a common 6-membered ring (7):



6 X = OMs, OTs, Br 7

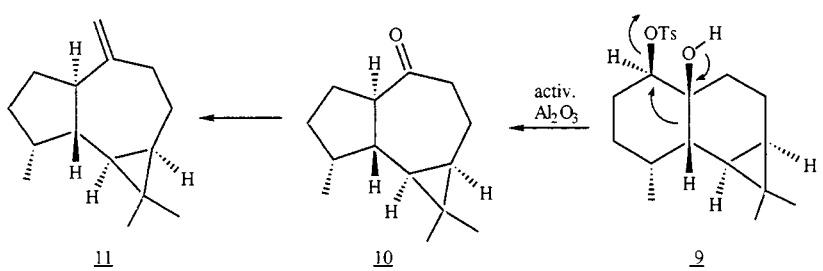
Scheme 7.1

In the synthetic direction, the rearrangement is favoured because the starting 1,2-diol (7, X = OH) may be prepared by hydroxylation of an exocyclic double bond (8) which assures the presence of two well differentiated OH groups (a primary and a tertiary alcohol) in the configuration shown in 7a. On the other hand, the presence of the bridged dimethyl-cyclobutane ring assures the energetically most favoured *anti* conformation of the primary OMs group to the bond which must migrate, so that the rearrangement occurs easily through a more or less concerted process (see Scheme 7.2).



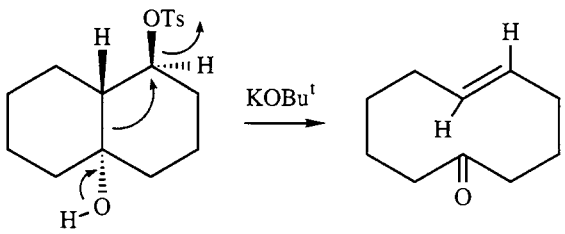
Scheme 7.2

Another example, which takes place in weakly basic conditions, is provided by the key step of the synthesis of aromadendrene (11) accomplished by Büchi and coworkers [4], in which a *cis*-decalin system (9) rearranges to a hydroazulene system (10) through a process induced by activated Al_2O_3 (Scheme 7.3).



Scheme 7.3

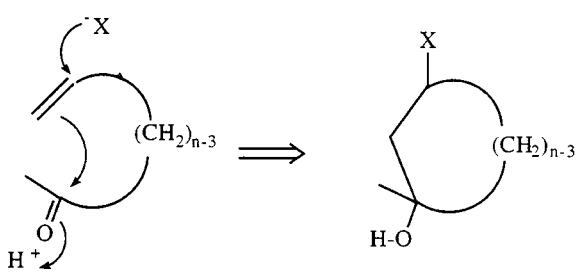
The base-catalysed Grob-type fragmentations of cyclic 1,3-diols monosulfonates, which have been referred to as "Wharton fragmentations" [5], are useful for the synthesis of functionalized medium-sized cycloalkenes. The *anti-periplanar* disposition of the two functional groups favours the elimination, taking place through a fast concerted process. For instance, Wharton and Hiegel [5b] have reported the formation of a 10-membered ring (13) from the decalin 12 (Scheme 7.4).



12 13

Scheme 7.4

Since "Wharton fragmentation" also takes place in monocyclic systems, a logical consequence -which represents in fact a broadening of heuristic principle HP-5 concerning "reconnections"- is that *wherever a double bond and a carbonyl group are separated by two or three carbon atoms, they can be reconnected to give a 5- or a 6-membered ring, respectively*, according to the following retrosynthetic process:

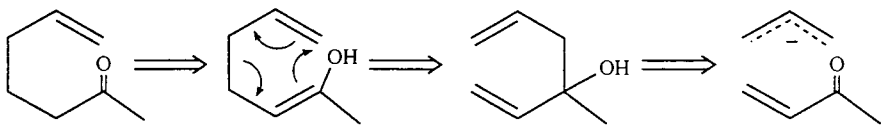


X = OTs, OMs, Br

n = 5 or 6

7.1.2. Cope and Claisen-type rearrangements

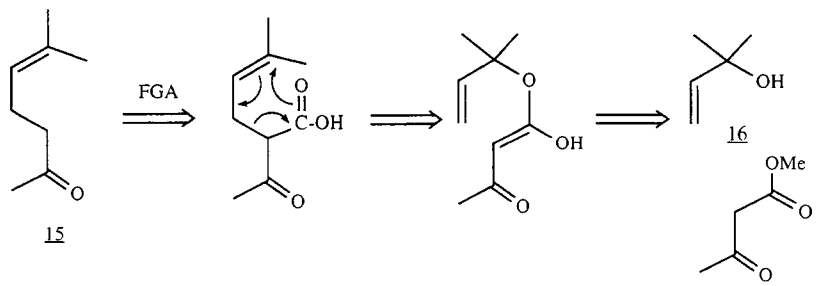
With respect to the above-mentioned unsaturated carbonyl compounds with a double bond and a carbonyl group separated by three carbon atoms (14), it can be stated here that they may be disconnected to an alkyl vinyl ketone and an allylic anion (Scheme 7.5), through an oxy-Cope rearrangement (*Cf.* Scheme 5.22).



14

Scheme 7.5

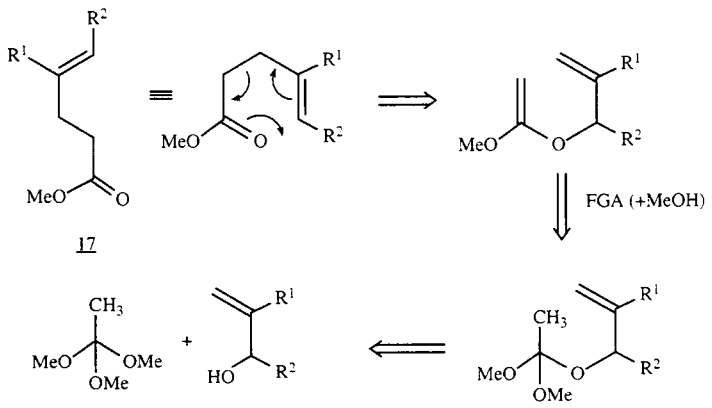
However, if only two carbon atoms are present (15) they may be disconnected to give an allylic alcohol 16 and the acetoacetic ester, through a retro-Carroll rearrangement [6] (Scheme 7.6).



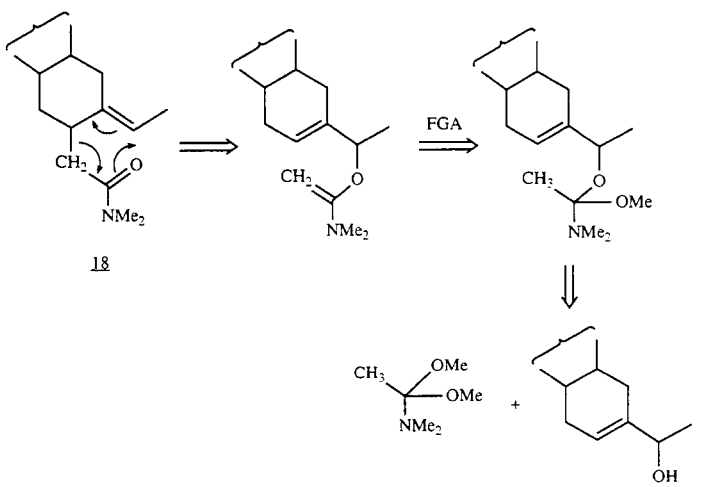
15

Scheme 7.6

In the particular case in which the carbonyl group belongs to a carboxylic acid derivative, such as an ester (17) or an amide (18) (or other functional groups which may be converted into it by a FGI), *then they may be disconnected according to the "orthoacetate-modification" of the retro-Claisen rearrangement* (Schemes 7.7 and 7.8) developed mainly by Eschenmoser [7] and Ziegler [8], independently, in the synthesis of alkaloids, and Johnson in a very simple and yet highly stereoselective synthesis of squalene [9].



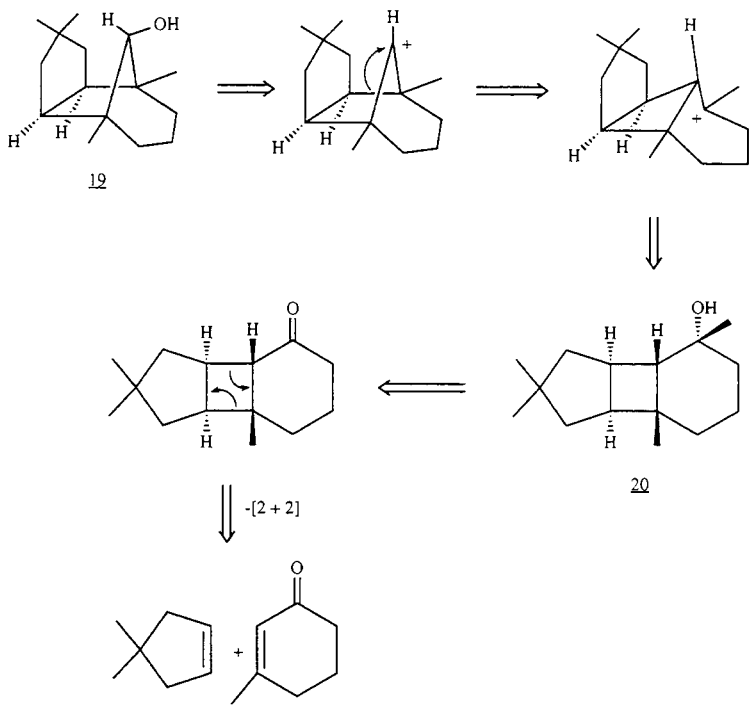
Scheme 7.7



Scheme 7.8

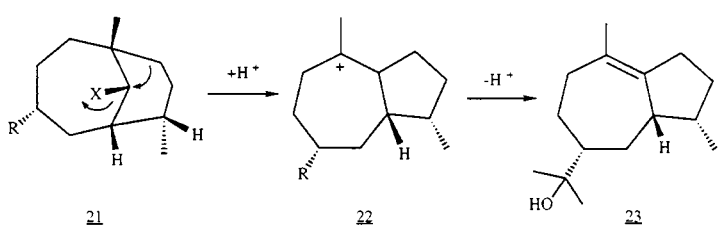
7.1.3. Wagner-Meerwein rearrangements

Related to the abovementioned internal fragmentations are the Wagner-Meerwein rearrangements which proceed through carbocation intermediates. A classical example is the synthesis of α-caryophyllene alcohol (19), in which the bridge present in the target molecule is created from a fused system (20) by a Wagner-Meerwein rearrangement induced by acid. The retro-synthetic process is shown in Scheme 7.9 [10].



Scheme 7.9

In contrast, in the formation of the hydroazulene ring of bulnesol (23) Marshall and Partridge [11] started from a bridged system (21) to arrive, through an intermediate carbocation 22, at the fused bicyclic system 23 (Scheme 7.10).



Scheme 7.10

7.2. Bridged systems

7.2.1. Strategic bonds: Corey's rules

In connection with the programme LHASA of "Computer Assisted Organic Synthesis" (see Chapter 14), Corey [12] developed an algorithm for determining the *strategic bonds* of polycyclic bridged structures [12b]. In this context, "strategic bonds" are those bonds whose disconnection leads to especially simple intermediate precursors in which the following structural features have been eliminated or, at least, minimised: i) appendages; ii) medium- and large-sized rings; iii) bridged rings and iv) appendages with chiral centres.

Because organic synthesis cannot be subjected to a rigorous mathematical analysis, the criteria for recognising "strategic bonds" have been derived heuristically. Although the algorithm implemented in LHASA for the selection of "strategic bonds" works on the bases of set theory (see below), Corey has stated six rules to define a "strategic bond", which may also be used in human synthetic analysis. A "strategic bond" must meet *all* of the following six requirements:

Rule 1: Because "normal-sized" rings are the most easily synthesised, *a strategic bond must belong (to be endo) to a four-, five-, six- or seven-membered "primary" ring*. A primary ring is one which cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another. For instance, the six-membered ring of structure 24 is not a primary ring. By contrast, such rings are designated as "secondary" rings.

24

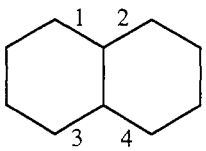
The envelope of two rings R_i and R_j is given by the "symmetrical difference",

$$R_i \oplus R_j = R_i \cup R_j - R_i \cap R_j$$

If n is the cyclic order, as we have already defined it (see Chapter 6), it is possible to demonstrate that the maximum number of rings is $2^n - 1$, and that there exist, as a minimum, n primary rings.

Rule 1 is restricted to primary rings because, in general, the progress of a synthetic ring-forming reaction is strongly affected by the size of the smallest ring containing the bond that is formed when such a bond is shared by two or more newly formed rings.

Rule 2: Two "sub-rules" should, in fact, be considered. 2A: *A strategic bond must be exo to another ring* (i.e., must be directly attached to another ring). This rule is justified because the disconnection of a bond which gives two functionalised appendages usually leads to a more complex synthetic sequence than a disconnection which leads to only one or no functionalised appendages. According to this rule, of the eleven bonds of a decalin such as 25 only bonds 1, 2, 3 and 4 are candidates for being considered strategic bonds.



25

2B: Because of the few known synthetic methods in which bonds are formed to a preexisting three-membered ring, *a strategic bond cannot be exo to rings of three atoms*. This condition limits the applicability of "sub-rule" A.

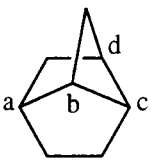
Rule 3: *A strategic bond must be in the ring which exhibits the greatest degree of bridging*. The "maximum bridging" ring is selected from the set of "synthetically significant rings" (s.s. rings), which is defined as *the set of all primary rings actually existing in the molecule plus all secondary rings with less than eight atoms.*

The "maximum bridging" ring of a molecular structure is defined as *the ring which has the maximum number of bridging atoms.* Notice that this definition is not equivalent to "the ring with the maximum number of bridgeheads" nor to "the ring which is bridged *most* to other rings".

Because of the subtlety of these concepts, some definitions are pertinent here. If two intersecting synthetically significant rings have more than one consecutive bond in common, the atom at each end of the common path is considered a *bridgehead*, provided that no other bond joins them directly. Then, given a pair of synthetically significant rings which have two bridgeheads, any path which joins them is a *bridge*. Furthermore, given any synthetically significant ring, two

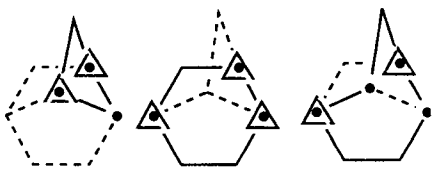
bridgeheads which belong to it constitute a pair of *bridging atoms* if a bridge -not included within the ring under consideration, but belonging to another synthetically significant ring- exists between them.

In order to illustrate the difference between these concepts, Corey analyses structure 26 in terms of the number of bridgehead atoms, the number of times bridged and the number of bridging atoms (the rings with the maximum number are indicated with **bold** numbers)



26

1 *2* *3*



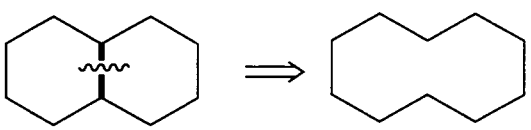
4 *5* *6*

It can be seen that the set of synthetically significant rings include the "primary rings" *1, 2, 3, 4* and the "secondary rings" *5* and *6*.

If the bridgehead atoms in structure 26 are designated as a, b, c and d, then the bridgehead atoms (•) in the synthetically significant rings are: *1* (a, b, d = 3); *2* (a, b, c, d = **4**); *3* (a, b, c = 3); *4* (b, c, d = 3); *5* (a, c, d = 3); *6* (a, b, c, d = **4**). On the other hand, the number of times bridged to other rings is, for each s.s. ring: *1* (2, 4, 5, 6 = **4**); *2* (1, 3, 4, 5 = **4**); *3* (5 = 1); *4* (1, 2 = 2); *5* (1, 2, 3 , 6 = **4**); *6* (5 = 1); and the bridging atoms (Δ) in each ring are: *1* (a, b, d = 3); *2* (a, b, c, d = **4**); *3* (a, c = 2); *4* (b, d = 2); *5* (a, c, d = 3); *6* (a, d = 2).

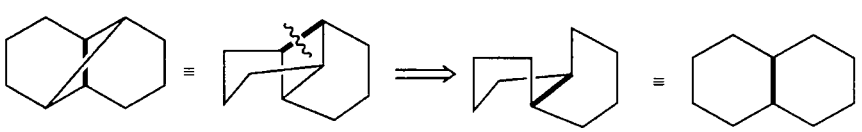
Of the six synthetically significant rings of structure 26 ring *2* is the one with the maximum number of bridging atoms (= **4**), in spite of the fact that ring *6* has the same number of bridgehead atoms and rings *1* and *5* are bridged the same number of times as ring *2*.

Rule 4: To avoid the generation of rings greater than seven-membered rings in retrosynthetic analysis, a bond may not be considered "strategic" if it is common to a pair of bridged or fused primary rings whose envelope is greater than or equal to eight. Such bonds may be designated "core bonds" and all other bonds in the cyclic system which are not "core bonds" may be designated "perimeter bonds". According to rule 4, *only "perimeter bonds" are candidates for "strategic bond" designation*. For instance, in the previously considered decalin 25, the central common bond (darkened in the diagram) is a "core bond" since its disconnection would lead to a ten-membered ring (27). The remaining bonds in 25 are "perimeter bonds".



25 27

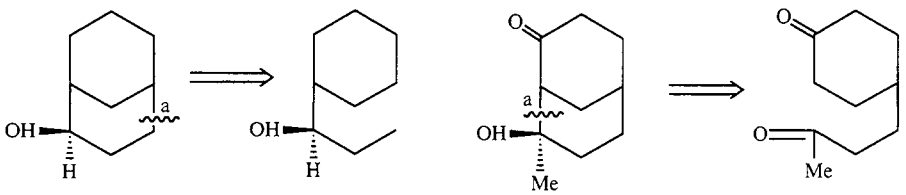
However, if there is another bond joining the two rings *directly* elsewhere (see 25a) then a "core bond" is still a candidate for strategic bond designation because the disconnection does not generate an eight-membered ring or larger (see 25a ⟶ 25). In the absence of the extra connecting bond, the central common bond must be again treated as a "core bond".



25a 25

Rule 5: *Bonds within aromatic rings are not considered to have strategic character*, because they mutually interact with each other and form an integral part of a single *kinetically* [13] stabilised system.

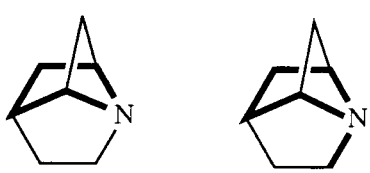
Rule 6: *None of the bonds which are part of a cyclic system linking a pair of common atoms* (i.e., fused, bridgedheads or *spiro*-ring junction atoms) *may be considered to be "strategic" if this cyclic system contains chiral centres.* In this way retrosynthetic cleavages which would leave chiral centres on side chains are avoided (see, 28 ⟶ 29). However, if the disconnection of the bond involves the simultaneous destruction of the chiral centre, and there are no other chiral centers in the resulting side chain, then the bond is still a candidate for being considered a strategic bond (30 ⟶ 31).



28 29 30 31

7.2.2. Appendix for polycyclic ring systems with C-heteroatom bonds

The same "heuristic principles" which are applied to carbocyclic compounds also hold true for simple heterocyclic compounds containing one heteroatom. However, in the case of bridged heterocyclic molecules a modified strategic bond selection must be applied. Besides the strategic bonds which meet Corey's six rules, the bonds directly attached to nucleophilic heteroatoms -such as O, S and N- are also strategic (*Cf.* heuristic principle HP-7), provided that they satisfy rules 2B, 4, 5 and 6. For instance, in compound 31a besides the five strategic bonds determined by rules 1-6 (cf. compound 26), the sixth darkened C-N bond in 31b is also a strategic bond.



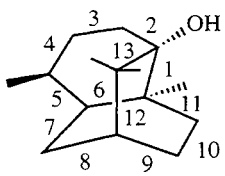
31a 31b

7.2.3 Examples of the application of rules 1-6 to carbocyclic networks for determining the "strategic bonds"

A good measure of the effectiveness of the strategic bond approach is -as observed by Corey- the comparison of the bond disconnections which it selects for a range of polycyclic bridged structures with synthetic routes which have actually been demonstrated by experiment. Corey found that in ten out of fourteen of the syntheses of bridged polycyclic compounds collected in "Art in Organic Synthesis" [14], the strategic bond procedure correctly identifies bond disconnections corresponding to those involved in the syntheses. The ten syntheses are those of: aspidospermine, copaene, helminthosporal, ibogamine, longifolene, lycopodine, morphine, quinine, strychnine and twistane. Of the remaining four syntheses, those of astarane and patchouli alcohol follow routes not generated by the strategic bond approach, but which involve bond-pair disconnecting transforms [(2 + 1) and (4 + 2) cycloreversions, respectively].

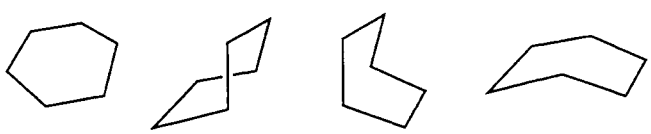
As an example of strategic bond selection let us consider the polycyclic network of patchouli alcohol (which is, in fact, a homoisotwistane) and see how a feasible synthetic route to its nor-derivative could actually be performed.

Patchouli alcohol (32):



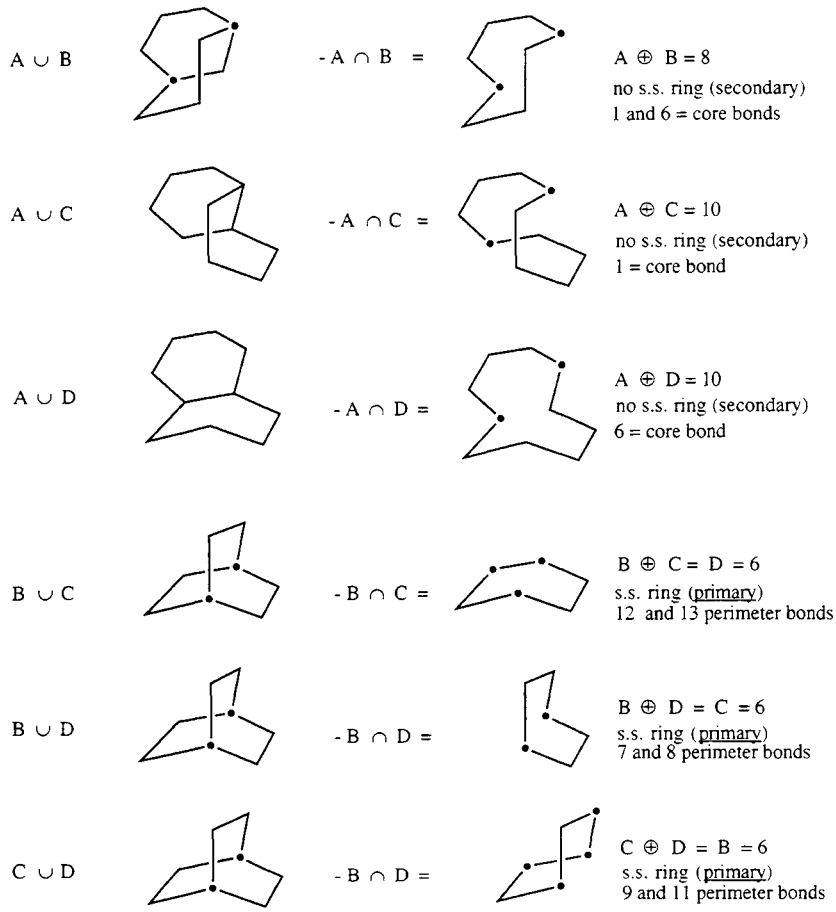
32

Cyclic order: 13 - 11 + 1 = 3, minimum number of primary rings. Actual number of primary rings = 4:

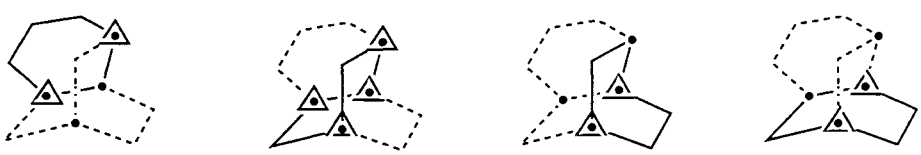


A B C D

Symmetrical differences: secondary rings, core bonds and bridgeheads:



Bridging sites: s.s. ring with maximum bridging atoms,



A

B
s.s. ring with
maximum bridging

C

D

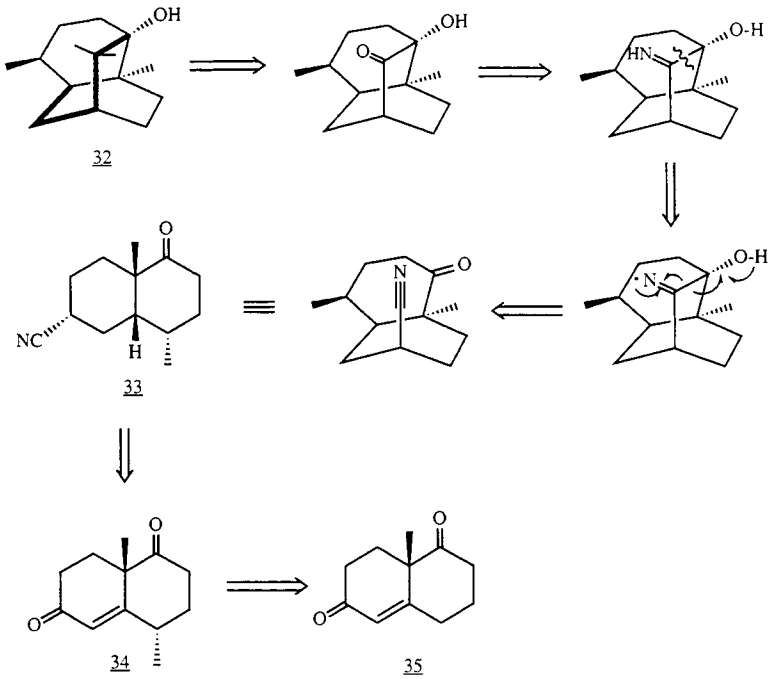
From a purely systematic point of view, it is convenient to present the results of strategic bond selection by means of a double entry table (see Table 7.1).

TABLE 7.1. Strategic bonds of patchouli alcohol skeleton

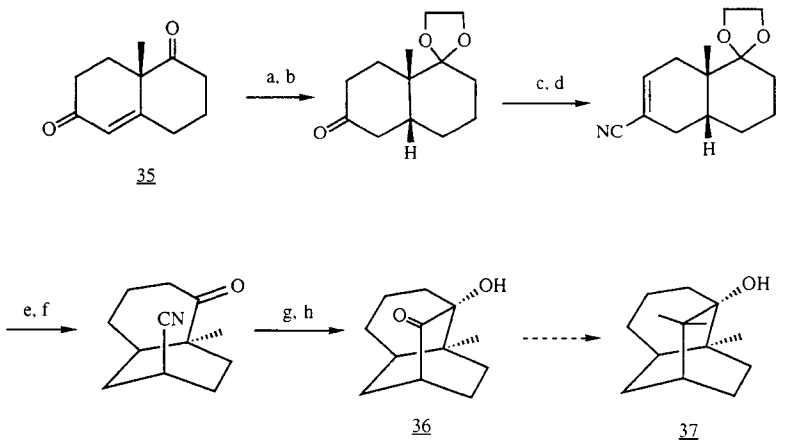
Rules \ Bonds	1	2	3	4	5	6	7	8	9	10	11	12	13
1	x	x	x	x	x	x	x	x	x	x	x	x	x
2	x	x	-	-	x	x	x	x	x	-	x	x	x
3	x	-	-	-	-	x	x	x	-	-	-	x	x
4	-	x	x	x	x	-	x	x	x	x	x	x	x
5	x	x	x	x	x	x	x	x	x	x	x	x	x
6	x	x	x	x	x	x	x	x	x	x	x	x	x
S.B.							x	x				x	x

It should be remembered that bond -strategic or not- disconnections may require some functional group manipulations. As already stated in *Heading 3.4.* the best way to proceed is by disconnecting the strategic bonds and then functionalise the resulting intermediates in such a way that the bond can be formed in the synthetic direction by known synthetic carbon-carbon bond-forming methods. In the above example, the disconnection of the strategic bond 13 leads to a *cis*-decalin 33, which is easily converted to the Wieland-Miescher ketone 35 (Scheme 7.11).

In practice, such synthetic scheme has been applied [15] to a formal synthesis of nor-patchoulol (37) which proceeds -via radical intermediates [16]- through the hydroxyketone 36 (Scheme 7.12).



Scheme 7.11



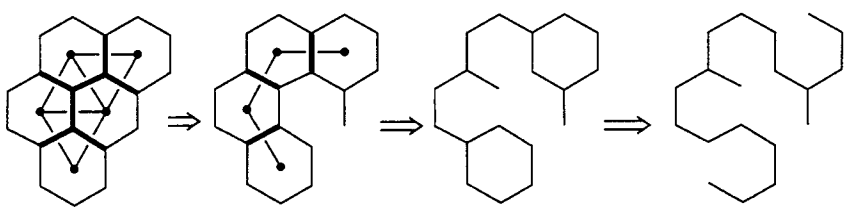
a) MED, *p*-TsOH, C_6H_6, Δ; b) H_2/Pd-C, EtOH; c) Me_3SiCN, KCN, 18-crown-6; d) $POCl_3$/Pyr; e) H_2/Pd-C, EtOH; f) Me_2CO, *p*-TsOH; g) Zn, Me_3SiCl; h) $Et_3N.HF$, H_2O

Scheme 7.12

7.2.4. Application of Corey's rules to polycyclic fused ring structures. The dual graph procedure

Corey's rules described above for determining strategic bonds were formulated specifically for *bridged* polycyclic networks and were not intended for polycyclic *fused* systems or for *spiro*-compounds. However, although they may be also applied to such systems -in which case rule 3, which is the most selective of the six rules, becomes meaningless-, in the case of fused systems the alternative method proposed by Corey based on the concept of the *geometric dual*[17] of the graph corresponding to the carbon network is more useful. This method provides a good guidance for the disconnection of polycyclic fused structures leading to more simple ring systems and/or chains with minimum branching. The method consists of disconnecting bonds which pertain to rings having "perimeter bonds" and the greatest number of "fused" atoms.

The method can be illustrated with a simple example: let us consider the diagram A which represents a pentacyclic fused system, as well as its *dual* in the graph theoretical sense. The thick lines are the "core bonds", as they were defined by rule 4. A strategic bond disconnection of the molecule can be effected as follows: i) Select the ring which has the largest number of core bonds and at least one noncore bond. Disconnect a noncore bond which is exo to the adjacent ring (A ⟶ B); ii) repeat process i) if necessary until the resulting *dual* is *linear*; iii) disconnect each noncore bond which is exo to two rings (B ⟶ C); iv) disconnect each bond endo to terminal rings at the connecting chain (C ⟶ D). The resulting intermediates B, C and D are then targets for further synthetic analysis.

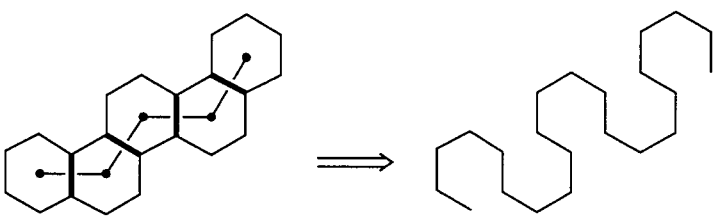


A B C D

[17] "Given a plane graph G, *its geometric dual G** is constructed as follows: place a vertex in each region (= chemical ring) and, if two regions have an edge x in common, join the corresponding vertices by an edge x' crossing only x" [17].

Some constraints must be added to this procedure, as for instance, in rule 6 which refers to the presence of chiral centres in newly generated appendages or side-chains, and also some extensions, for example the appendix referring to the presence of nucleophilic heteroatoms.

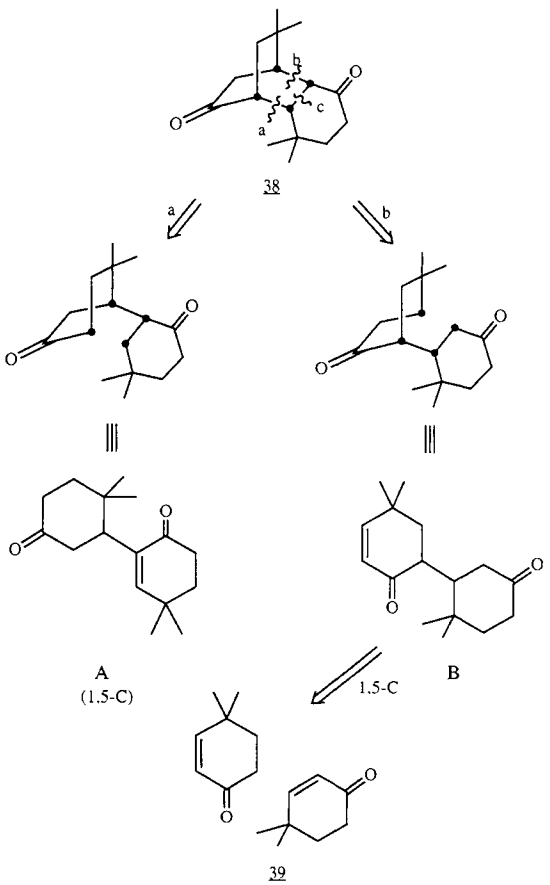
The application of this procedure to the fused polycyclic compound E, which already has a linear dual and only the last two steps (iii-iv) apply to it, leads to a linear acyclic structure F which may be traced back to the biogenetic cyclisation of squalene to lanosterol via cationic intermediates, as well as to the stereospecific cationic cyclisation of polyolefins studied by Johnson [18].



E F

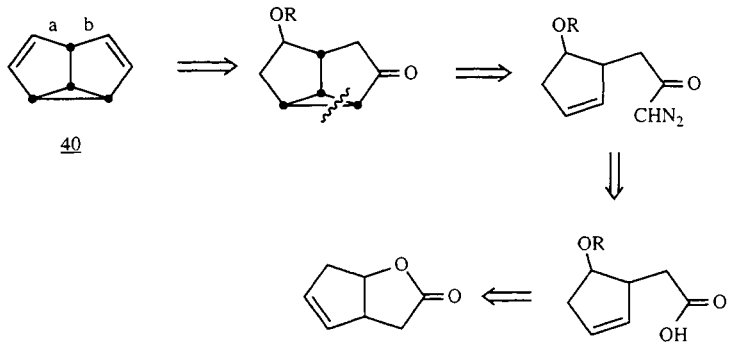
7.2.5. The "common atoms" and the molecular complexity approaches

In fact, the concept of "strategic bond" was already implicit in an early approach by Corey in connection with the synthetic analysis of longifolene [19], in which he refers to the disconnections of the bonds between "common atoms" as the most promising ones in order to generate simple intermediate precursors. "Common atoms" are defined as ring-member atoms which are bonded to *three* or *four* other ring members, but not two, which would then be *fused* atoms. Although Warren [20], defines "common atoms" as "all the atoms which belong to more than one ring", in practice, he rejects the bond disconnection between the atoms which are only common to two rings (*fused* atoms). For instance, in the generation of intermediate precursors of structure 38, of the three possible disconnections of bonds between the common atoms only a and b are considered because they give simple precursors. In fact, disconnection of bond b leads to a precursor B which can be disconnected into two identical moities 39; i.e., compound 38 can be advantageously synthesised by a reflexive convergent synthesis starting from a single starting material as simple as 39 (Scheme 7.13).



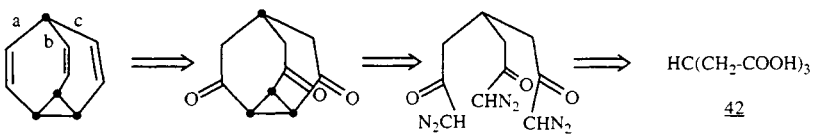
Scheme 7.13

The "common atom" approach is really operating when considering bond-pair disconnections, as in the case of semibullvalene (40) [21] (Scheme 7.14) and bullvalene (41). This compound does not have, strictly speaking, a typical polycyclic bridged network (bonds designated as a, b and c in structure 41 are the only "strategic bonds" according to Corey's rules), nevertheless the "common atom" approach offers a limiting case of simplification, since a *three-bond* disconnection -after substitution of the double bonds by equivalent synthons- allows the tricyclic structure to be reduced to an open chain precursor 42 [22]. The actual synthesis benefits from the high degree of symmetry present in the molecule since a C_3 axis of symmetry is mantained all along the synthetic sequence (Scheme 7.15).



40

Scheme 7.14



41 42

Scheme 7.15

Another alternative approach to the Corey's rules for the selection of "strategic bonds" are the "complexity indices" based on the mathematical model proposed by Bertz [23] which allow the "quantification" of the molecular complexity and to determine whether a given disconnection is indeed simplifying and how much so.[18] The indices predict "strategic bonds" quite well, with the exception of those which are "core bonds" since the limitations imposed by Corey's rule number 4 do not apply here.

7.2.6. Curran's retrosynthetic analysis of fused and bridged polycyclic systems through homolytic disconnections

After introducing the algorithm for strategic bond selection developed in connection with "computer-assisted synthetic analysis" (see Part B), we can now return to the use of radical intermediates in the synthesis of monocyclic (and polycyclic) compounds (see *Heading 6.1.3*).

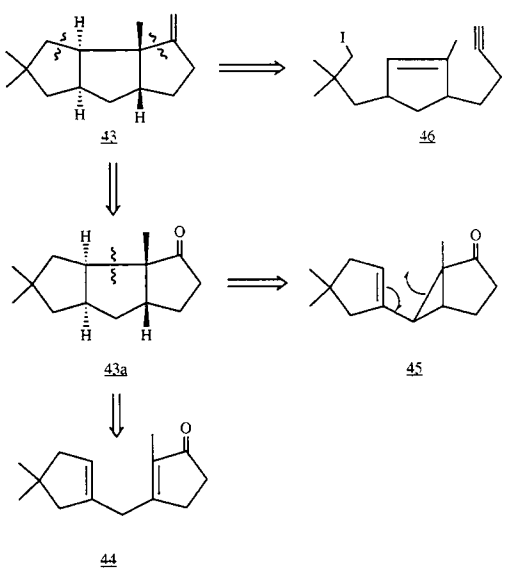
In fact, the reported synthesis of nor-patchoulol (37) (Scheme 7.12) is a good example of how the concept of "strategic bond" is suitable for the synthesis of

[18] See Appendix A-1.

bridged molecules proceeding through radical intermediates. However, an examination of the most recent syntheses of natural products exhibiting pentagonal fused polycyclic systems accomplished via radical intermediates indicate that the *graph dual* approach is not especially suited for the homolytic disconnections of such systems. In fact, owing to the intrinsic "symmetry" involved in the homolytic cleavage of a bond, this type of disconnection is very well suited for vicinal bond-pair disconnections (or "tandem radical strategy"), in which the radical generated in the first reaction is used as the precursor in the second one.

Compare, for instance, three possible disconnections of hirsutene (43): two proceeding according to the *dual graph* strategy (43 ⟹ 44 and 45) [24] [25], and another involving homolytic bond-pair disconnections (43 ⟹ 46) [26] (Scheme 7.16).

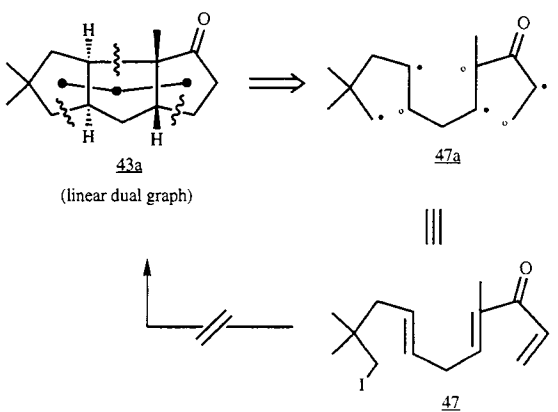
In practice, it was found that whereas the synthesis of hirsutene according to the *dual* strategy met with success under thermal conditions, but at temperatures as high as 580 °C, under photochemical conditions it afforded the unnatural *cis, syn, cis* configuration of some intermediates which then need further elaboration. Although the transformations 44 ⟶ 43a and 45 ⟶ 43a by a [2 + 2] -cycloaddition and a vinylcyclopropane rearrangement, respectively, may involve intermediates with a more or less biradical character, they are not typical radical reactions such as the ones we are considering here.



Scheme 7.16

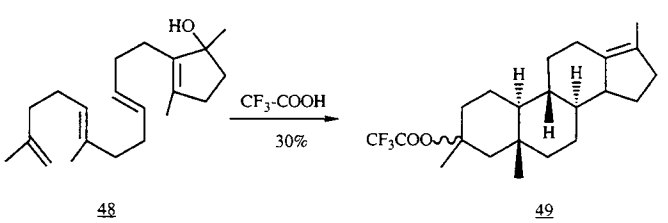
By contrast, in the synthesis of Curran and Rakiewicz (43 $\Longrightarrow$ 46) [26] following the bond-pair strategy, hirsutene (43) is directly obtained in 65% yield in one step from the properly functionalised intermediate 46 by homolytic iodine abstraction (see below, Scheme 7.21). This synthesis involves typical radical cyclisations in which there is a radical donor and a radical acceptor (see below).

Keeping in mind that the *dual graph* procedure provides good guidance for the disconnection of polycyclic fused structures leading not only to more simple ring systems (disconnection of just one noncore bond which is exo to two adjacent rings, 44 or 45), but to open chains with minimum branching as well, if we apply all the steps indicated in *7.2.4* to the *linear dual* 43a we will arrive at the open chain compound 47a. Functionalisation of 47a will afford the compound 47 (Scheme 7.17). Radical cyclisation of 47 to 43a, however, would require three 5-endo cyclisations which are too slow to be synthetically useful.



Scheme 7.17

It is worthwhile remembering once more that the cationic cyclisation of 48 yields, by contrast, the six-membered rings of compound 49 [27] (Scheme 7.18):



Scheme 7.18

As stated by Giese [28] these results may be explained in terms of two different transition states. Whereas theoretical calculations favour, in the case of radicals, an unsymmetrical transition state in which the distances between the attacking radical and the two olefinic carbon atoms of the double bond are unequal, the cations attack the centre of the double bond where there is the maximum electron density. In this context, we have already referred to Baldwin's rules which have been heuristically derived and represent an empirical approach to the same question.

In fact, the formation of five-membered rings during the radical cyclisation has been used extensively in the past few years for the synthesis of several polyquinanes.

Rather recently, Curran has published an important account of radical reactions and retrosynthetic planning [29], in which he introduces a convenient symbolism in order to incorporate radical reactions into standard retrosynthetic analysis.

Examples taken either from his own laboratory or from the recent chemical literature allow Curran to show how retrosynthetic analysis can generate ideas for new methods and reagents, as well as for new synthetic strategies in which homolytic cleavage of bonds are taken into account.

We have already referred to the retrosynthetic analysis of dissonant open chain molecules (see *Heading 5.5*). In this chapter we will deal with Curran's ideas in connection with fused and bridged polycyclic systems present in many natural products. Emphasis on cyclisations leading to 5-membered rings is maintained because:

1) *Cyclisations are usually faster for the formation of pentagonal rings than for any other ring size.*

2) *The regioselectivity for 5-exo cyclisations is often outstanding*, and

3) *High stereoselectivity is achieved in radical cyclisations leading to pentagonal rings.*

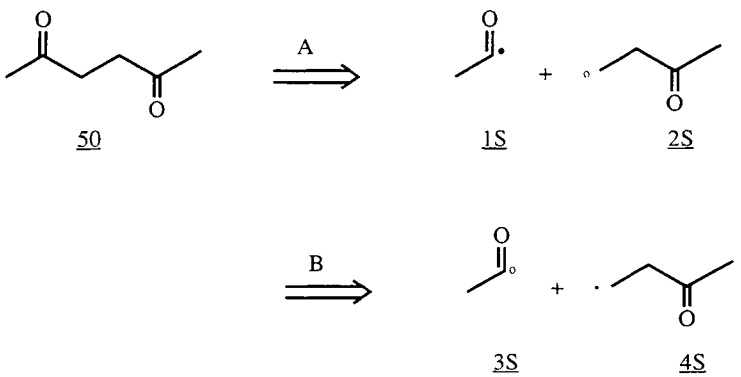
An exhaustive review of radical reactions in natural products synthesis, bearing either 5- or 6-membered rings, has been reported recently by Curran and his associates [30].

The strategies and symbolism developed by Curran for radical reactions [29] parallel, in some way, all that we have learned about polar or ionic reactions.

As we have seen above (see *Heading 5.5*), two fragments to be coupled by a radical reaction are represented with "dots" instead of the signs + or -. However, the radical/radical coupling is only a quite limited and rare process. More often, a bond

is cleaved retrosynthetically in a homolytic manner to give a pair of fragments or synthons, one of which is a radical donor and the other a radical acceptor. Curran uses "closed dots" (•) for radical donors and "open dots" (o) for radical acceptors (Scheme 7.19). Since homolytic cleavage of bonds is not associated with the polar character conferred by the heteroatoms (functional groups) present in the molecule, bonds that would have been left intact in standard retrosynthetic analysis can now be cleaved, and then formed by radical addition or cycloaddition reactions.

There are always two ways in which a bond can be homolytically cleaved, provided that the cleavage is not symmetrical, i.e., that the bond being cleaved does not join two identical fragments (as we have seen above, *Heading 5.5*):

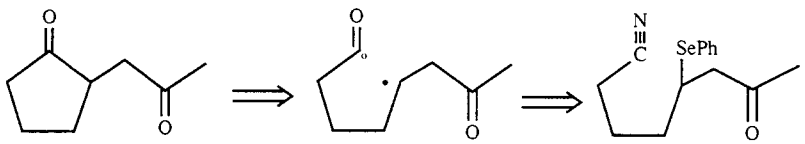


Scheme 7.19

As in the heterolytic cleavage of bonds, the resulting synthons must be elaborated to give the reagents or synthetic intermediates that should be used in the laboratory. In our example, the dissonant 1,4-carbonyl system can be synthesised in the laboratory following either route A or B.

For the route A, acyl radicals donors like 1S are readily generated from acyl selenides (1Sa) or acyl cobalt derivatives (1Sb); and radicals acceptors 2S are usually multiple bonds as in methyl vinyl ketone (2Sa) -although some homolytic substitutions are possible. On the other hand, nitriles (3Sa) are useful acceptors (3S) in radical cyclisations and 4Sa is an obvious synthon equivalent of radical donor 4S (See Table 7.2).

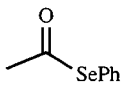
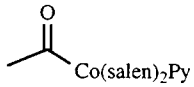
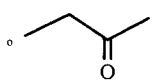
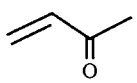
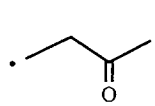
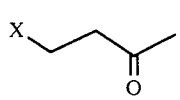
Since acetonitrile itself is a poor radical acceptor, strategy B is more suitable for intramolecular cyclisations (Scheme 7.20).



1,4-D
51

Scheme 7.20

TABLE 7.2. Equivalent synthons of radical donors and radical acceptors

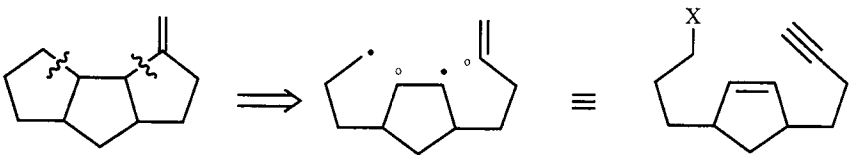
Strategy	synthon	synthon equivalent
A	 1S	 1Sa or  1Sb
A	 2S	 2Sa
B	 3S	-C≡N 3Sa
B	 4S	 X = halogen, selenide, xanthate, etc. 4Sa

With this new notation, we can now consider briefly the retrosynthetic analysis of some triquinanes and propellanes discussed by Curran [29].

As we will see, the general strategy for synthesising this pentagonal polycyclic system requires the homolytic disconnection of two vicinal bonds that are exo to the "central" ring, which remains intact (see Schemes 7.21 and 7.22). In the synthetic direction all the cyclisations must be, according to Baldwin's rules, 5-exo.

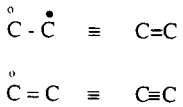
a) Linear triquinanes

retrosynthesis:

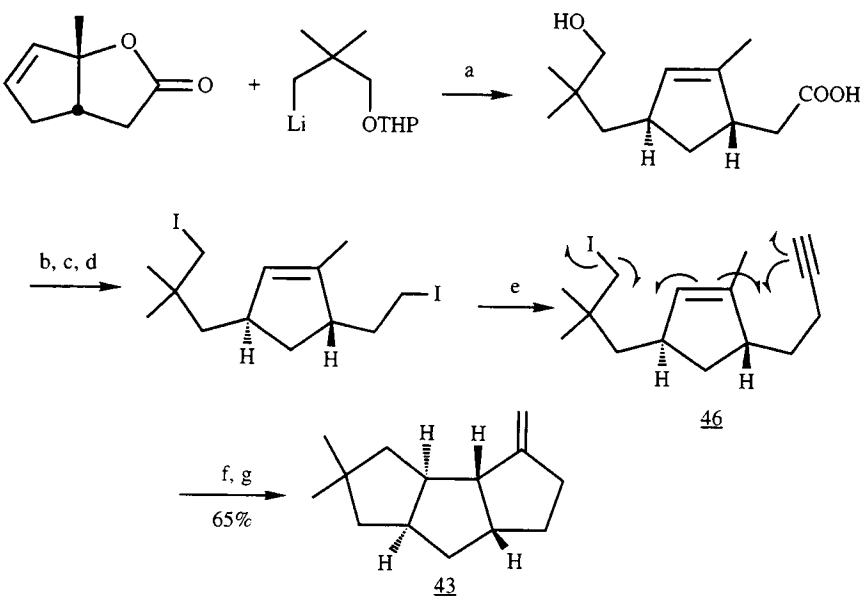


43b

equivalent synthons:



synthesis of hirsutene (43) [26] [29]:

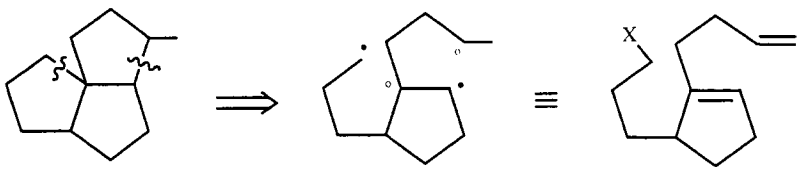


a) CuBr, H^+; b) $LiAlH_4$; c) Tf_2O; d) I^-; e) LiC≡CTMS; f) Bu_3SnH; g) $TolSO_2H$

Scheme 7.21

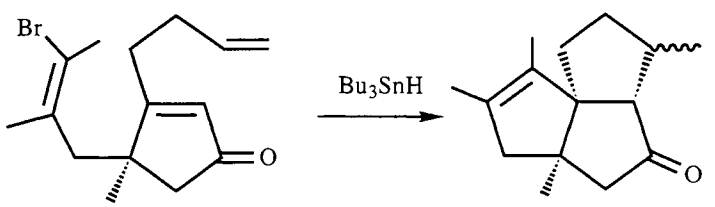
b) Angular triquinanes

retrosynthesis:



52a

synthesis of oxosilphiperfolene (53) [29] [31]:



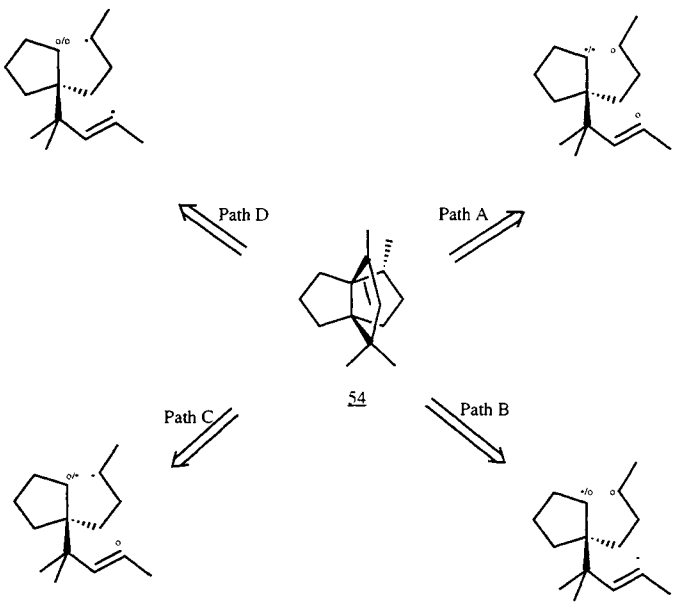
53a 53

oxosilphiperfolene

Scheme 7.22

c) Propellane triquinanes

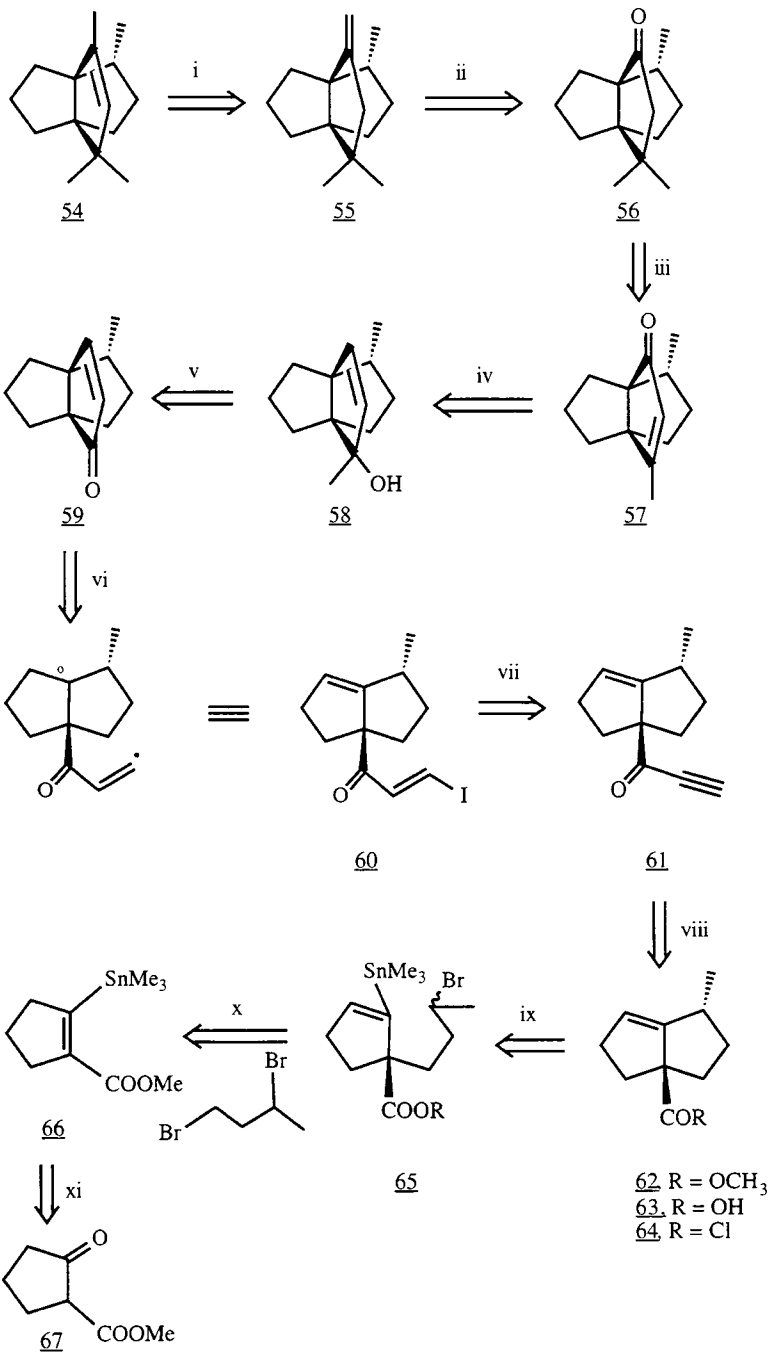
retrosynthesis: propellanes are a more complicated synthetic problem. Propellanes have three rings, any one of which can be chosen as the "central" ring, and there are two different ways to arrange geminal side chains; moreover, the two radical cyclisations from each precursor can be conducted in any of four different ways and with two different orders. Consequently, Curran identifies 48 different possible routes for synthesising the propellane triquinane modhephene (54). Scheme 7.23 summarises eight (four in two different orders) of them.



Scheme 7.23

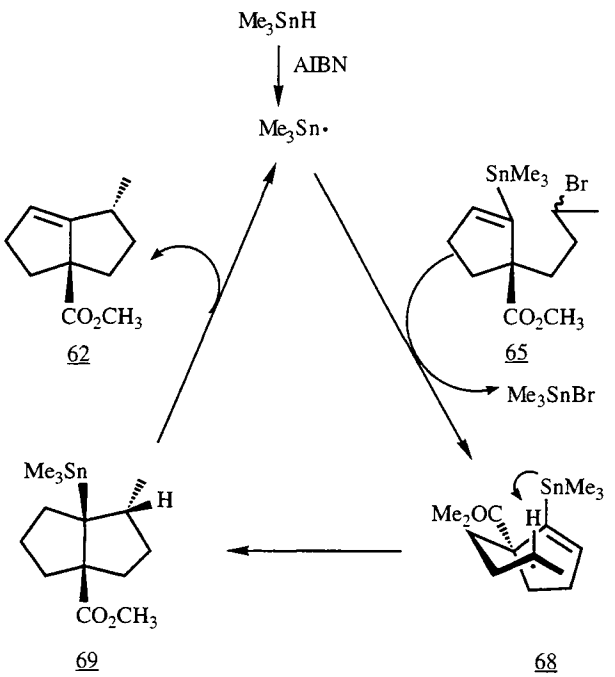
From an exhaustive retrosynthetic analysis and from the experimental work performed by Curran [29] [32], it was clear that the synthesis of modhephene required an elaborate strategy. In the first place, the tandem radical cyclisation should be conducted individually rather than just in one step since it allows more flexibility. In the second place, Curran's observation that the precursor of modhephene (54) could be the olefinic exocyclic derivative 55 allows the application of a series of heuristic principles already familiar to us, which greatly simplifies the retrosynthetic analysis and leads to diquinane 62, and, finally, through a second radical retroannulation to the very simple cyclopentanone derivative 67 (Scheme 7.24).

The retrosynthesis involves the following transformations: i) isomerisation of the endocyclic doble bond to the exo position; ii) substitution of the terminal methylene group by a more stable carbonyl group (retro-Wittig reaction); iii) nucleophilic retro-Michael addition; iv) reductive allylic rearrangement; v) dealkylation of tertiary alcohol; vi) homolytic cleavage and functionalisation; vii) dehydroiodination; viii) conversion of ethynyl ketone to carboxylic acid derivative; ix) homolytic cleavage and functionalisation; x) 3-bromo-debutylation; xi) conversion of vinyl trimethylstannane to methyl 2-oxocyclopentanecarboxylate (67).


i
ii
iii
iv
v
vi
vii
viii
ix
x
xi
54
55
56
57
58
59
60
61
62, R = OCH3
63, R = OH
64, R = Cl
65
66
67
SnMe3
Br
COOR
COOMe
COR
O
OH

Scheme 7.24

The synthesis of modhephene (54), which proceeds according to plan in an overall yield of >16%, with complete control of relative stereochemistry, demonstrates the ability of radical cyclisations to form propellane systems and generate highly crowded neopentyl quaternary centres. The accepted pathway for the cyclisation of the vinyl trimethylstannane 65 is shown in Scheme 7.25. The chair-like transition state 68, in which the methyl substituent on the radical is pseudoequatorial, accounts for the observed endo stereoselectivity.



Scheme 7.25

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8. STEREOCHEMICAL CONTROL IN MONOCYCLIC AND POLYCYCLIC SYSTEMS

8.1. Introduction

Although the present Chapter is devoted to the last of the three aspects involved in the synthesis of a complex organic compound, its purpose is not to offer an introduction to "Stereochemistry" from a structural point of view, but to give a general insight into the methods most commonly used to exert some kind of "stereochemical control".

Usually, the formation of a new chiral centre involves the conversion of a prochiral sp^2 carbon atom into one with sp^3 hybridisation, the methods most generally used being the aldol and related condensations, pericyclic reactions (especially the Diels-Alder reaction), epoxidation, cyclopropanation and additions to double bonds (hydrogenation and hydroboration). Another possibility is the conversion of a prochiral sp^3 carbon atom into a chiral centre, as for instance in the α-substitution (alkylation, halogenation, etc.) of a ketone.

The steric course of such conversions depends upon several factors, in particular:

i) the original conformation (Prelog's rule and Cram's rule),

ii) the ease with which the reagents may approach each other (steric and proximity effects),

iii) the energy of the transition states (Curtin-Hammett principle), and

iv) the stability of the reaction products (in equilibration processes).

In this context, it is worthwhile distinguishing between two kinds of stereoselectivity:

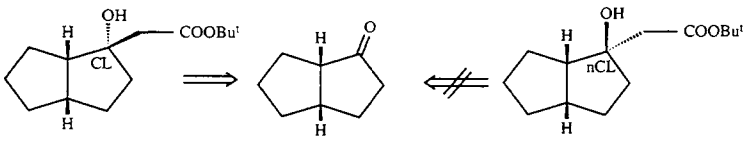
i) diastereoselectivity, which refers to the relative configuration, and

ii) enantioselectivity, which refers to the absolute configuration.

When the target molecule bears several chiral centres, the most obvious simplification in the retrosynthetic analysis is *to eliminate all the chiral or stereogenic centres and then to design the synthesis with as much stereoselectivy as possible* (for the concept of "selectivity" see below *8.2*). However, as pointed out by Corey

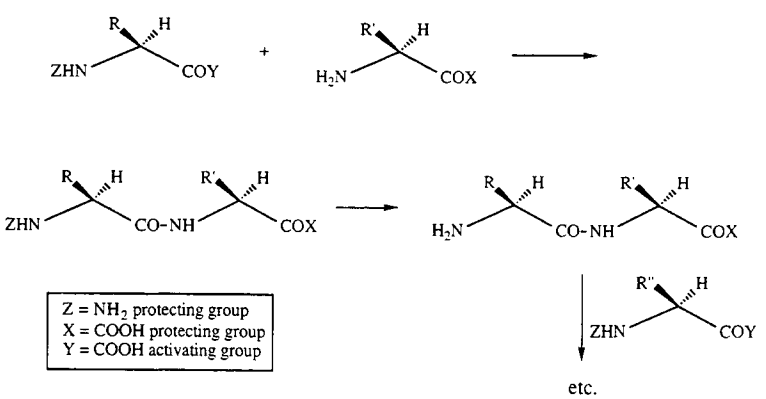
[1], since not all stereocentres can be selectively eliminated by a transform with stereocontrol, it is convenient to distinguish between *clearable* and *non-clearable stereocentres.* The *clearability* of a chiral centre is a function of both the availability of stereoselective transforms and the structural features in the target molecule. Obviously, the synthetic stereocomplexity depends not only on the absolute number of stereocenters, but also on the number of *non-clearable stereocentres.*

A good example of clearable and non-clearable stereocentres is found in the two following stereoisomers of bicylo[3.3.0]octan-2-one, in which the shape of the molecule *forces* the attack of the nucleophile to the carbonyl group from the convex face (attack at the β-face).

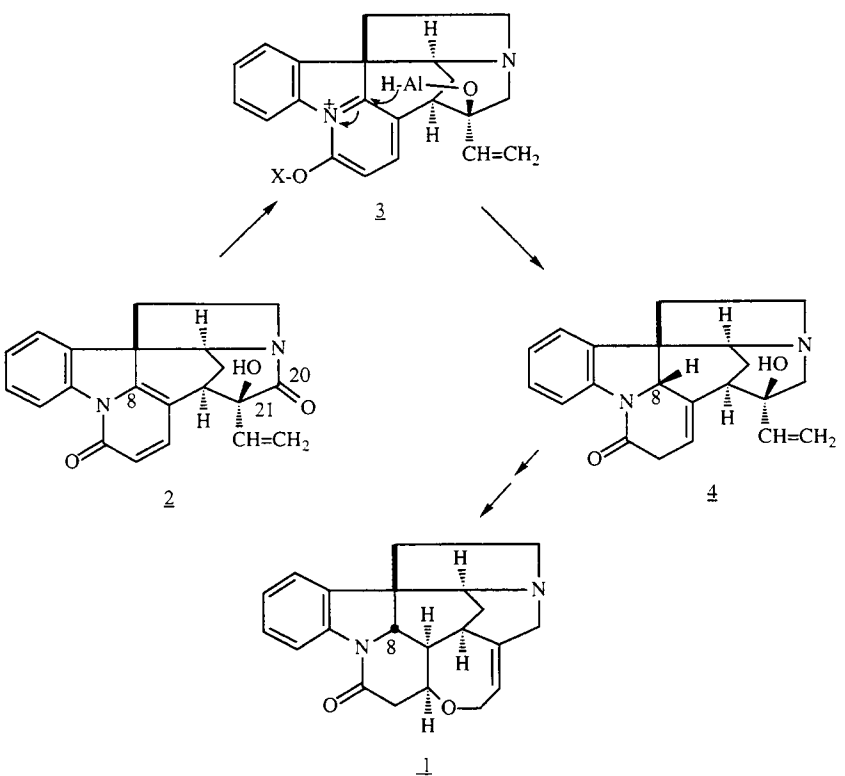


CL = clearable nCL = non-clearable

For an efficient stereochemical control the configuration of each isolated centre and also the interaction of one centre with the others must be taken into account. In the extreme case in which the centres are far enough apart that there is no interaction, the problem of a stereoselective synthesis may be very difficult, since it is not possible to exert any kind of stereocontrol. However, even in such a case some simplifying techniques are also possible, whether starting from synthons in which all the chiral centres in their absolute configuration are already present, or by using dissymmetric reagents or catalysts. The first technique is the one usually used in peptide synthesis, in which the starting materials are the optically active aminoacids:

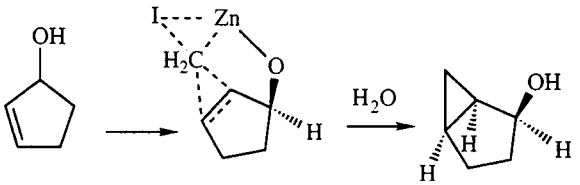


In less repetitive syntheses, it is possible to use remote functional groups as "control elements", a technique which depends more upon the opportunist tactics developed in the course of a synthesis rather than of a premeditated strategy. Such is the case, for instance, of the synthesis of strychnine (1) by Woodward [2], in which after synthesising the intermediate 2 a hydrogen at C(8) must be introduced onto the β-face (4), i.e., onto the most hindered concave face of the molecule (Scheme 8.1). Usually the reduction with a metal hydride would lead to the α-C(8)-H isomer (i.e., the hydride ion will atack from the less hindered face of the molecule), however in the present case the β-OH group at C(21) acts as a control element and, besides the reduction of the amide at C(20), a hydride ion attacks at C(8) from the β-face by an intramolecular transfer of the complex C(21)-O-Al-H (3).



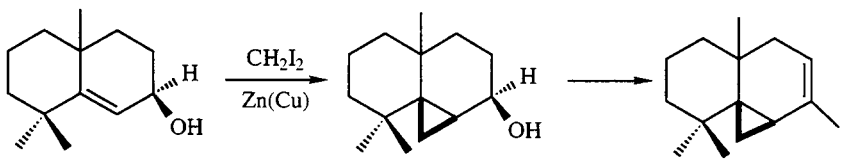
Scheme 8.1

A simpler example of this kind of stereochemical control is the cyclopropanation of cyclopenten-2-ol (5) by the Simmons-Smith reagent in which the *cis*-biciclo[3.1.0]hexan-2-ol (7) is the diastereomer exclusively formed. As in the case of the hydrogen in strychnine, the methylene enters stereoselectively by intramolecular transference from an intermediate complex (6).



5 6 7

An application of this type of stereochemical control is found in the synthesis of thujopsene (8) [3] (Scheme 8.2).



8

Scheme 8.2

When the chiral centres interact, then the different diastereomers, as well as the transition states leading to them, have different energies and it is possible to exert a *thermodynamic control* as well as a *kinetic control.* A stable configuration can be obtained by an equilibrating process, or thermodynamic control, as well as by a kinetically controlled stereoselective process. In contrast, a thermodynamically less favorable configuration usually requires a rigorous kinetic control (though a *correction* of configuration may be effected by an SN2 reaction). Therefore, the stereochemical control of a synthesis requires the application of the principles of conformational analysis, the application of equilibrating processes and a good knowledge of the different highly stereoselective synthetic methods available nowadays to the synthetic organic chemist.

8.2. Specificity, selectivity, order and negative entropy

The concept of "selectivity" must be clearly distinguished from the term "specificity" [4][5]. *Specific*, applied to a reaction, means that two (or more) isomeric starting materials give -under the same reaction conditions- different reaction products which are also isomers. Depending upon the isomers we may be considering, we may refer to "regiospecificity" (structural isomers) or to "stereospecificity" (either diastereospecificity or enantiospecificity). For instance, the formation of *meso*-2,3-dibromobutane by addition of bromine to (*E*)-2-butene, in contrast with the formation of the *d,l* - 2,3-dibromobutene from the (*Z*)-2-butene, is a case of diastereospecificity.

On the other hand, *selective*, usually applied to a synthesis, means that of all the possible isomers only one isomer is obtained. However, if the reaction product was/is a mixture of isomers one could speak then of the "degree of selectivity". Since usually one of the isomers will be the predominant isomer, we may say that the reaction (or the synthesis) is *selective* with respect to this particular isomer. As in the case of "specificity", we may refer to "regioselectivity" or to "stereoselectivity" (either diastereoselectivity or enantioselectivity) and may say, for instance, that a synthesis is 80% diastereoselective. According to the most updated terminology "diastereomers" are all the "stereoisomers" that are not "enantiomers", so geometrical isomers are also included in such a definition.

In contrast with the concept of "selectivity", "specificity" does not admit degrees: a reaction *is* or *is not* "specific". Diels-Alder cycloadditions, for instance, are "diastereospecific" in the sense that two diastereomeric dienophiles (the *Z* and the *E* isomers) react with the same diene, under similar reaction conditions, to give two diastereomeric adducts. Although specific reactions are always selective, the reverse is not true.

Notice that "stereoselectivity" means "order"; and order means "negative entropy" which, in turn, means "rigidity", "lack of flexibility" or "absence of degrees of freedom". It is always easier to exert stereochemical control in rigid monocyclic or polycyclic systems than in the more flexible open-chain compounds (remember the limitations imposed by Corey's rule number 6; see *7.2.1*).

Therefore, a fundamental axiom in the synthesis of complex organic compounds bearing chiral centres is the necessity of resorting to rigid structures whether in the starting materials (monocyclic or polycyclic molecules) or in the transition states (as in pericyclic reactions, for instance) in order to ensure an

efficient stereocontrol. One of the most common strategies used in flexible cyclic or linear open-chain compounds (to which we will refer as the "classical solution") is to introduce temporary rings or bridges into the starting materials, carry out the required sterochemical control and then to eliminate the auxiliary rings or bridges. By contrast, the most modern strategies (or the "contemporary solution") use the starting materials without any kind of modification and resort to "pericyclic or concerted reactions" which proceed through highly ordered transition states with a high negative entropy of activation. The different situations with which the chemist may be faced with are illustrated in Diagram 8.1.

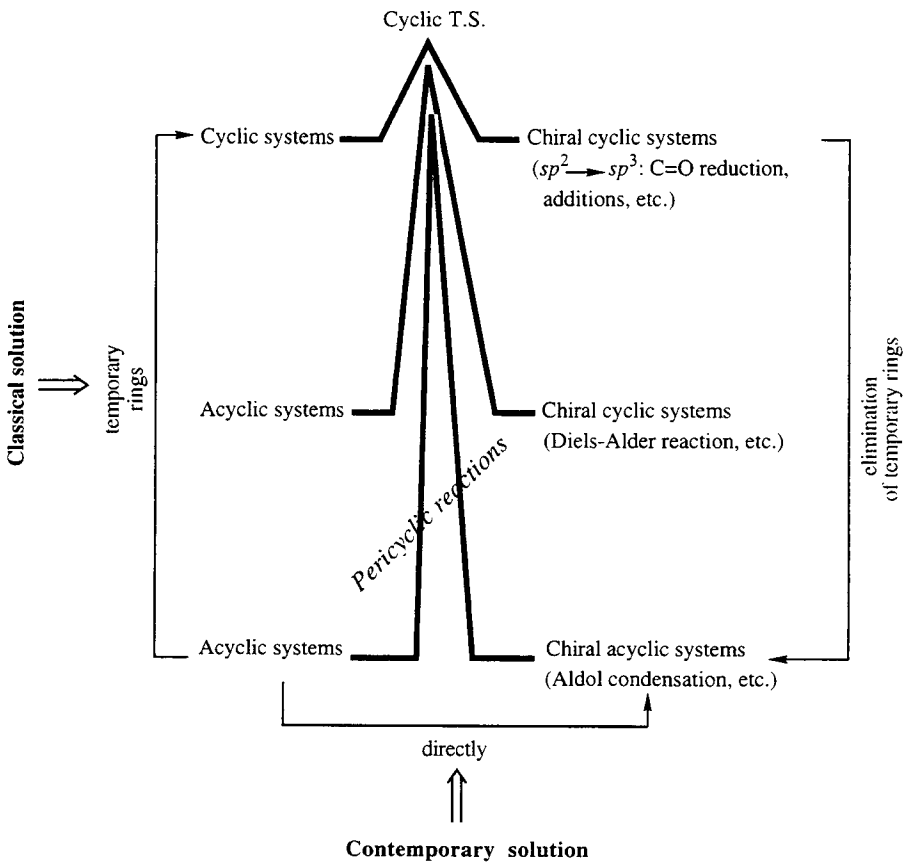
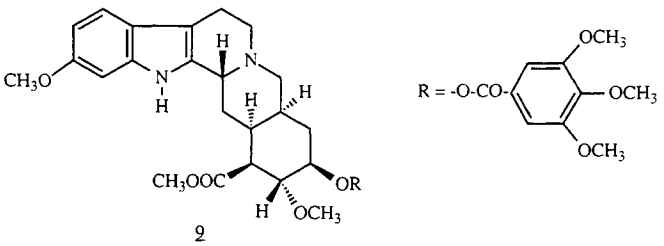


Diagram 8.1

8.3. Diastereoselectivity in monocyclic and polycyclic systems

8.3.1. Conformational stereochemical control

The importance of conformational analysis is made evident, for instance, in the total synthesis of reserpine (9) in which Woodward [6] introduced *conformational stereochemical control*, in two versions: thermodynamic control and kinetic control.



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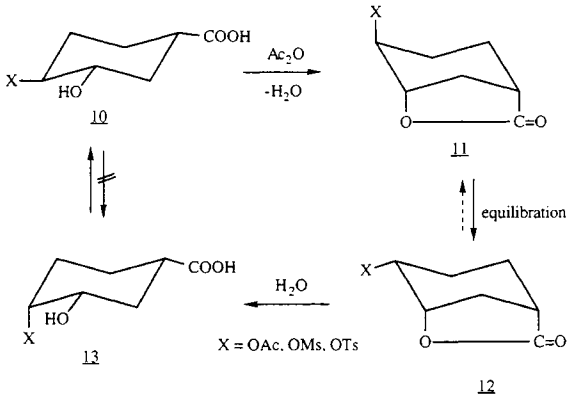
A simpler related example of *thermodynamic conformational control* is [7] the equilibration of an equatorial substituent (10) to the less favoured axial position (13) by changing the conformation of a ring (see Scheme 8.3). For this, the less stable conformation is "frozen" by formation of a rigid bridge (11) and the substituent which is now axial is solvolysed, under equilibrating conditions, to the more stable equatorial position (12). After the hydrolytic opening of the auxiliary bridge, the ring adopts the original conformation and the substituent takes up the less stable axial conformation:

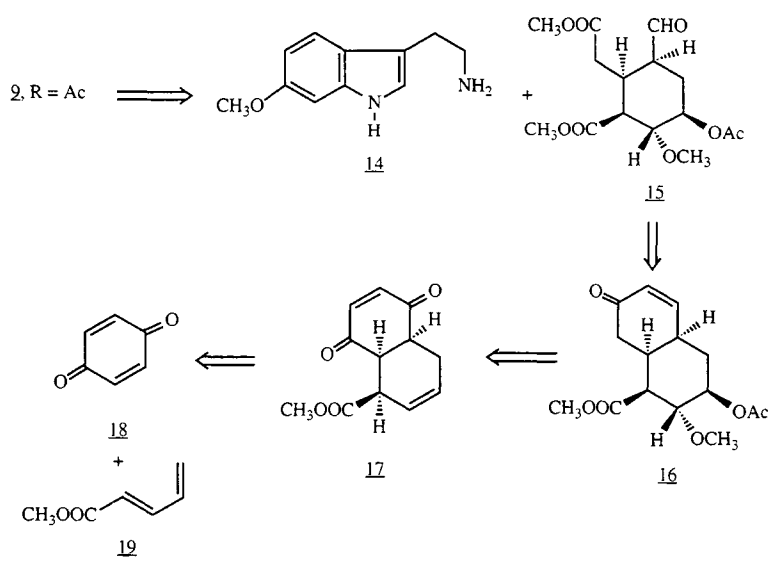


10 11 13 12

"Thermodynamic conformational stereochemical control"

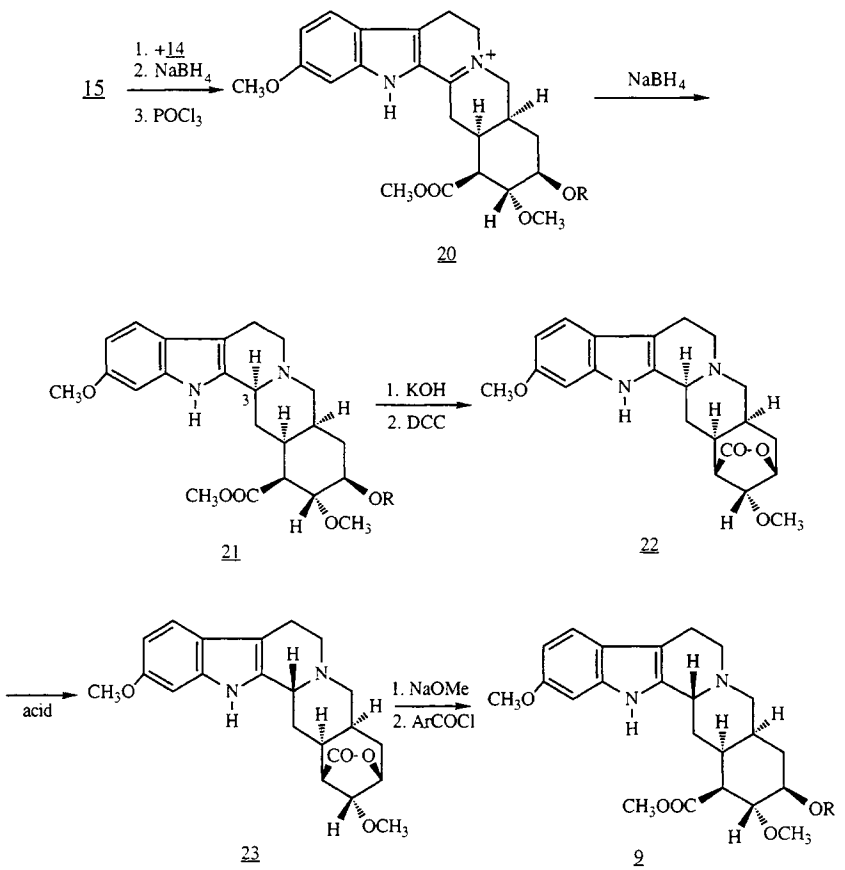
Scheme 8.3

Reserpine (9), which is an alkaloid isolated from the roots of *Rauwolfia serpentine* and has six chiral centres, was synthesised by Woodward and his associates [6] in a highly stereoselective fashion. Proceeding in the retrosynthetic direction, the application of the "heuristic principles" leads to Scheme 8.4, which involves the following transformations: i) FGI (9, R = Ac); ii) disconnection of the bonds directly joined to the nucleophilic nitrogen atom, to give ultimately 6-methoxytryptamine (14) and a cyclohexane ring (15), bearing an aldehyde and an ester group, which holds five of the six chiral centres present in the target molecule 9; iii) reconnection of the aldehyde and the ester functional groups to a new six-membered ring by introducing an "extra" carbon atom (such a reconnection, however, offers multiple advantages since, in the synthetic direction, it ensures the adequate oxidation level, allows Woodward to resort to a Diels-Alder condensation which will ensure the *cis*-configuration of the resulting decalin and the β-configuration of the carboxylic ester group (16), and creates a more rigid system which will allow a better stereochemical control of the two remaining chiral centres); iv) adjustment of the oxidation level and elimination of two chiral centres (17) to give a double bond which allows the Diels-Alder cycloreversion leading to 1,4-benzoquinone (18) and the doubly unsaturated ester (19) as the starting materials.



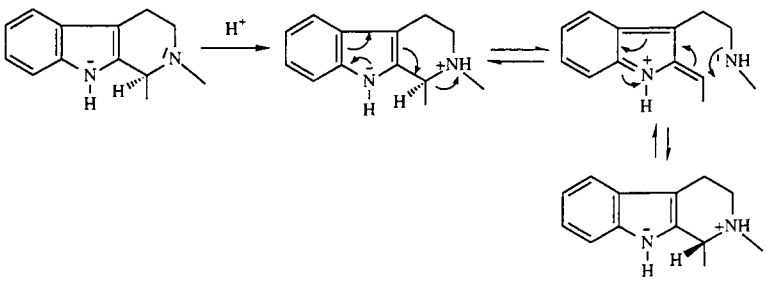
Scheme 8.4

In the synthetic direction, the coupling of the aldehyde-ester 15 with 6-methoxytryptamine (14), followed by a Bischler-Napieralski condensation [8] under the conditions shown in Scheme 8.5, leads to compound 21 whose configuration at C(3) is the reverse of the one present in reserpine (9), since it is kinetically formed by attack of a hydride ion to the iminium double bond of 20 from the convex (less hindered) α-face. It was at this stage of the synthetic sequence that Woodward made use of "thermodynamic conformational stereochemical control". For this, Woodward hydrolysed the two ester groups of 21 and created -by means of a dehydrating agent, such as DCC-, a lactone bridge between the free carboxyl and hydroxyl groups which forces a conformational change of the entire polycyclic system to the less stable conformer 22 which is now "frozen" by the lactone bridge.



Scheme 8.5

Equilibration under acid conditions (pivalic acid was used because it is a non-nucleophilic weak acid) epimerises the hydrogen at C(3) from the α- to the β-configuration because the axially oriented indole ring joined to ring C of the polycyclic system changes from the β-configuration, in which strong and highly destabilising 1,3-diaxial interactions are present, to the more stable α-configuration equatorially oriented (23).[19] The accepted mechanism for the equilibration process is as follows (see, however, ref. 9).



After opening the lactone ring with NaOMe, rings and substituents take up the original conformations. Esterification of the free OH group gives finally reserpine (9).

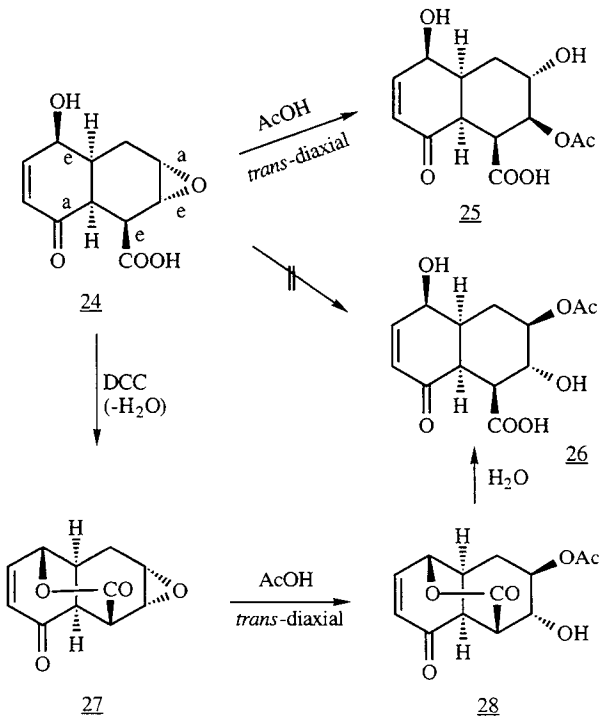
The *conformational kinetic control* of the chiral centres present in a molecule may be exemplified by the *trans*-diaxial opening of an epoxide i rf a polycyclic system [7]. In this case, the less stable conformation is also "frozen" by forming an auxiliary lactone bridge, which reverses temporarily the conformations of the rings and the substituents.

The opening of the epoxide in the *cis*-decalin 24 by acetic acid leads exclusively to the hydroxyacetate 25 (through a kinetically controlled *trans*-diaxial opening) rather than to the wanted diastereomer 26 (*cf.* the stereochemistry of the "southern" part of reserpine). To obtain the correct diastereomer the epoxy-lactone 27 is first formed (Scheme 8.6). Thus the conformation of the *cis*-decalin system, and therefore that of the substituents, is reversed. The kinetic *trans*-diaxial opening of the epoxide occurs in a regio- and stereoselective manner to afford compound 28 in which the substituents have the correct position and configuration (α-OH, β-OAc),

[19] It should be remembered once more that the use of molecular models ("ball-and-stick", as well as Dreiding or similar) is always essential for fully understanding the conformational and configurational changes involved in multistep syntheses of complex organic compounds

though in the less stable axial conformation. However, hydrolysis of the lactone bridge allows the *cis*-decalin to take up the original conformation with the substituents equatorially oriented (26).

In the synthesis of reserpine by Woodward (see Scheme 8.5) the stereochemical control of the five chiral centres follows a more elaborated route, but equally efficient and elegant.



Scheme 8.6

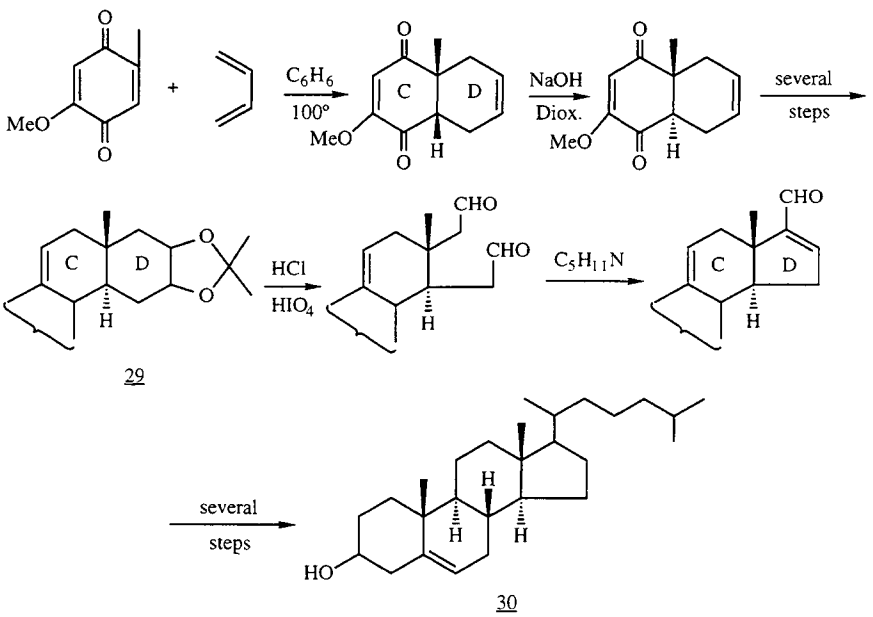
In fact, there is a great variety of methods for achieving the synthesis of less stable configurations, which depend upon steric and proximity effects. Such processes, as for instance the reduction of an 11-ketosteroid with sodium borohydride to give the axially disposed 11-β-OH, are explained by the attack of the reagent from the less hindered α-face of the molecule.

8.3.2. Configurational stereochemical control

Sometimes, in order to exert the pertinent stereochemical control, instead of inducing a conformational change, it is necessary to resort to a change of

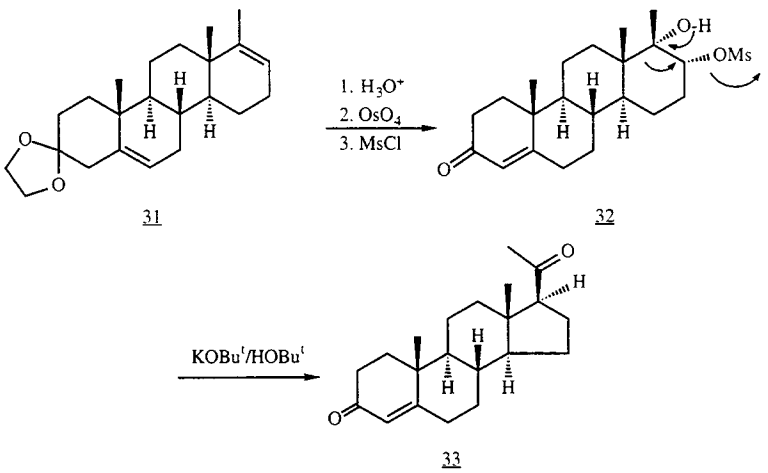
configuration which is more "expensive" from an energy point of view since the cleavage of some bonds is involved. For instance, most of the syntheses of steroids are based in the fact that the fusion between two six-membered ring have the more stable *trans*-configuration. However, in some instances it is possible to exert a regio- and a steroselective control starting from a *cis*-configuration in spite of the fact that the target molecule has a *trans*-configuration. The thermodynamic equilibration -usually through a base-catalysed enolisation- is carried out once the regio- and the stereoselective control have been exerted. Such is the case, for instance, in the syntheses of cortisone and conessine which have been discussed in the first Chapter (see Scheme 1.3).

On the other hand, in the synthesis of cholesterol (30) by Woodward and coworkers [10] the less stable *trans*-configuration between rings C and D is attained through a *homosteroid* (29), i.e. a steroid analogue in which the C/D indane system is substituted by a decalin in which the *trans*-configuration is the thermodynamically favoured (Scheme 8.7). The conversion of the six-membered ring into one of five members is carried out at a later stage, under conditions that do not affect the preformed *trans*-junction.



Scheme 8.7

Similarly, the synthesis of progesterone (33) by Stork and McMurry [11] also proceeds through a *homosteroid* 31 (Scheme 8.8), the conversion of the six-membered ring to the five-membered ring taking place directly in the last step of the synthesis (32 ⟶ 33), according to a pinacol-type rearrangement (*Heading 7.1*).



31 32 33

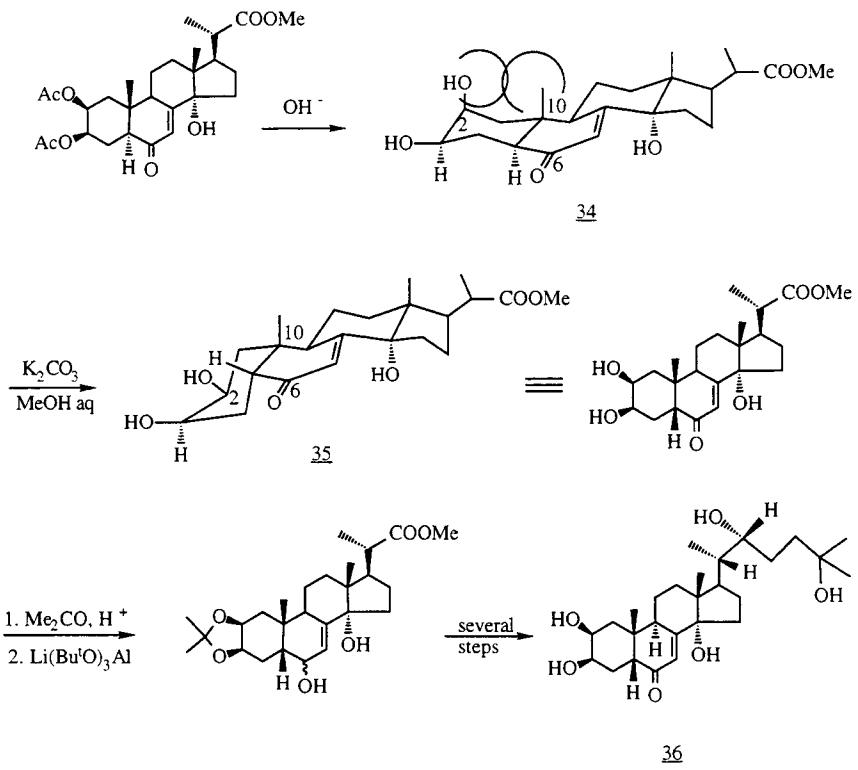
Scheme 8.8

8.3.3. Proximity effects

Although *trans*-decalins are thermodynamically more stable than the corresponding *cis*-decalins and it is possible to effect their transformation under equilibrating conditions, the synthesis of the insect hormone ecdysone (36), carried out by the Syntex group [12], offers an example of stability inversion due to the existence of 1,3-diaxial interaction (see Table 8.1) [13]. Thus, the intermediate 34 isomerises, under basic conditions, to the *cis*-A/B configuration (35) owing to the strong steric interaction between the 2-β-hydroxy group and the 10-β-methyl group (Scheme 8.9).

TABLE 8.1. Energies of 1,3-diaxial interactions

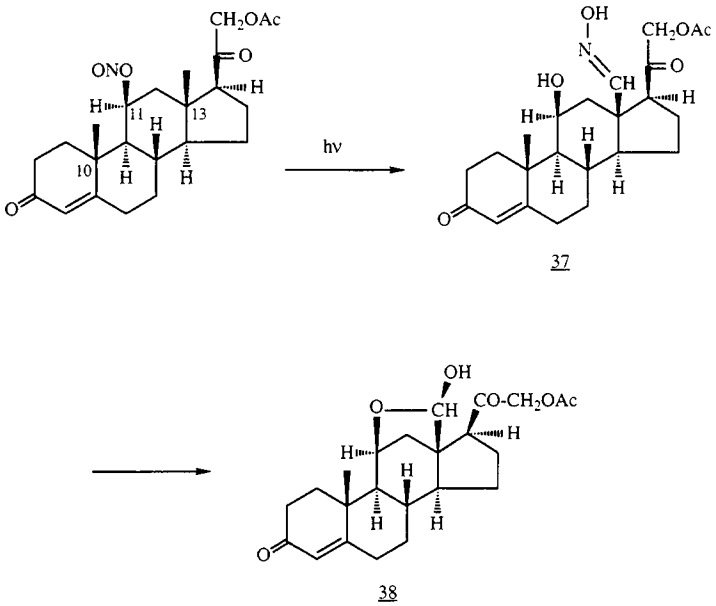
X	-OH	-OAc	CH_3	CH_3
Y	-OH	-OAc	-OH	CH_3
(Kcal/mole)	1.9	2.0	2.4	3.7



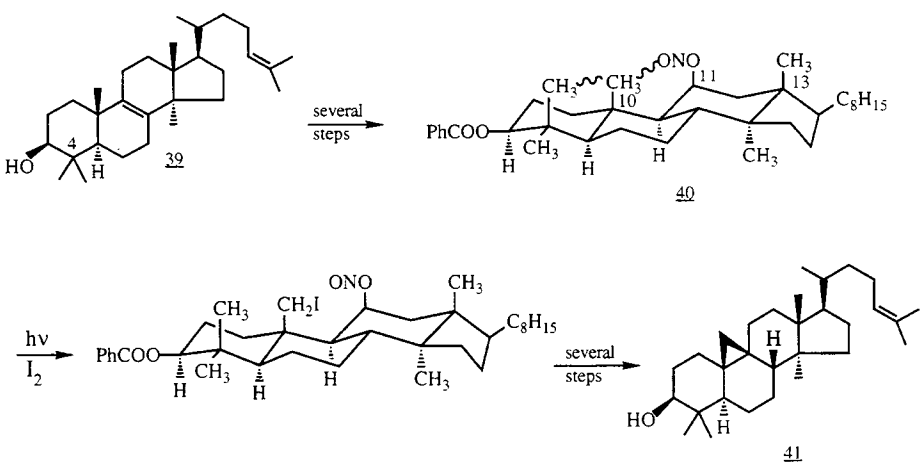
Scheme 8.9

A very elegant application of 1,3-diaxial interactions is found in Barton's partial synthesis of aldosterone (38) [14], in which an axial methyl group at C(13) is functionalised (37) by photolysis of a nitrite at C(11) which is also axially oriented [15] (Scheme 8.10).

Notice that the methyl group at C(10) is also properly oriented to interact with the nitrite group at C(11) and, in fact, it is always more or less affected. Barton [16] himself, in his synthesis of cycloartenol (41), from lanosterol (39), took advantage of this fact and succeeded in attaining the preferential functionalisation of the methyl group at C(10), versus the one at C(13), due to the presence of new 1,3-diaxial interactions between a methyl group at C(4) and the methyl at C(10), in the intermediate 40, which buttress the methyl group at C(19) closer to the nitrite group at C(11) (Scheme 8.11).



Scheme 8.10



Scheme 8.11

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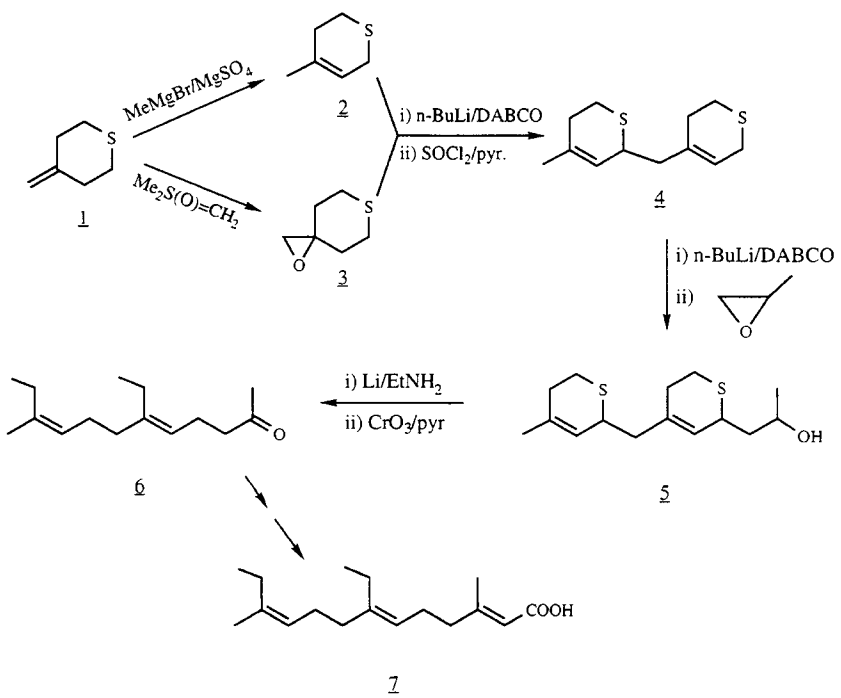
9. ACYCLIC STEREOSELECTION
I: STEREOCONTROLLED ALDOL CONDENSATIONS

9.1. Temporary bridges and auxiliary rings as control elements in acyclic diastereoselection

Since diastereoselection in linear systems may be very difficult to achieve, in the past few years chemists have developed different strategies aimed at solving the problem (see Diagram 8.1). As has already been stated, the "classical solution" is to introduce temporary bridges or auxiliary rings which are then eliminated after the stereoselection has been accomplished.



Scheme 9.1

9.1.1. The sulphur atom as bridging element

Particularly useful is the introduction of a sulphur atom as bridging element. One of the most classical examples, in which the sulphur atom introduces the necessary "rigidity" in order to ensure a complete acyclic diastereoselection of polyolefins, is the synthesis of the C_{18}-juvenile hormone [1] (Scheme 9.1).

Starting from dihydrothiopyrans 2 and 3, the key intermediate 5 was prepared, from which the C_{18}-JH (7) was synthesised by reductive desulphuration.

9.1.2. Woodward's synthesis of erythronolide A

Let us consider Woodward's synthesis of erythronolide A -the aglycone of the antibiotic erythromycin A- which was published posthumously [2].

Erythronolide A (8) is a 14-membered macrolide, with ten chiral centres. Because a 14-membered ring is not only as flexible as a linear open-chain, but also prone to experience several kinds of transannular interactions, any kind of stereochemical control must be exerted in the corresponding open-chain derivative,[20] i.e. in the seco-acid 9, or in the linear fragments resulting from its disconnection, which should be immobilised or "frozen" in someway.

Woodward's synthesis starts by recognising a hidden or "*pseudo*-potential" symmetry in the seco-acid 9 [*Cf.* the stereochemistry of the C(4)-C(6) fragment with that of the C(10)-C(12) fragment]. The retrosynthetic process involves (Scheme 9.2), in the first place, the disconnection of the C(2)-C(3) and C(8)-C(9) bonds to give a propionic acid fragment and two linear chains 10a and 10b, which have the same α,β-unsaturated ketone (11) as the common precursor. However, in order to achieve a complete stereoselection, the ketone 11 is "frozen" by means of two temporary sulphur bridges (Scheme 9.3), so the actual intermediate is the *cis*-dithiadecalin 12, the retrosynthetic analysis of which leads finally to the starting materials 15 and 16. In the synthetic direction (Scheme 9.4) the stereochemically controlled functionalisation of *cis*-dithiadecalin 12 gives the intermediates 18 and 19, corresponding to the linear fragments 10a and 10b.

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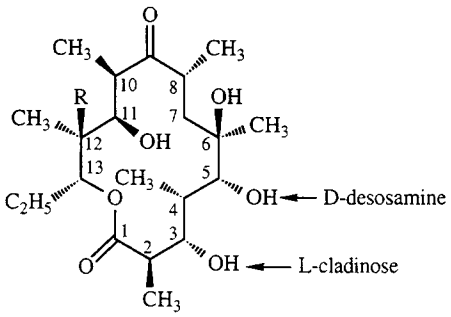
[20] However, epoxidations of more rigid unsaturated macrolides have been succesfully achieved in model studies. See, for instance, W.C. Still and A.G. Romero, *J. Am. Chem. Soc.* **1986**, *108*, 2105; and S.L. Schreiber, T. Sammakia, B. Hulin, and G. Schulte, *J. Am. Chem. Soc.* **1986**, *108*, 2106.



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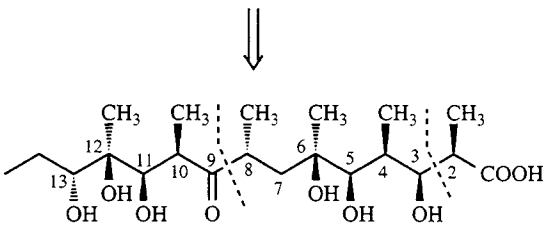
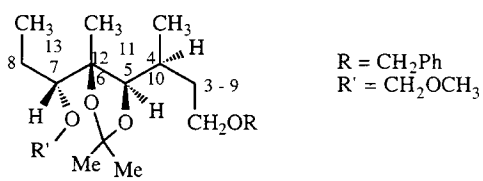
Erythronolide A, R = OH
" B, R = H



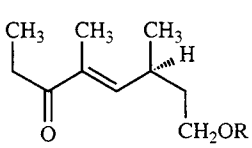
9

seco-acid



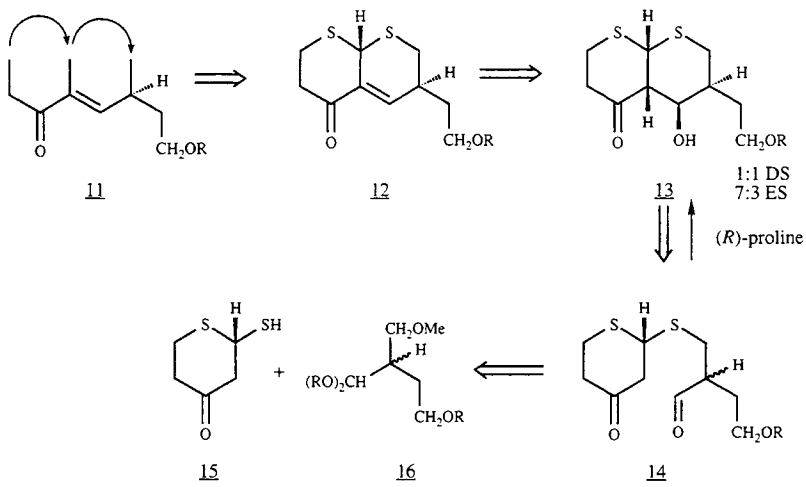
R = CH_2Ph
R' = CH_2OCH_3

10 a,b



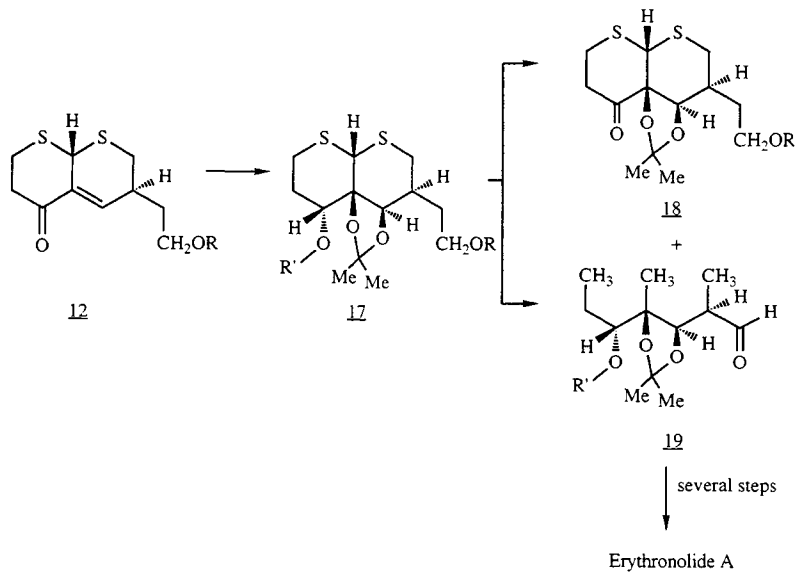
11

Scheme 9.2



Scheme 9.3

Although we consider here the synthesis only from the point of view of *diastereoselection*, because the aldol condensation (14 ⟶ 13) is induced by (*R*)-proline the synthesis is, in fact, an *enantioselective* synthesis.



Scheme 9.4

9.2. Diastereoselective control through highly ordered transition states

In contrast to the "classical solution" we have just discussed, we will now consider the aldol condensation -one of the most important carbon-carbon bond formation reactions [3], in both the laboratory and Nature[21] - as an example of the "contemporary solution" to the problem of acyclic stereoselection. As a reversible reaction, the design of highly stereoselective aldol and related reactions demands that all the stereochemical aspects involved in the C-C bond formation are kinetically controlled.

9.2.1. Diastereoselective aldol condensations and related reactions. The geometry of enolates

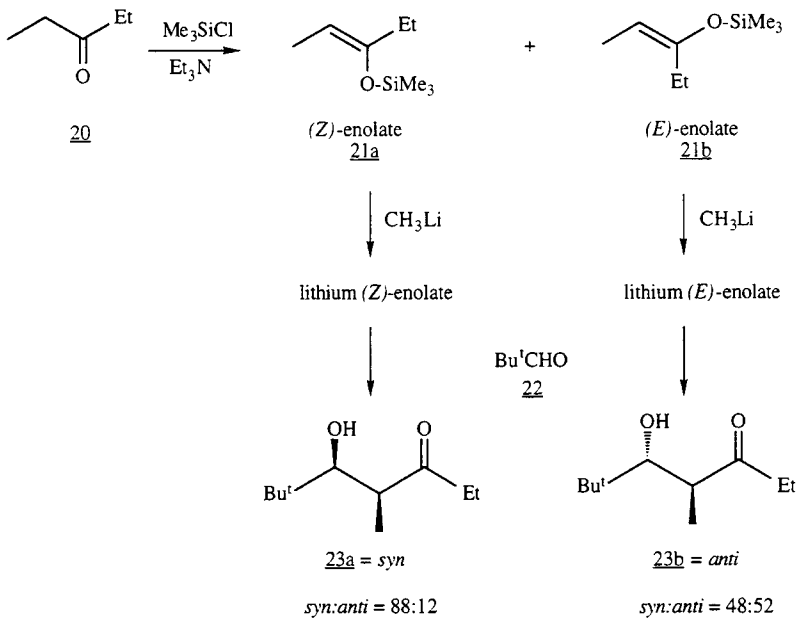
In 1957 Zimmerman and Traxler [4] suggested that the Reformatsky and the Ivanov reactions probably proceed through six-membered transition states in a "chair-like" conformation. On the other hand, Dubois and Fellmann [5], presented in the early 70's circumstantial evidence that the stereochemistry of the products resulting from aldol condensations depends upon the geometry of the enolate double bond. Thus, starting from 3-pentanone (20) -a symmetrical ketone to avoid problems of regiochemistry- they prepared the kinetic trimethylsilyl enolethers, according to the method of Stork [6], and separated the (*Z*)- and the (*E*)-isomers (21a and 21b) by preparative vapour phase chromatography (v.p.c.). From each one of the pure isomers, by treatment with methyllithium, the corresponding (*Z*)- and (*E*)-lithium enolates, respectively, were prepared. Each enolate was then reacted with 2,2-dimethylpropanal (22), and the *syn*-adduct (23a) was obtained as the predominant isomer (ratio *syn:anti* = 88:12) from the (*Z*)-enolate and practically a 1:1 mixture from the (*E*)-enolate (ratio *syn:anti* = 48:52) (Scheme 9.5).[22]

Although good diastereoselectivity, favouring the *syn* isomer is observed in the case of the (*Z*)-enolate, which allows a cause-and-effect relationship to be established, the same cannot be said in the case of the (*E*)-enolate.

---

[21] As stated by Sir John W. Cornforth, "Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations" [3f].

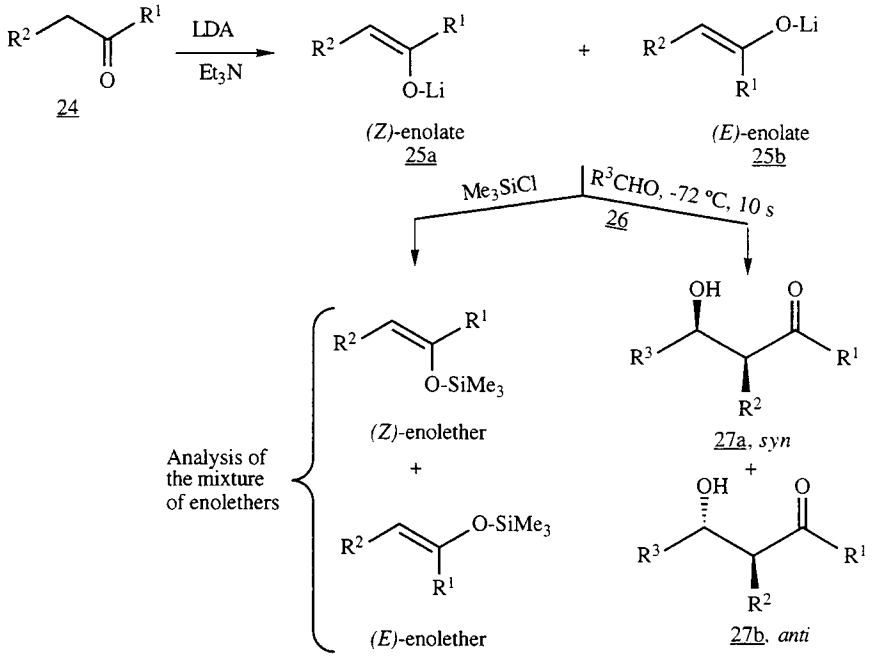
[22] The *"syn, anti"* terminology, proposed in ref. 7 and 8, rather than the *"erythro, threo"* used earlier, appears to have now been accepted for general use.



Scheme 9.5

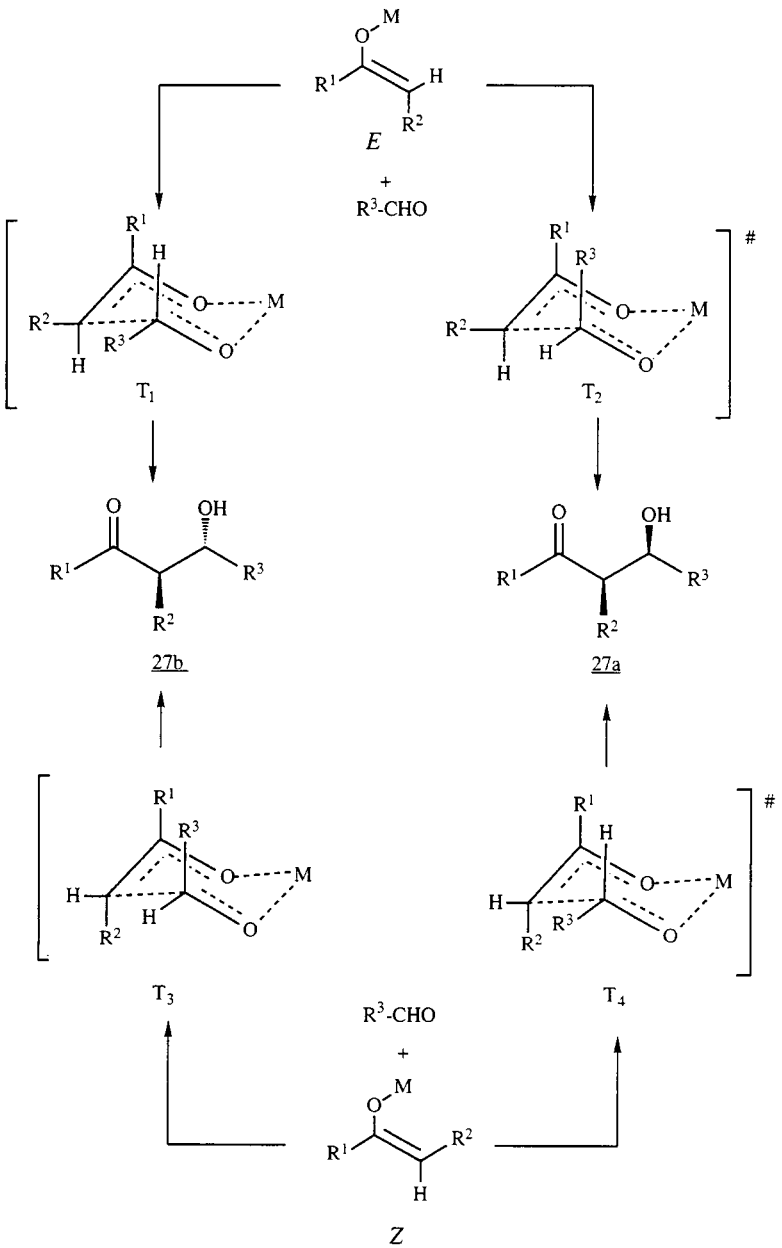
However, later on, Heathcock and his associates [9], working under strictly kinetic conditions (dropwise addition of the ketone to LDA in THF solution, at -78 °C), obtained compelling evidence of the relationship existing between the geometry of the enolate and the relative configuration of the resulting aldol, provided that the substituent R^3 of the aldehyde 26 is large enough, so as to govern the stereochemistry of the transition state. In such a case, the observed diastereoselectivity is good in the cases of both enolates: the (Z)-enolate (25a) gives the *syn*-diastereomer (27a) predominantly, and the (*E*)-enolate (25b) the *anti*-diastereomer (27b) (Scheme 9.6). With small substituents, which are less sterically demanding, the reaction affords little or no diastereoselectivity.

When the steric requirements of R^1 are important the (Z)-enolate (25a) is the predominant isomer and the resulting aldol is the *syn*-isomer. As the size of R^1 decreases the diastereoselectivity also decreases.



Scheme 9.6

These results may be interpreted in terms of 1,3-diaxial interactions between R^1 and R^3 present in the "chair-like" six-membered transition states postulated by Zimmerman and Traxler, which favour the transition states T_I and T_4 for the *(E)*- and *(Z)*-enolates, respectively, as shown in Diagram 9.1. Nevertheless, the presence of 1,2-*gauche* interactions between R^2 and R^3 and the participation of distorted or "boat-like" transition states [10], have also been invoked in some instances in order to account for the opposite *syn:anti* ratios observed in some experimental results with magnesium *(Z)*-enolates and pivaldehyde (22) [5], and for the lower selectivity observed for *(E)*-enolates in contrast with *(Z)*-enolates [11]. If R^2 is a sterically demanding group the 1,2-gauche interaction between R^2 and R^3 may raise the heat of formation of the transition state T_4, favouring either the T_3 or more likely a boat-like transition state T_B and the *anti*-isomer (27b) is then obtained from the *(Z)*-enolate (see Diagram 9.2).



(M = Li, MgL, ZnL, BL_2, AlL_2, etc.).

Diagram 9.1

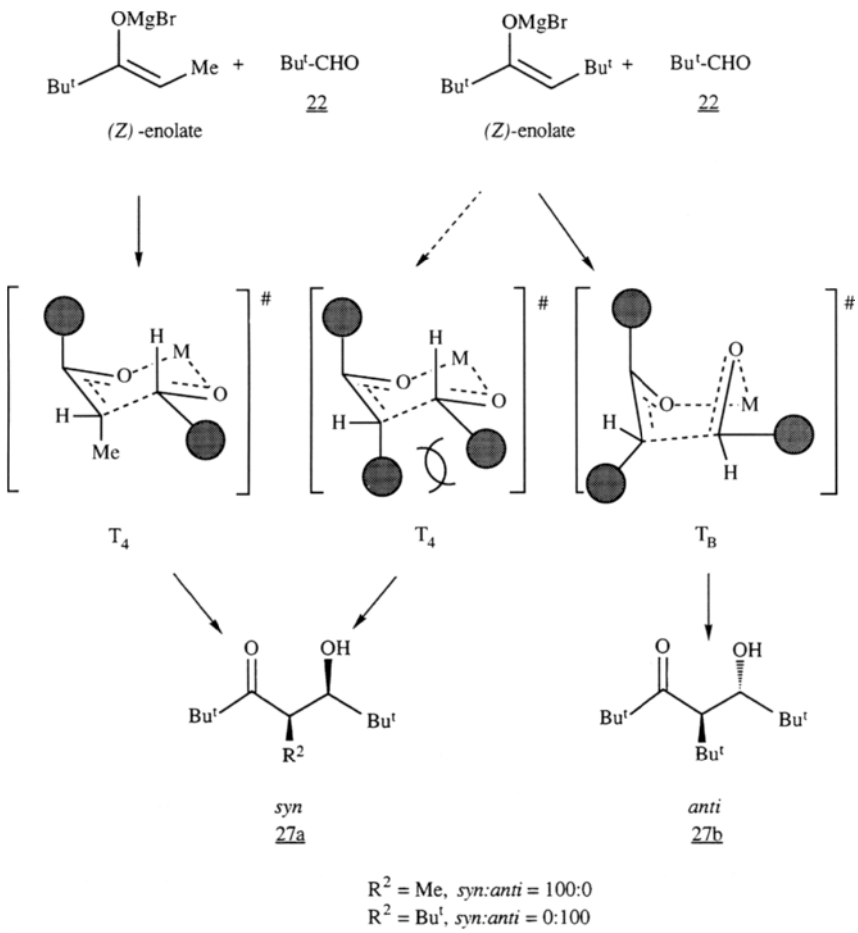
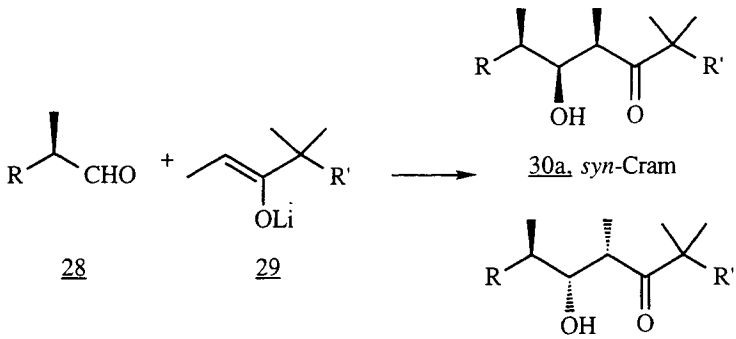


Diagram 9.2

In all the examples commented upon so far, we have dealt with reactions with *internal diastereoselective induction*. However, when a chiral centre is already present in one of the components [12] we must refer then to a *relative diastereoselective induction*, and Cram's rule [13] must be taken into account when the chiral centre is present at the α-position of the aldehyde (28). For instance, in the reaction shown in Scheme 9.7 of the four possible diastereomers only two are formed, the Cram-*syn*-aldol 30a being the predominant diastereomer (see below *9.3.3*).



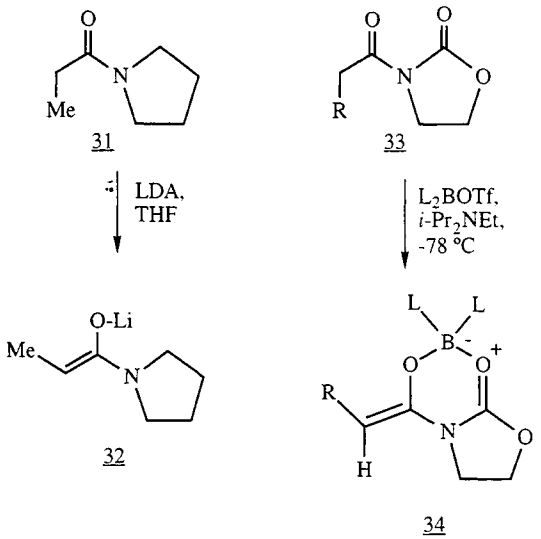
a) R = Ph R' = $OSiMe_3$
b) R = $MeOCOCH_2CH_2$ R' = CH_3

Aldehyde	enolate	30a:30b ratio
28b	29a	86:14
28b	29b	74:26
28a	29a	81:19

Scheme 9.7

9.2.2. Boron enolates as "modulators" in acyclic diastereoselection

A further step towards improved selectivity in aldol condensations is found in the work of David A. Evans. The work of Evans [3a] [14] is based in some early observations from Meyers' laboratory [15] and the fact that boron enolates may be readily prepared under mild conditions from ketones and dialkylboron triflates [16]. Detailed investigations with *N*-propionylpyrrolidine (31) indicate that the enolisation process (LDA, THF) affords the enolate 32 with at least 97% *(Z)*-diastereoselection (Scheme 9.8). Finally, the observation that the inclusion of potential chelating centres enhance aldol diastereoselection led Evans to study the boron enolates 34 of *N*-acyl-2-oxazolidones (33), which allow not only great diastereoselectivity (favouring the *syn*-isomer) in aldol condensations, but offer a possible solution to the problem of *enantioselective* total syntheses (with selectivities greater than 98%) of complex organic molecules (see below, *9.3.2*), by using a recyclisable chiral auxiliary.



Scheme 9.8

According to the Zimmerman and Traxler model, good selectivities can only be attained, in aldol and related condensations, by using substituents large enough to originate strong repulsive 1,3-diaxial interactions in the "highly ordered" chair-like six-membered cyclic transition states, in such a manner that selectivity decreases rapidly by decreasing the steric requirements of the substituents. However, boron enolates allow better diastereoselections [14] than enolates of alkali- and alkaline earth-metals because the B-O and B-C bond distances are shorter (see Table 9.1), so that the transition states are more compactly tied and, therefore, are more sensitive to steric effects. On the other hand, the presence of the ligands L attached to the boron atom introduce new 1,3-diaxial repulsions that favour the transition states in which such interactions are minimised.

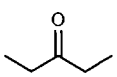
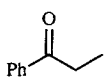
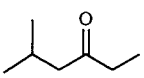
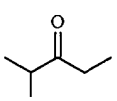
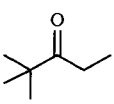
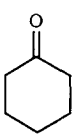
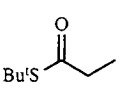
TABLE 9.1. Enolate bond distances

bond		distance
M-O	(M = Li, Mg, Zn, Al)	2 Å
B-O		1.4 Å
B-C		1.5 Å

Diagram 9.3 shows the 1,3-diaxial interactions operating in the different transition states T_1, T_2, T_3 and T_4. We can see how starting from the *(E)*-enolate the trasition state T_1, which leads to the *anti* isomer (27b), is energetically favoured over T_2 in which there exist three (R^1-R^3, R^1-L and R^3-L) 1,3-diaxial interactions. In the case of the (*Z*)-enolate the situation is reversed, the most favoured transition state being T_4, which leads to the *syn* isomer (27a).

Table 9.2 summarises some of the results reported by Evans and coworkers in aldol condensations of boron enolates with benzaldehyde [14].

TABLE 9.2. Aldol condensations of dialkylboron enolates with benzaldehyde

$RCOCH_2CH_3$	L_2BOTf	conditions [a] enolate formation	enolate ratio [b] *Z*:*E*	aldol ratio [c] 27a:27b	yield, % [d]
	L = *n*-C_4H_9	-78 °C, 30 min	>99:1	>97:3	73
	L = *n*-C_4H_9	-78 °C, 30 min (lutidine)	69:31	72:28	76
	L = C_5H_9	0 °C, 30 min	82:18	84:16	86
	L = *n*-C_4H_9	25 °C, 1 h	>99:1	>97:3	82
	L = *n*-C_4H_9	-78 °C, 30 min 0 °C, 30 min	>99:1	>97:3	82
	L = *n*-C_4H_9	-78 °C, 30 min 0 °C, 1 h	45:55	44:56	(92)
	L= C_5H_9	0 °C, 30 min	19:81	18:82	87
	L = *n*-C_4H_9	35 °C, 2 h	>99:1	>97:3	65
	L= *n*-C_4H_9	-78 °C, 1 h	--	33:67	(71)
	L = C_5H_9	-78 °C, 1 h	--	32:68	74
	L = *n*-C_4H_9	0 °C, 30 min	≤5:95	10:90	80
	L = C_5H_9	0 °C, 30 min	≤5:95	5:95	90

[a] Base i-Pr_2NEt; [b] ratios determined by conversion to TMS enolethers; [c] ratios determined by ^{1}H-NMR; [d] isolated yields (values in parenthesis determined by ^{1}H-NMR).

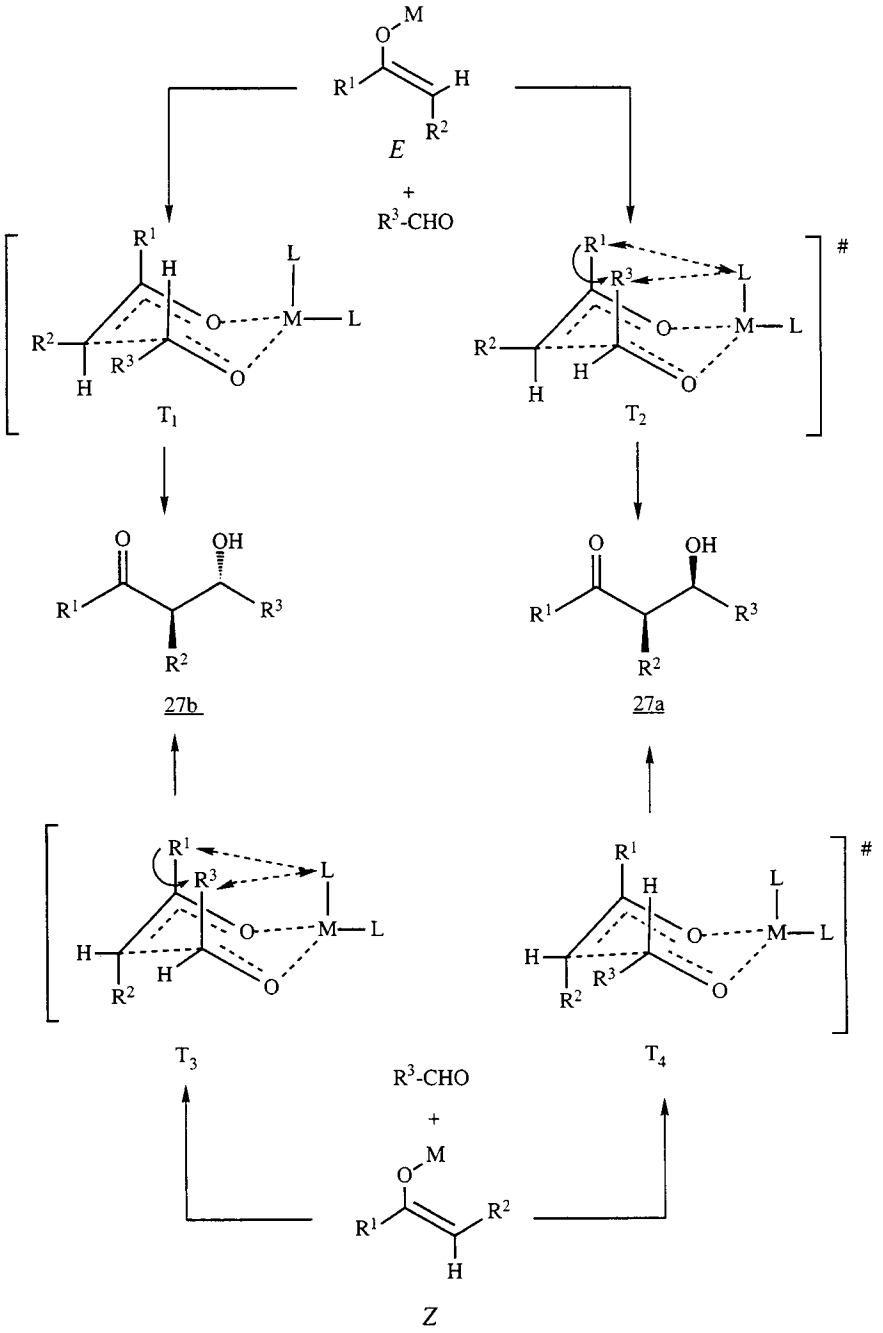
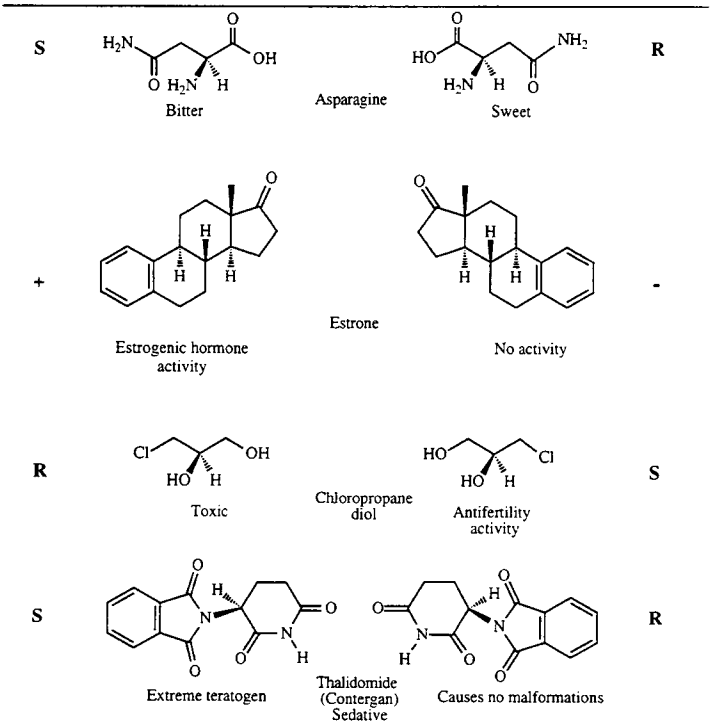

M
O
R1
H
R2
E
+
R3-CHO
R1
H
L
O
M
L
R2
R3
H
O
T1
R1
R3
L
O
M
L
R2
H
H
O
T2
#
O
OH
R1
R3
R2
27b
27a
R1
R3
L
O
M
L
H
R2
H
O
T3
R1
H
L
O
M
L
H
R2
R3
O
T4
#
R3-CHO
+
M
O
R1
R2
H
Z

Diagram 9.3

9.3. Enantioselective control

The paramount importance of enantioselective synthesis for the preparation of optically pure compounds becomes evident when considering the different pharmacological activities displayed by the two enantiomers of a chiral organic molecule (see Table 9.3) and the danger that the pharmacological use of racemates entails. In spite of this potential danger, it has been estimated that only 5% of the drugs having chiral molecular structures are synthesised nowadays in the pure optically active form.

TABLE 9.3. Absolute configuration and biological activity [17]

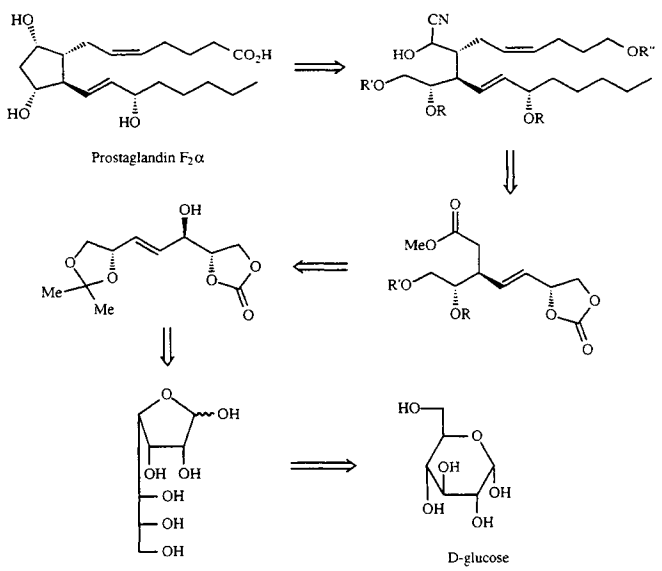


A well known example of tragic consequences is provided by "Thalidomide" (or "Contergan") which was commercialised in the 60's: whereas the (*R*)-enantiomer shows a weak sedative activity, the enantiomer of (*S*)-configuration, administered together in the racemate, caused in the expectant mothers a teratogenic effect (malformations) on the foetus.

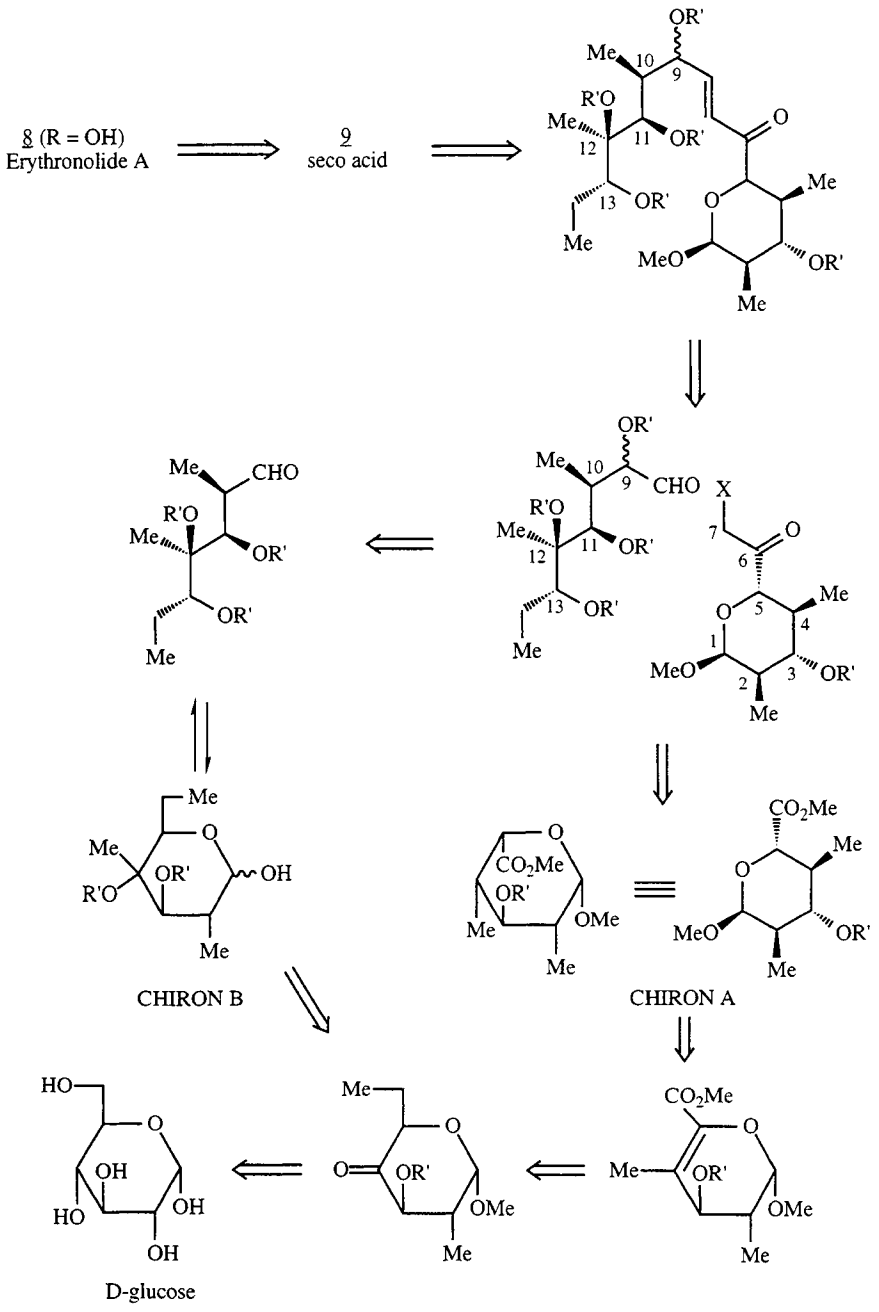
9.3.1. Strategies

Until very recently, the strategy most generally used to obtain enantiomerically pure substances was to work with the racemic mixtures all along the synthetic sequences and to carry out the resolution into optically active forms only in the final steps of the synthesis. However, it was soon evident that in the case of compounds of industrial interest which involve complex synthetic sequences, the strategy was not economically feasible since it meant not only wasting half of the material at the end of the synthesis, but also all the expenses of processing it had to be accounted for. For this reason, as early as 1960, Velluz and his coworkers [18] developed some industrial syntheses of steroids in which they carried out the resolution at the very first possible opportunity, thus avoiding processing of the unwanted isomers. A more elegant strategy is to start from naturally occurring optically active compounds, such as aminoacids, sugars and terpenes [19].

Examples are the synthesis of prostaglandin F_2 and erythronolide A (8) from D-glucose, by Stork [20] and Hanessian [19] and their coworkers, respectively, whose retrosynthetic pathways are shown in Schemes 9.9 and 9.10. For more details concerning this strategy, known as "the chiron approach", see the book by Hanessian [19].



Scheme 9.9



Scheme 9.10

Finally, another possibility is to design enantioselective syntheses by using external chiral auxiliaries either in catalytic or in stoichiometric quantities [21]. Since these strategies are nowadays of great interest in organic synthesis, we will consider here some of the most recent results achieved in enantioselective aldol condensations, as well as in the asymmetric epoxidation and hydroxylation of olefinic double bonds.

9.3.2. Enantioselective aldol condensations: Chiral enolates. "Simple asymmetric induction"

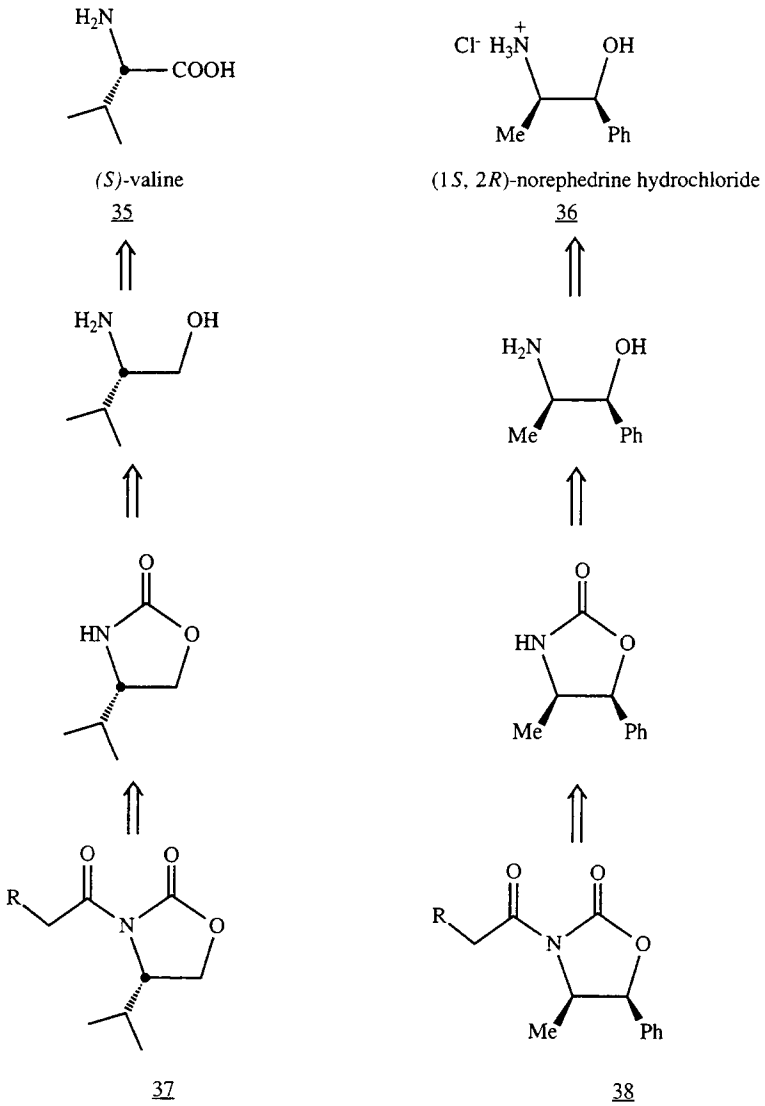
If stoichiometric quantities of the chiral auxiliary are used (i.e., if the chiral auxiliary is covalently bonded to the molecule bearing the prochiral centres) there are in principle three possible ways of achieving stereoselection in an aldol adduct: i) condensation of a chiral aldehyde with an achiral enolate; ii) condensation of an achiral aldehyde with a chiral enolate, and iii) condensation of two chiral components. Whereas Evans [14] adopted the second solution, Masamune studied the "double asymmetric induction" approach [22a]. In this context, the relevant work of Heathcock on "relative stereoselective induction" and the "Cram's rule problem" must be also considered [23]. The use of catalytic amounts of an external chiral auxiliary in order to create a local chiral environment, will not be considered here.

The central point of Evans's methodology is the induction of a π-enantiotopic facial differentiation through a conformationally rigid highly ordered transition state. Since the dialkylboron enolates of *N*-acyl-2-oxazolidinones exhibit excellent *syn*-diastereoselectivity (*syn:anti* >97:3) when reacted with a variety of aldehydes, Evans [14] studied the aldol condensation with the chiral equivalents 37 and 38, which are synthesised from *(S)*-valine (35) and the hydrochloride of (1*S*, 2*R*)-norephedrine (36) (Scheme 9.11), respectively, and presently are commercially available.

In fact, the usefulness of chiral oxazoline enolates in asymmetric synthesis had been already demonstrated by Meyers [24]. Evans obtained enantiofacial selectivities (or enantiomeric excesses = e.e) equal to or greater than 99% (Table 9.4).

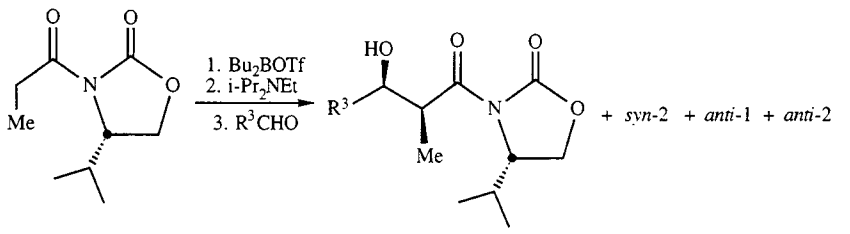
The chiral *N*-propionyl-2-oxazolidinones (37 and 38) play the role of recyclisable chiral auxiliaries, which can be smoothly removed from the aldol adducts 39 and 40 with aqueous potassium hydroxide in methanol to give the

corresponding acids 41a and 42a, without racemisation at either centre (Scheme 9.12). The acids can be methylated with diazomethane or alternatively, 39 and 40 can be directly transformed into the corresponding methyl esters 41b and 42b with sodium methoxide in anhydrous methanol.



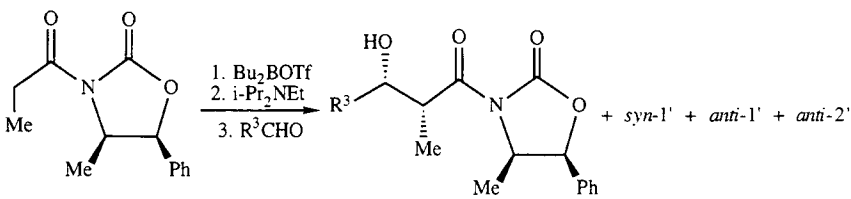
Scheme 9.11

TABLE 9.4. Aldol condensation of 37 and 38 with representative aldehydes



37, R = Me

39, *syn*-1

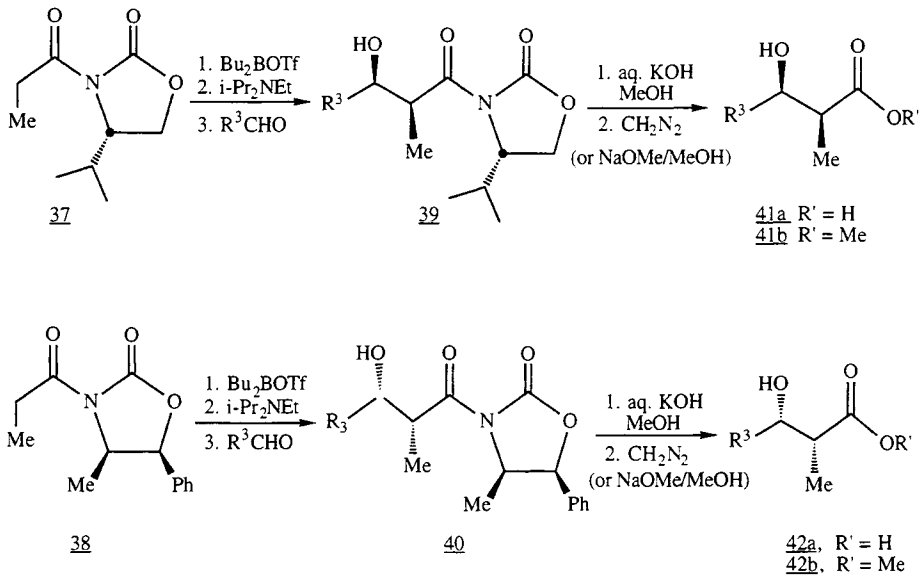


38, R = Me

40, *syn*-2'

Imide	R^3CHO	Boron-aldol kinetic ratios				Lithium-aldol kinetic ratios			
		syn-1/2 (% yield)[a]	*syn*-2/1	*anti*-1/2	*anti*-2/1	*syn*-1/2	*syn*-2/1	*anti*-1/2	*anti*-2/1
37	PhCHO	99.8 (88%)	0.04	0.14	0.06	9.8	29.5	59.0	1.7
38	PhCHO	>99.9 (89%)	<0.1	<0.1[b]		8.5	28.6	62.7[b]	
37	Me_2CHCHO	99.4 (78%)	0.2	0.2	0.2	10.6	11.0	71.4	7.0
38	Me_2CHCHO	99.8 (91%)	0.04	0.15[b]		13.2	8.1	78.7[b]	
37	*n*-C_4H_9CHO	99.0 (75%)	0.7	0.1	0.1	14.3	3.7	24.4	57.6
38	*n*-C_4H_9CHO	99.9 (95%)	0.1	<0.1[b]		16.7	18.0	65.3[b]	
38	Furaldehyde	≥99.3 (91%)	-	-	-	-	-	-	-

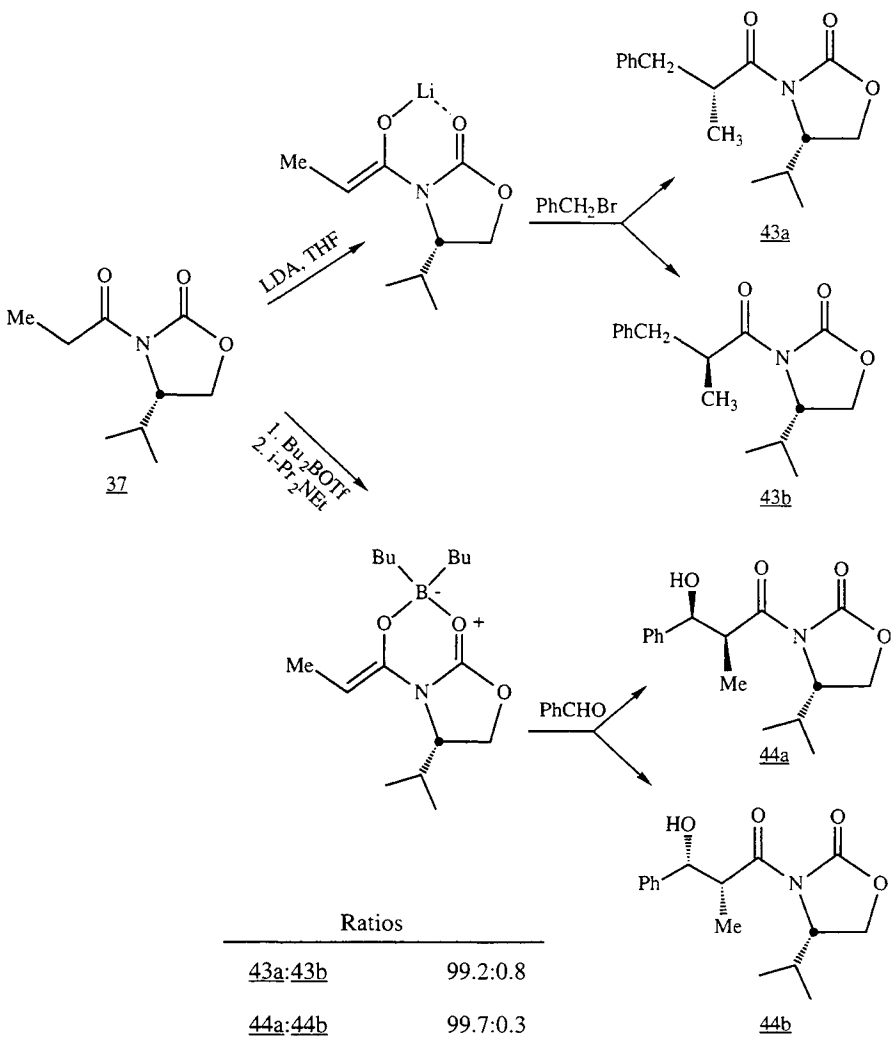
[a] Isolated yields; [b] the second *anti* isomer was not formed or did not resolve on the GC.



Scheme 9.12

The *syn*-configuration of the resulting aldols 41 and 42 can be deduced from the coupling constants in the ^{1}H-NMR spectra (4.5 Hz), and the absolute stereochemical assignments were made by degradative removal of the hydroxyl group and correlation of the resulting α-substituted carboxylic acids.

The chiral *N*-propionyl-2-oxazolidones (37 and 38) are also useful chiral auxiliaries in the enantioselective α-alkylation of carbonyl compounds, and it is interesting to observe that the sense of chirality transfer in the lithium enolate alkylation is opposite to that observed in the aldol condensation with boron enolates. Thus, whereas the lithium enolate of 37 (see Scheme 9.13) reacts with benzyl bromide to give predominantly the (2*R*)-isomer 43a (ratio 43a:43b = 99.2:0.8), the dibutylboron enolate reacts with benzaldehyde to give the (3*R*, 2*S*) aldol 44a (ratio 44a:44b = 99.7:0.3). The resultant (2*R*) and (2*S*)-3-phenylpropionic acid derivatives obtained from the hydrolysis of the corresponding oxazolidinones indicated the compounds to be optically pure substances.

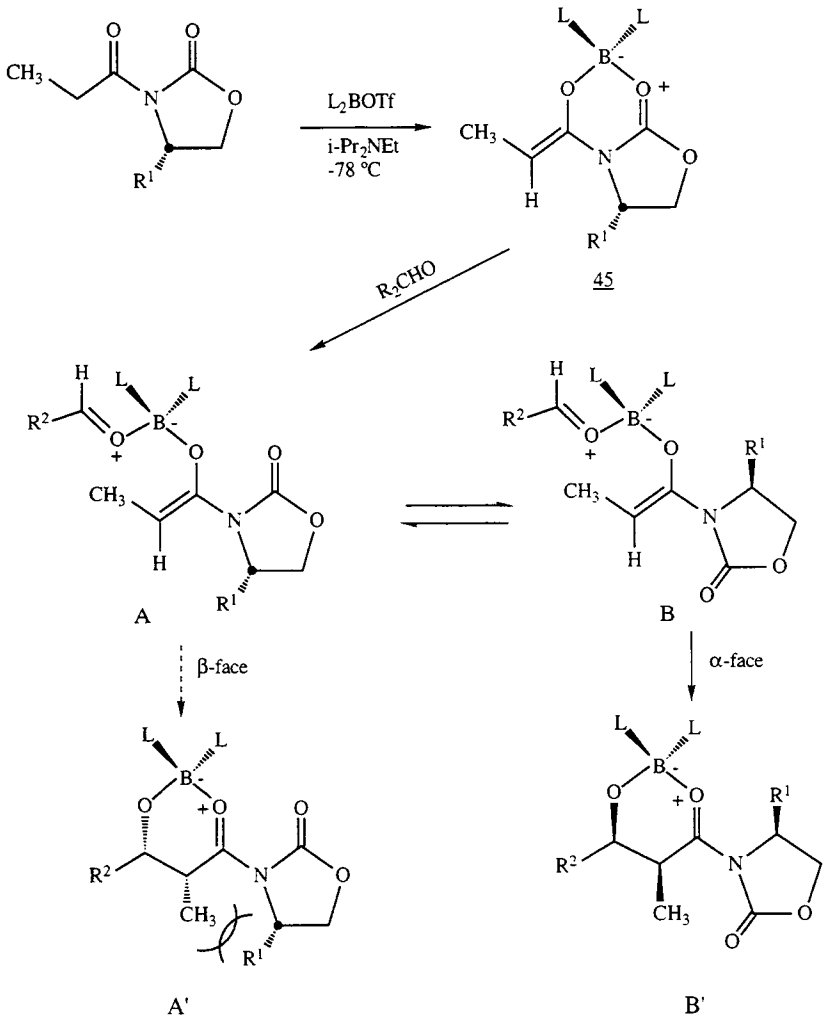


Ratios	
43a:43b	99.2:0.8
44a:44b	99.7:0.3

Scheme 9.13

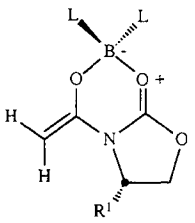
Although the results are easily rationalised in the case of the α-alkylation (attack of the electrophile at the *Re* face, i.e., attack from the less hindered α face), in the aldol condensation it is somewhat more difficult to rationalise and several factors should be considered. According to Evans [14] one possible explanation for the diastereofacial selection observed for these chiral enolates is illustrated in Scheme 9.14. In the aldol reactions, the more basic carbonyl group of the aldehyde partner interacts with the chelated boron enolate 45 to give the "complex" A which may

equilibrate to conformer B. In the respective aldol transition states leading to *syn* diastereomers A' and B', it may be assumed that developing imide resonance will fix the chiral auxiliary in one of the in-plane conformations illustrated in products A' and B'. Examination of molecular models shows that developing $CH_3 \leftrightarrow R_1$ allylic strain steric interaction [25] disfavours that transition state leading to A'. These steric considerations are largely attenuated in the transition state leading to the observed *syn* adduct B'.



Scheme 9.14

Further support for this explanation is the fact that the chiral acetate enolates derived from *N*-acetyl-2-oxazolidone (46), in which the developing $R_1 \leftrightarrow CH_3$ interaction leading to diastereomer A' is absent, exhibit only poor diastereofacial selection.



46

It is worthwhile emphasising that the abovementioned syntheses using chiral auxiliaries covalently bound to the substrate bearing the prochiral center prior to the creation of the new asymmetric centre mean converting the problem of enantiofacial recognition into a problem of diastereofacial selectivity; i.e. the pair of enantiomers 41 and 42 are actually obtained from hydrolysis of two different diastereomers 39 and 40. In fact, "direct enantioselectivity" can only be attained by using an external chiral catalyst,[23] as shown in Figure 9.1 [26].

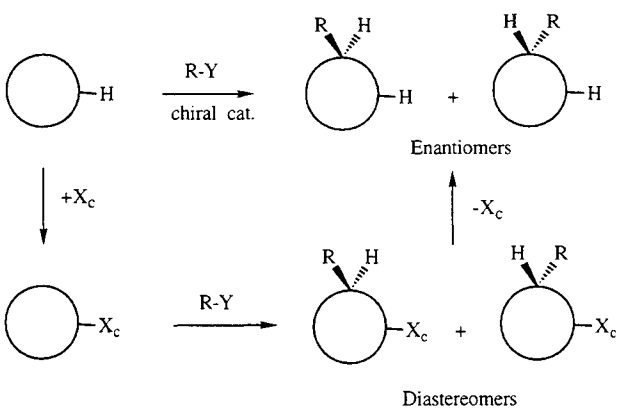
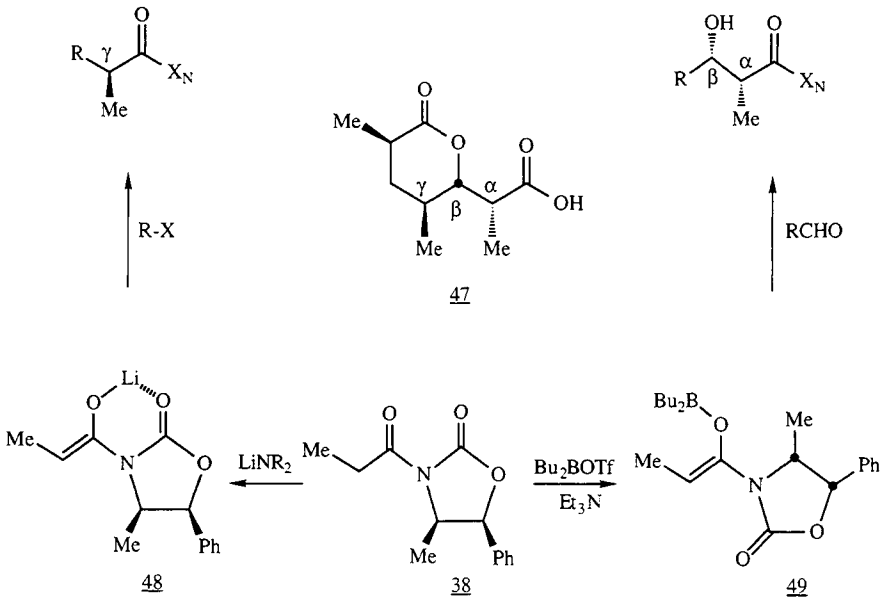


Figure 9.1

[23] A particular case is "absolute asymmetric induction" which requires a chiral physical force-such as circularly polarised light- rather than a chiral chemical reagent.

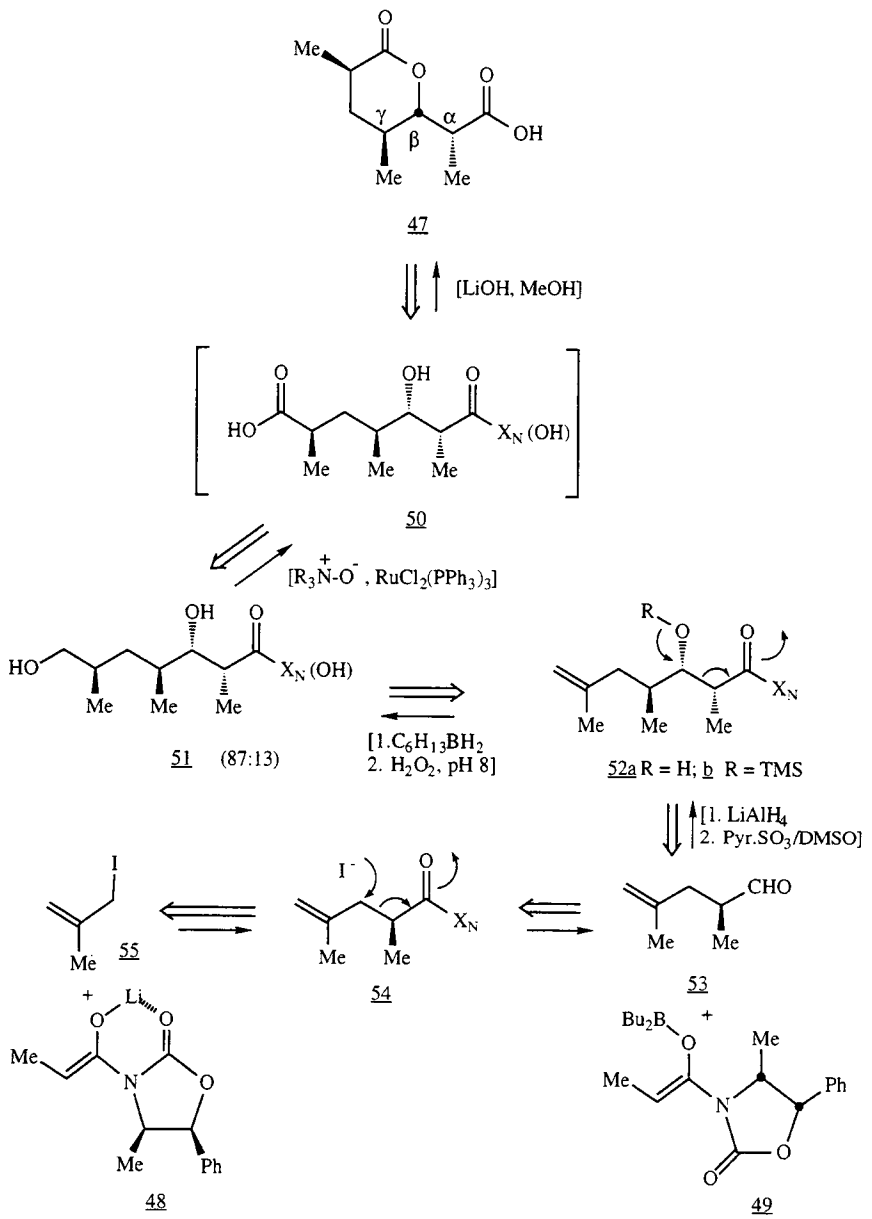
As a model study for this methodology, Evans and Bartrolí carried out the synthesis of (+)-Prelog-Djerassi Lactonic acid 47 [14b] [27], which is a degradation product of either methymycin or narbomycin [28] and has some of the important structural features present in macrolide antibiotics.

The synthesis illustrates the utility of the chiral propionimide 38 in highly diastereoselective alkylation and aldol processes, which proceed *via* lithium enolate 48 and dibutylboron enolates 49 (Scheme 9.15).



Scheme 9.15

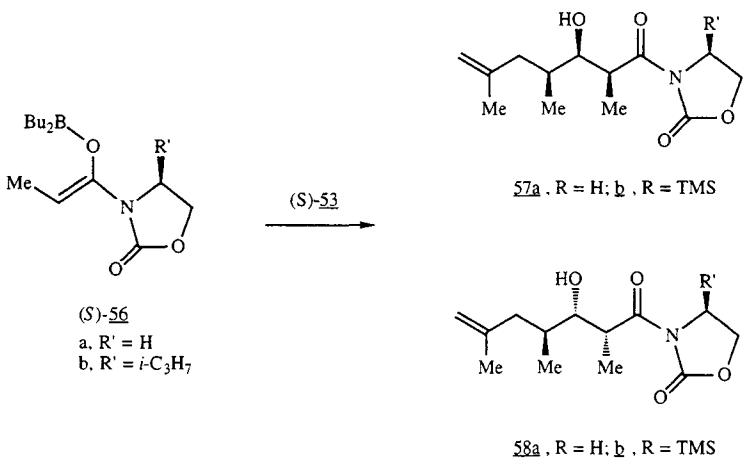
The retrosynthetic analysis of the target molecule 47, which is shown in Scheme 9.16, allows to reduce it to very simple starting materials, such as 2-methyl-2-propene iodide (55) and the chiral *N*-propionyl-2-oxazolidone 48. The normal arrow (⟶) with the reagents between square brackets [ ] shows the sequence in the synthetic direction.



Scheme 9.16

Notice that the aldol condensation of the boron enolate 49 with the aldehyde (*S*)-53 affords, after recrystallisation, the diastereomerically homogenous *syn*-anti-Cram aldol adduct 52a. The stereochemical control in this process is remarkable.

Diastereomer analysis on the unpurified aldol adduct 52b revealed that the total *syn*:*anti* diastereoselection was 400:1 whereas enantioselective induction in the *syn* products was 660:1. On the other hand, Evans in some complementary studies also found that in the condensation of the chiral aldehyde 53 with an achiral enolate 56a only a slight preference was noted for the anti-Cram aldol diastereomer 58a (58a:57a = 64:36). In the analogous condensation of the chiral enolate 56b, however, the *syn*-stereoselection was approximately the same (57b:58b ≥ 400:1) as that noted for enolate 49 but with the opposite sense of asymmetric induction (Scheme 9.17). Therefore, it can be concluded that enolate chirality transfer in these systems strongly dominates the condensation process with chiral aldehydes.



(*S*)-56
a, R' = H
b, R' = *i*-C_3H_7

Scheme 9.17

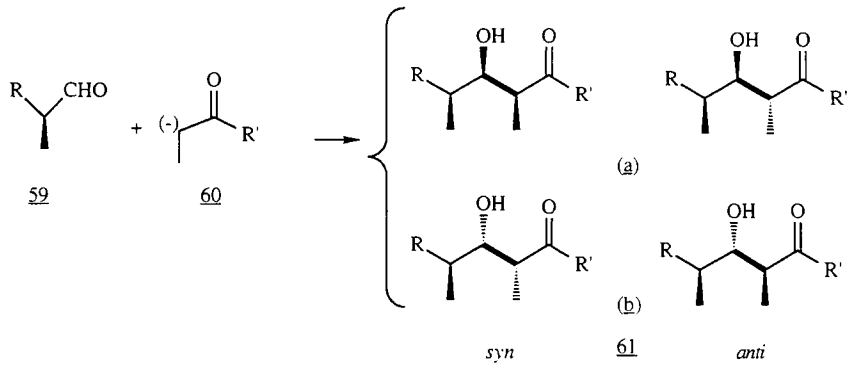
9.3.3. Relative stereoselective induction and the "Cram's rule problem": "Double stereodifferentiation".

The above observations are quite pertinent here since they introduce us to "relative stereoselective induction" (or "double stereodifferentiation") studied by Heathcock [23][24] and to "double asymmetric induction" [29] developed by Masamune [22].

Heathcock examined the aldol condensations of aldehydes already having one or more chiral centres in which case the carbonyl faces are diastereotopic, rather than enantiotopic, and there are four relative ways in which such aldehydes can react

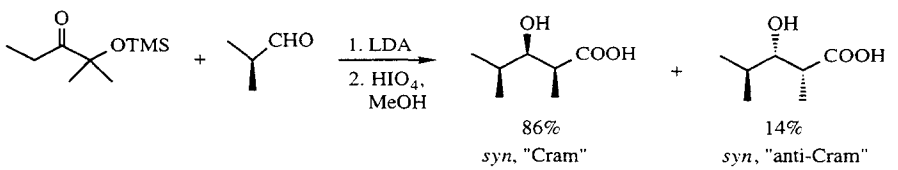
[24] Heathcock avoids the word "asymmetric" since it may induce confusion in the cases involving racemates. See footnote on page 60 of ref. 23.

with achiral enolates (Scheme 9.18). This is in fact the problem which Cram and Prelog examined systematically many years ago, to which Heathcock refers to as the "Cram's rule problem" [23].



Scheme 9.18

In fact, even if simple stereoselection can be reasonably controlled, using *syn* and *anti* selective reagents[25] mixtures of "Cram " and "anti-Cram" diastereomers are always obtained as shown in Scheme 9.19, where only the (Z)-enolate is formed:



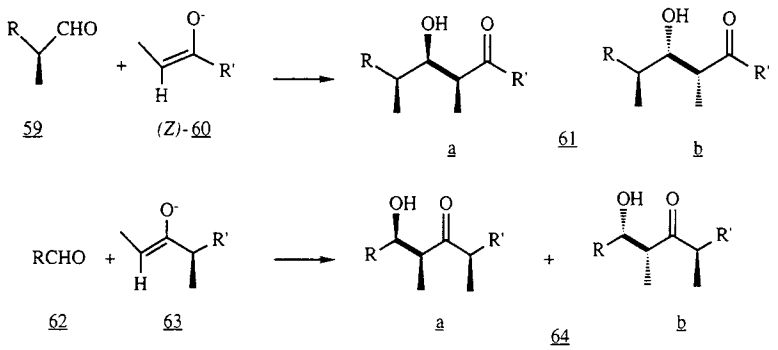
Scheme 9.19

Although a diastereoselectivity ratio of 6:1 may seem quite acceptable, it is not good enough for the synthesis of a compound which requires repetitive additions of this type. As stated by Heathcock, if a synthesis requires, for instance, five condensations, each proceeding with 80% stereoselectivity, the overall stereochemical yield will be only 33%.

Following Heathcock's reasoning, suppose that an achiral enolate (60) reacts with chiral aldehydes (59) to give the two possible *syn* aldols 61a and 61b in a 10:1

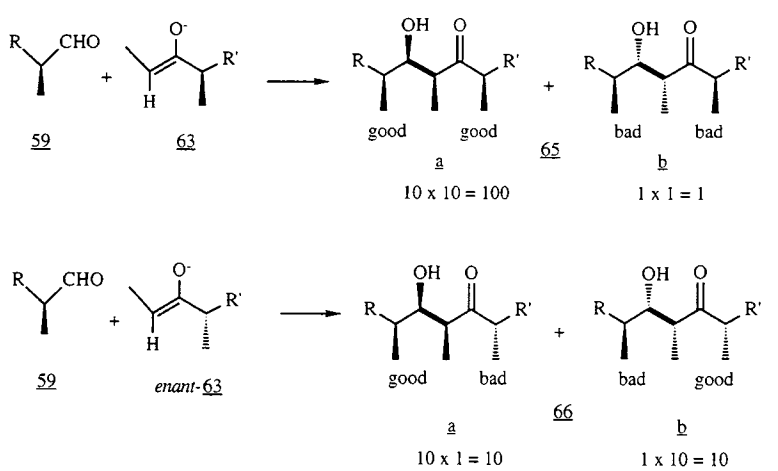
[25] That is to say, starting either from a *(Z)*- or an *(E)*-enolate, respectively.

ratio, and that a chiral enolate 63 reacts with achiral aldehydes 62 to give also the corresponding *syn*-aldols 64a and 64b in the same 10:1 ratio (Scheme 9.20):



Scheme 9.20

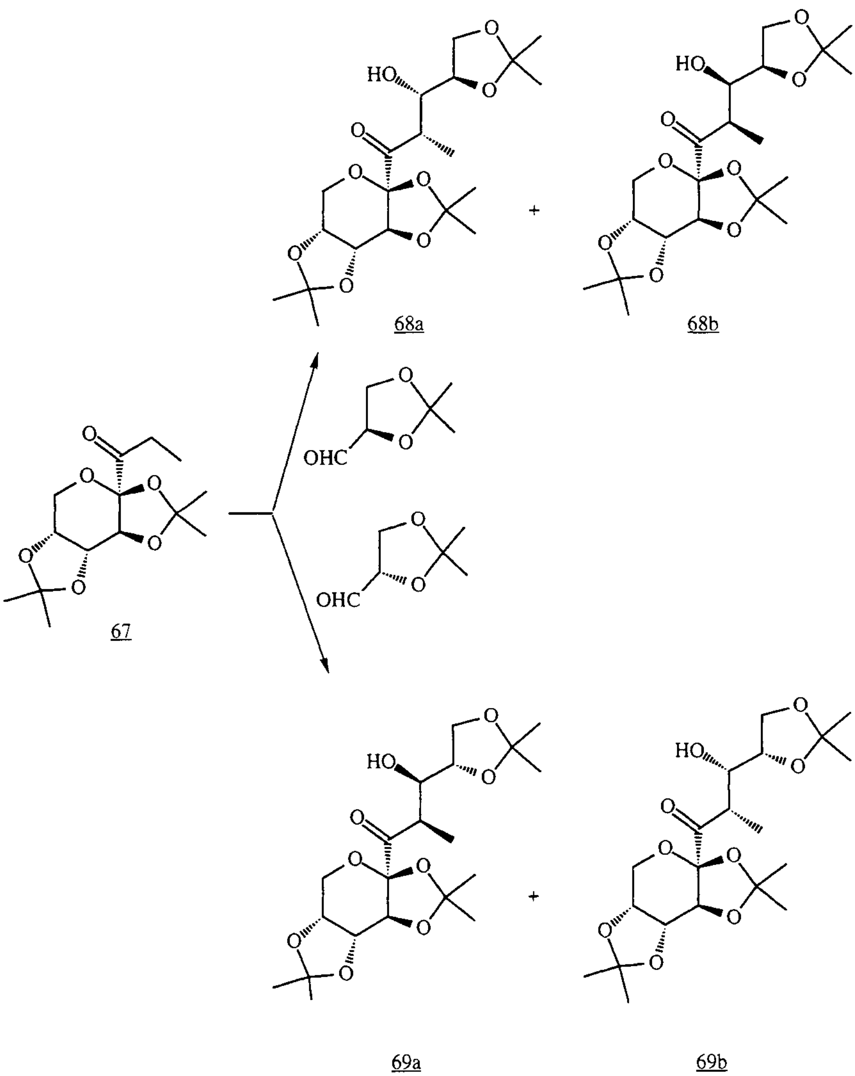
Now, if we allow one enantiomer of the chiral aldehyde 59 to react with the two enantiomers of the chiral enolate 63, in one case the two chiral reagents will both promote the same absolute configuration at the two new chiral centres (65a). However, no such effect will be observed in the other possible combination (*cf.* 65) (Scheme 9.21). In the first case, the effective "Cram's rule selectivity" shown by the aldehyde will be greater than in its reactions with achiral enolates. For the selectivities chosen the "Cram:anti-Cram ratio" should be in our example of the order of 100:1 (see below *9.3.4.*, Masamune's "double asymmetric induction").



Scheme 9.21

As we will see below, the terminology "good-good" and "good-bad" or "bad-bad" is equivalent to the "matched" and "mismatched pair" of Masamune.

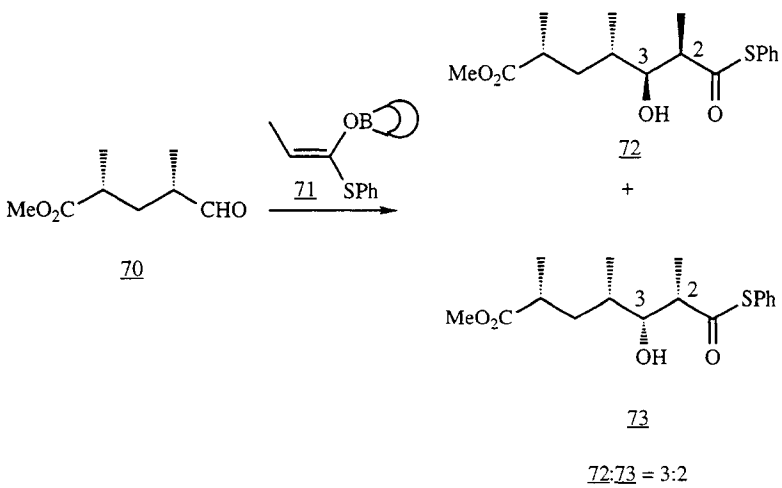
In order to test these assumptions Heathcock prepared different chiral ketones. Thus, the aldol condensation of the fructose-derived ketone 67 and the acetonide of (*R*)-glyceraldehyde gave poor results in the double stereodifferentiation, since an almost equal mixture of the two *syn*-aldols 68a and 68b were obtained. However, the reaction with the (*S*)-aldehyde gave only one *syn* adduct (69a) (Scheme 9.22):



Scheme 9.22

9.3.4. "Double asymmetric induction"

In Masamune's approach [22] chiral boron enolates are reacted with chiral aldehydes, in such a manner that a "double asymmetric induction" takes place with enantioselectivities >100:1. In order to evaluate the efficiency of this methodology, it is convenient to compare the results obtained in the "double asymmetric induction" with those obtained in the condensation of an achiral (*Z*)-enolate, such as 71 (to which the element oxygen has arbitrarily been assigned the highest priority), with a chiral aldehyde, such as the (-)-dimethylglutaric hemialdehyde (70), which provides an approximately 3:2 mixture of 72 and 73 (Scheme 9.23). It should be noted that: i) the two substituents at the 2,3-position in both adducts 72 and 73 exhibit the same relative *syn*-configuration but are opposite in terms of absolute configuration and ii) the 3:2 ratio is the diastereofacial selectivity for the chiral aldehyde 70. This ratio represents roughly the degree of diastereoselection that can be attained in the aldol condensation of 70 without resorting to "double asymmetric induction".

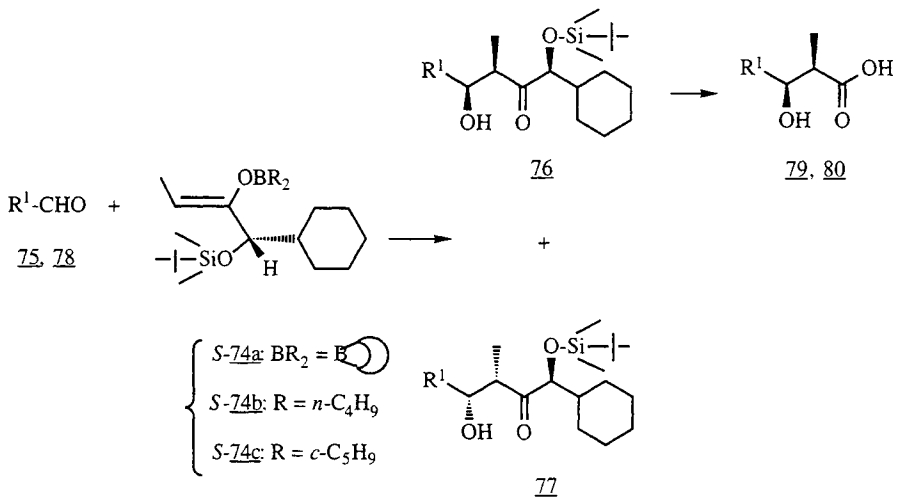


(71 is a borabicyclo[3.3.1]non-9-yl derivative)

Scheme 9.23

The next step was, therefore, to develop chiral enolates which show high diastereoselectivities (≥100:1) in single asymmetric reactions. Of the many chiral (*Z*)-enolates which were prepared and studied by Masamune and his associates, those shown (74) in Scheme 9.24 -prepared from optically pure (*S*)- and (*R*)-mandelic acid- meet the requirements set for a chiral reagent [22c]. Thus, the chiral

aldehyde 75 undergoes an aldol condensation with (*S*)-74c (which is the most stereoselective, but the least reactive, of the three boron enolates 74a-74c) to give a 100:1 mixture of diastereomers 76 and 77.



Scheme 9.24

With a branched aldehyde, such as isobutyraldehyde 78, the selectivity of the reaction is very high (76:77 > 100:1; Table 9.5), even with the less selective (but more reactive) boron enolate (*S*)-74a.

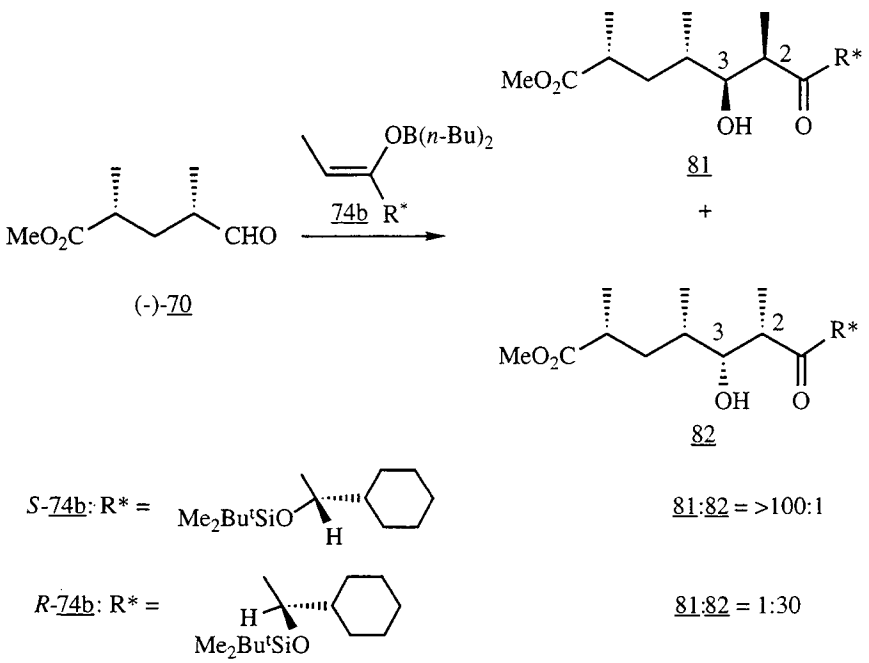
TABLE 9.5. Reaction of aldehydes with boron enolates 74

Aldehyde	R^1	Boron enolate	76:77	Acid*
75	$PhCH_2OCH_2CH_2$	(*S*)-74a	16:1	79
		(*S*)-74b	28:1	
		(*S*)-74c	100:1	
78	$(CH_3)_2CH$	(*S*)-74a	>100:1	80
		(*S*)-74b	>100:1	
		(*S*)-74c	no reaction	

*Main product

Treatment of a mixture of 76 and 77 with hydrogen fluoride (or fluoride anion) followed by sodium metaperiodate affords the corresponding 2,3-*syn*-3-hydroxy-2-methylcarboxylic acids 79 and 80 in enantiomeric excesses higher than 98%. Therefore, with the proper selection of the ligands attached to the boron atom, the stereofacial selectivity of 74 exceeds 100:1.

We can now consider the reaction between the *chiral* aldehyde (-)-70 with the *chiral* enolate (*S*)-74b (Scheme 9.25). This aldol condensation affords two diastereomers 81 and 82 in a ratio of >100:1. A change in the chirality of the enolate reverses the result. Thus, the reaction of (-)-70 with (*R*)-74b leads to the formation of 81 and 82 in a ratio of 1:30, favouring therefore 82 with respect to 81.



(-)-70 + *S*-74b: matched pair; (-)-70 + *R*-74b: mismatched pair

Scheme 9.25

The significance of the results of these two reactions is threefold: 1) both ratios are far greater than the 3:2 ratio obtained with the achiral enolate; ii) the chirality of R* in 74b is directly correlated with the stereochemistry at the 3,4-positions of the

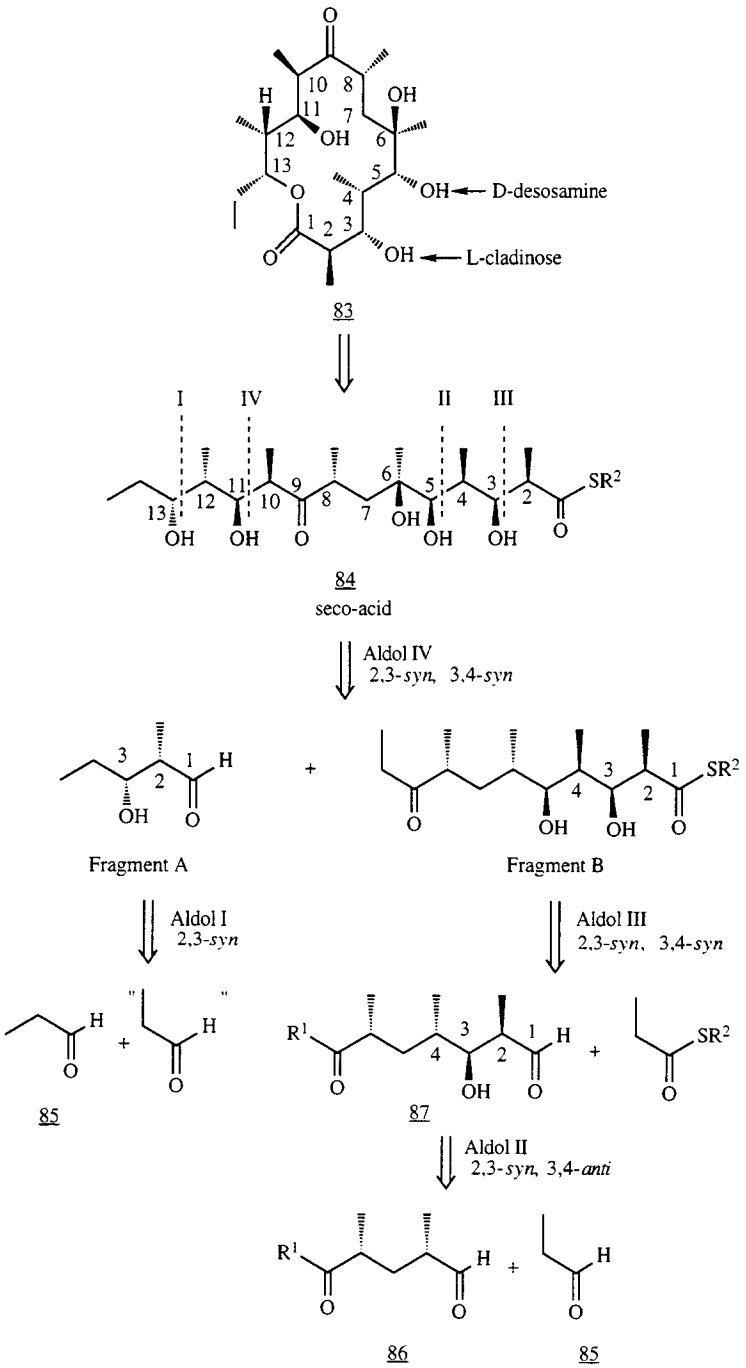
reaction products and therefore either the 2,3-*syn*-3,4-*anti*- or 2,3-*syn*-3,4-*syn* system can be obtained in a preselected manner, and, finally iii) the two reactions (-)-70 + (*S*)-74b and (-)-70 + (*R*)-74b are example of "matched" and "mismatched" pairs, respectively, in which the "multiplicavity" of the two diastereofacial selectivites (3:2 and 100:1) is roughly realised.

According to Masamune, in a "matched pair" the diastereoselectivity of both reactants are acting in concert and the degree of double asymmetric induction is approximately the product (a x b) of the selectivities of the substrate (a) and the reagent (b). In contrast, in a "mismatched pair" the diastereoselectivities of both reactants are counteracting each other and the degree of double asymmetric induction is the quotient (a ÷ b) of the selectivities of the substrate (a) and the reagent (b). The values of diastereofacial selectivities are selected in such a way as to be greater than 1.

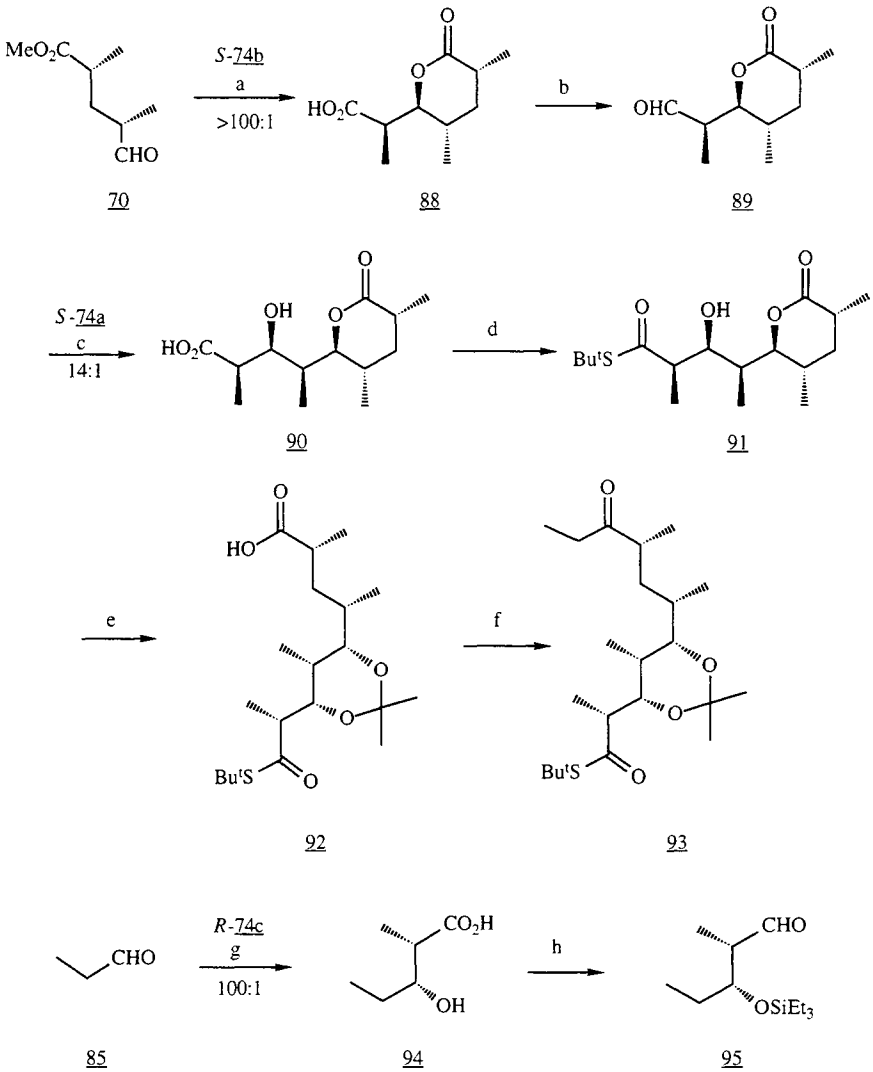
The potential of "double asymmetric induction" is shown in the synthesis of 6-deoxyerythronolide B (83) accomplished by Masamune and coworkers in 1981 [22d].

Disconnection of the seco-acid 84 into fragments A and B, as shown in Scheme 9.26, immediately suggests the order in which the aldol condensations must be effected to arrive at the target molecule.

Note that aldol condensations I, II and III concern the creation of a relative configuration 2,3-*syn*, which can be easily achieved starting from the (*Z*)-enolates 74a-74c. Scheme 9.27 summarises the synthesis of 93 and 95, which are equivalent to fragments B and A, respectively. Compound 88 is the abovementioned Prelog-Djerassi lactonic acid 47 which is obtained in optically pure from (>98% ee). On the other hand, for the stereochemical control of the aldol condensation IV a different methodology is necessary whih involves the coupling of two structurally *predefined* reactants and which will not be discussed here (Scheme 9.28). An important feature of this reaction is that the coordination of Li^+ with the oxygen atom at the β-position of the aldehyde 95 is mainly responsible for the observed stereoselection [22e].

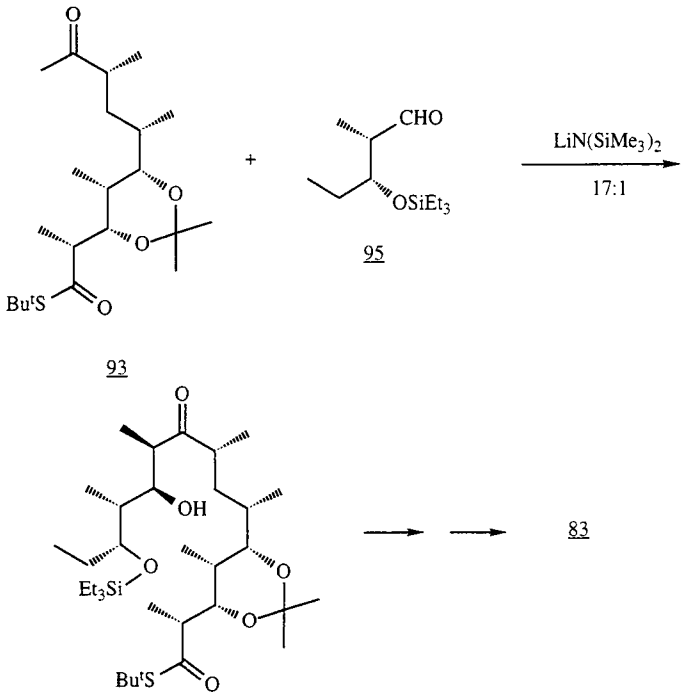

D-desosamine
L-cladinose
83
seco-acid
84
Aldol IV
2,3-syn, 3,4-syn
Fragment A
Fragment B
Aldol I
2,3-syn
Aldol III
2,3-syn, 3,4-syn
85
87
Aldol II
2,3-syn, 3,4-anti
86
85

Scheme 9.26



a) HF; $NaIO_4$, 85%; b) $(COCl)_2$; H_2, 5% $Pd/BaSO_4$, $(Me_2N)_2C{=}S$, 95%; c) *n*-Bu_4NF; $NaIO_4$, 71%; d) $ClCO_2Et$,C_5H_5N $TlSBu^t$; e) KOH; Bu^tPh_2SiCl; $CH_2{=}C(OMe)Me$, TFA; *n*-Bu_4NF, 46% yield from 90; f) $(COCl)_2$, $LiCuEt_2$, 84%; g) HF; $NaIO_4$, 85% yield from 85; h) CH_2N_2; Et_3SiCl, DIBAL; PCC, 75%.

Scheme 9.27

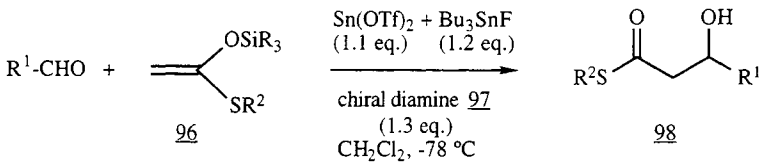


Scheme 9.28

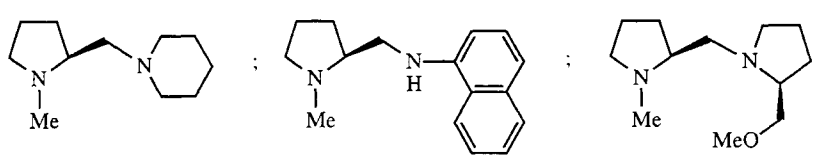
9.3.5. Scope and limitations of enantioselective aldol condensations. Recent advances

Although in the recent years the stereochemical control of aldol condensations has reached a level of efficiency which allows enantioselective syntheses of very complex compounds containing many asymmetric centres, the situation is still far from what one would consider "ideal". In the first place, the requirement of a substituent at the α-position of the enolate in order to achieve good stereoselection is a limitation which, however, can be overcome by using temporary bulky groups (such as alkylthio ethers, for instance). On the other hand, the (*E*)-enolates, which are necessary for the preparation of 2,3-*anti* aldols, are not so easily prepared as the (*Z*)-enolates and furthermore, they do not show selectivities as good as in the case of the (*Z*)-enolates. Finally, although elements other than boron -such as zirconium [30] and titanium [31]- have been also used succesfully much work remains to be done in the area of catalysis. In this context, the work of Mukaiyama and Kobayashi [32a,b,c] on asymmetric aldol reactions of silyl enol ethers with aldehydes promoted by tributyltin fluoride and a chiral diamine coordinated to tin(II) triflate

deserves to be mentioned here (Scheme 9.29). Although the original procedure uses stoichiometric quantities of promotors it opened a more promising way than other self-immmolative asymmetric processes developed so far [22b] [33]. In fact, recently Mukaiyama and his associates [32c,d] have developed a catalytic asymmetric aldol reaction based in this procedure.



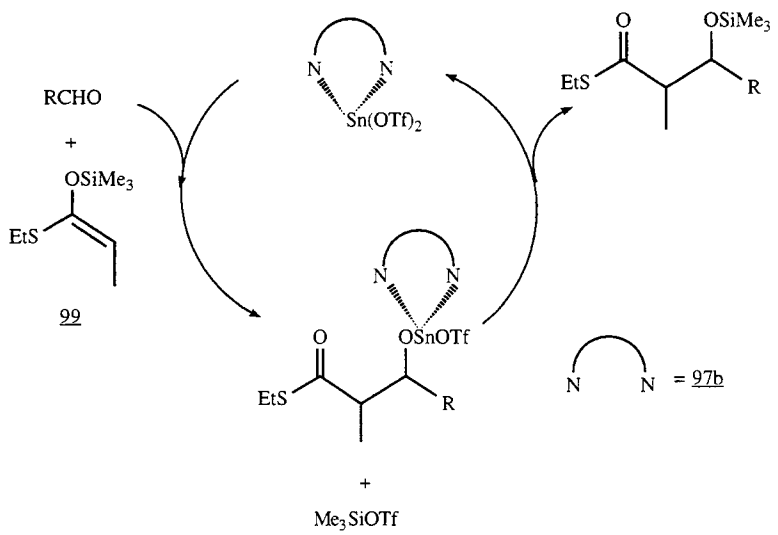
R^1	R^2	97	Yield %	ee%
Ph	Et	97a (Bu_3SnF not added)	74	0
Ph	Et	97a	78	82
Ph	Et	97b	52	92
Ph	Et	97c	74	78
Ph	Bu^t	97a	73	86
Pr^i	Et	97a	77	95
Bu^t	Et	97a	90	>95



97a 97b 97c

Scheme 9.29

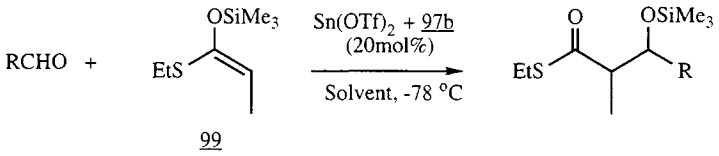
On the other hand, the method of Mukaiyama can be succesfully applied to silyl enol ethers of acetic and propionic acid derivatives. For example, perfect stereochemical control is attained in the reaction of silyl enol ether of *S*-ethyl propanethioate with several aldehydes including aromatic, aliphatic and α,β-unsaturated aldehydes, with *syn:anti* ratios of 100:0 and an ee >98%, provided that a polar solvent, such as propionitrile, and the "slow addition procedure " are used. Thus, a typical experimental procedure is as follows [32e]: to a solution of tin(II) triflate (0.08 mmol, 20 mol%) in propionitrile (1 ml) was added (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (97b, 0.088 mmol) in propionitrile (1 ml). The mixture was cooled at -78 °C, then a mixture of silyl enol ether of *S*-ethyl propanethioate (99, 0.44 mmol) and an aldehyde (0.4 mmol) was slowly added to this solution over a period of 3 h, and the mixture stirred for a further 2 h. After work-up the aldol adduct was isolated as the corresponding trimethylsilyl ether. Most probably the catalytic cycle is that shown in Scheme 9.30.



Scheme 9.30

Table 9.6 shows the effect of both the addition time and the polarity of the solvent, as well as the nature of the aldehyde, in the catalytic asymmetric aldol condensation promoted by tributyltin fluoride and a chiral diamine coordinated to tin(II) triflate.

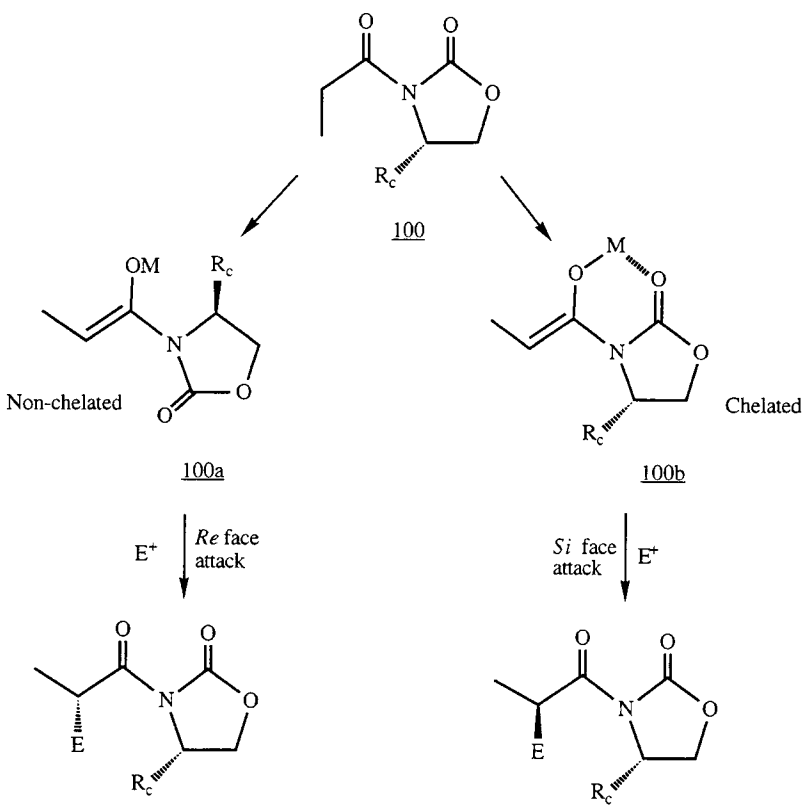
TABLE 9.6. Effect of addition time and polarity of the solvent



R = Ph		Solvent: CH_2Cl_2	
Addition time/h	Yield/%	*syn/anti*	ee/%
0	88	53/47	48
2	85	54/46	52
4	84	88/12	85
6	86	89/11	87
9	**86**	**93/7**	**91**
12	72	92/8	86
R = Ph		Solvent: C_2H_5CN	
Addition time/h	Yield/%	*syn/anti*	ee/%
0	81	70/30	69
2	79	79/31	82
3	**77**	**92/8**	**90**
4	80	90/10	89
6	74	90/10	89
8	77	92/8	89
		Solvent: C_2H_5CN	
Addition time/3h	Yield/%	*syn/anti*	ee/%
R = Ph	77	93/7	90
R = (*E*)-$CH_3(CH_2)_2CH$=CH	73	97/3	93
R = C_7H_{15}	**80**	**100:0**	**>98**
R = c-C_6H_{11}	**80**	**100:0**	**>98**

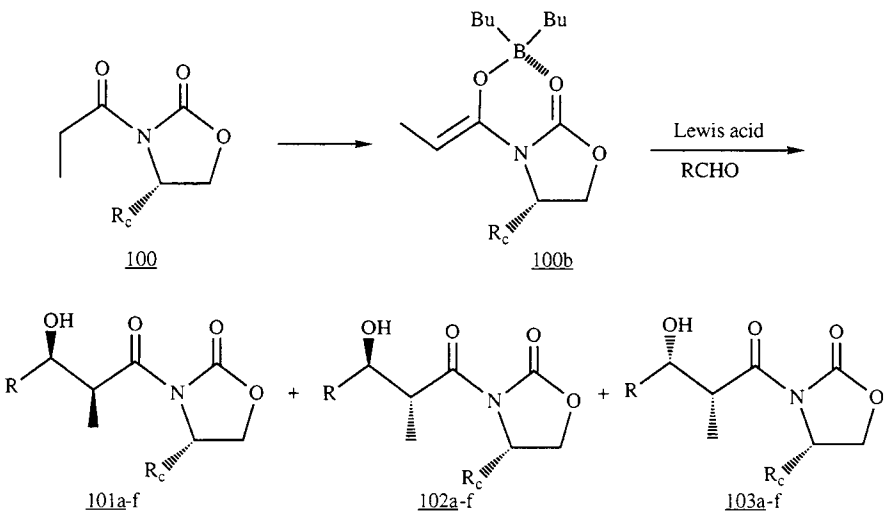
Concerning the preparation of *anti*-aldols some very interesting papers have recently appeared in the chemical literature. C.H. Heathcock and his group at Berkeley, have been particularly active in this field [34]. They started their work having two goals in mind: 1) to find an efficient asymmetric *anti*-aldol method, and 2) to develop a more general methodology that would allow the synthesis of several of the possible aldol stereoisomers from the same carbonyl precursor simply by slight modifications of the reaction conditions [34d].

As shown in Scheme 9.31, the (*S*)-enolate (100a), from Evans reagent 100, reacts on its *Re* face if the metal is not coordinated to the oxazolidone carbonyl group at the time of electrophilic attack, which is the normal situation in an uncatalysed boron enolate aldol reaction (see Scheme 9.14) and on the *Si* face if the metal is coordinated to the oxazolidone carbonyl group (100b), which is the normal situation in enolate alkylation (see *9.3.2*).



Scheme 9.31

This dual behaviour must allow control of the configuration at the α carbon atom in an aldol reaction, provided that one can control whether or not the metal is chelated at the time the aldol condensation occurs. Thornton and Nerz-Stormes [35] reported an approach to this problem by using titanium enolates to obtain "non-Evans" *syn*-aldols. On the other hand, Heathcock and his associated found that aldehydes react with chelated boron enolates 100b to afford the *anti*-aldols 102 or the "non-Evans" *syn*-aldols 103 depending upon the reaction conditions (Scheme 9.32).



R, a = Bu^i; b = Et; c= Pr^i; d = Bu^t; e = 2-allyl; f = Ph

Scheme 9.32

The Berkeley group studied the following different experimental conditions: A) addition of Lewis acid, at -78 °C, in one portion to the boron enolate in CH_2Cl_2 solution, followed by addition of the aldehyde in a 30-min period; B) addition of Lewis acid via syringe in a 3-4 h period after the aldehyde has been added in one portion; C) the aldehyde was precomplexed with Lewis acid in CH_2Cl_2 at -78 °C and the boron enolate was added to the cold solution. The results are summarised in Table 9.7.

TABLE 9.7. Lewis Acid Mediated Aldol Condensations of Boron Enolate 100b with Isobutyroaldehyde[a]

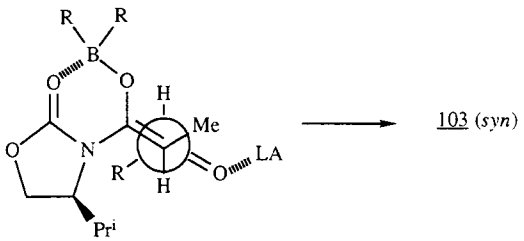
entry	method	Lewis acid	equiv[b]	101c:102c:103c	%yield[c]
1	C	$TiCl_4$	0.5	0:20:80	d
2	C	$TiCl_4$	1.0	0:17:83	71
3	C	$TiCl_4$	2.0	0:16:84	83
4	A	$TiCl_4$	1.0	0:11:89	77
5	C	$SnCl_4$	0.5	0:95:5	51
6	C	$SnCl_4$	1.0	0:71:29	65
7	C	$SnCl_4$	2.0	0:13:87	60
8	B	$SnCl_4$[e]	1.0	0:92:8	76
9	C	Et_2AlCl	0.5	68:28:4	91
10	C	Et_2AlCl	1.0	4:88:8	71
11	C	Et_2AlCl	2.0	0:95:5	63

[a] $R_c = Pr^i$; [b] Equivalents Lewis acid per equivalent of aldehyde; [c] Product ratios and yields were determined by integration of the ^1H NMR spectra of the product mixture using an internal standard. The yield given is the total yield of aldol mixture; [d] The yield in this run was not determined; [e] In this run the enolate was formed with dicyclohexylboron triflate and Huning's base; 1.5 equivalents of aldehyde were used.

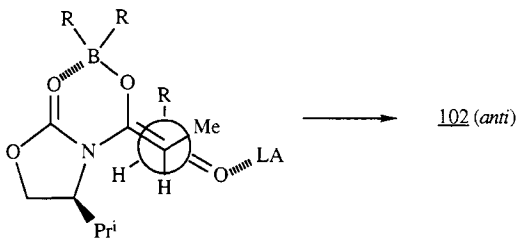
The most general conclusion is that in almost all of the Lewis acids tested the normal Evans *syn*-aldol 101 is formed in only trace amount, if at all. The unique behaviour of the different Lewis acids may be summarised as follows: $TiCl_4$ *shows* syn *selectivity regardless of stoichiometry*; Et_2AlCl *is* anti *selective regardless of stoichiometry and* $SnCl_4$ *shows* syn *or* anti, *depending on whether an excess of aldehyde* (entry 5) *or Lewis acid* (entry 7) *is used.*

According to Heathcock and his associates the configurational dependence on the ratio of Lewis acid to aldehyde must be related to steric effects, and they conclude that the aldols 103 and 102 result from the open transition states **A** and **B,** respectively (Scheme 9.33). If the Lewis acid is small, transition state **A** is preferred because it minimises gauche interactions about the forming bond, but if the Lewis

acid is large, then the transition state **B** becomes competitive because of the methyl-Lewis acid interaction in **A**.



A: favoured for small Lewis acids



B: favoured for large Lewis acids

Scheme 9.33

Whereas Et_2AlCl acts as a large Lewis acid, always giving *anti* aldols because the O-Al bond is short and the ligands relatively bulky, $SnCl_4$ and $TiCl_4$ are effectively smaller because of the longer Sn-O and Ti-O bond lengths and the stereoselectivity depends upon the protocol used. The slow addition of the Lewis acid (Table 9.7, entry 8) to aldehydes gives a reactive 2:1 complex in which the effective bulk of the Lewis acid is increased because of its octahedral coordination; therefore, the modified protocol B (footnote [e] in Table 9.7)[26] gives *anti* aldols. On the other hand, since Et_2AlCl is not capable of forming a pentacoordinated 2:1 complex, it shows no change in selectivity in changing the equivalents of Lewis acid.

Although the results of Table 9.7 clearly demonstrated that the Berkeley group succeeded in their efforts, since it is possible to synthesise 101, 102 and 103 from

[26] When using method B (slow addition of Lewis acid) the uncatalysed reaction leading to 101 tends to compete. For this reason is best to use dicyclohexylboron enolate, since it is less reactive than the dibutylboron enolate under uncatalysed conditions.

the same enolate by simply changing the reaction conditions, the selectivities are not so good as the ones attained in the synthesis of *syn* aldols (80-95% diastereoselectivity). With all the aldehydes studied method A gives the "non-Evans" *syn* aldol 103, with stereoselectivities in the range 6:1-15:1. Method C, especially with Et_2AlCl, is the most useful method for the preparation of mixtures of aldols, in which the *anti* aldol is the predominant isomer: with aliphatic aldehydes the *anti:syn* ratios range from 6:1 to 20:1. However, with benzaldehyde the ratio is only 3:1.

Despite the fact that diastereoselectivities are not "ideal" yet, the products are usually crystalline and are easily purified by chromatography, providing access to multigram quantitites of very high enantiomeric purity.

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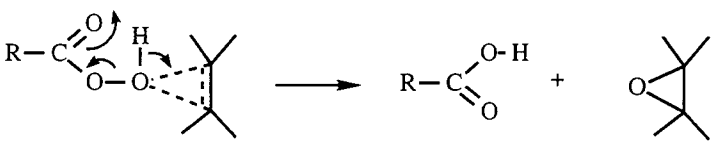
Chapter 10

10. ACYCLIC STEREOSELECTION II: ASYMMETRIC EPOXIDATION AND DIHYDROXYLATION OF OLEFINIC DOUBLE BONDS

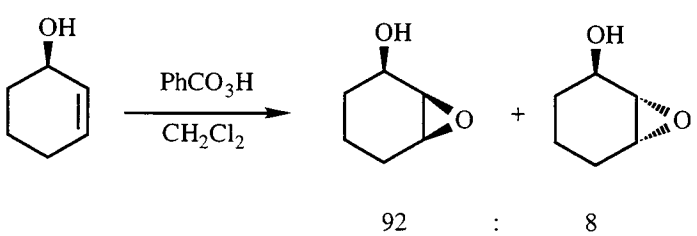
10.1. Epoxidation of olefinic double bonds

Epoxidation of olefinic double bonds by organic peracids is a well known reaction whose scope, reliability and usefulness in organic synthesis was established largely by the work of Swern [1], who was also the first to show that the reaction is stereospecific.

The accepted mechanism for this reaction was proposed by Bartlett, and it is shown in the following equation:



On the other hand, H.B. Henbest realised that adjacent polar functional groups have a directing effect on the epoxidation of alkenes as well as on other related reactions [2]. A very well known example is the *syn*-directing effect of an allylic hydroxyl group in epoxidations of cyclic alkenes (Scheme 10.1):



Scheme 10.1

10.1.1. Sharpless asymmetric epoxidation of allylic alcohols

Although it was also Henbest who reported as early as 1965 the first asymmetric epoxidation by using a chiral peracid, without doubt, one of the methods of enantioselective synthesis most frequently used in the past few years has been the "asymmetric epoxidation" reported in 1980 by K.B. Sharpless [3] which meets almost all the requirements for being an "ideal" reaction. That is to say, complete stereofacial selectivities are achieved under catalytic conditions and working at the multigram scale. The method, which is summarised in Fig. 10.1, involves the titanium (IV)-catalysed epoxidation of allylic alcohols in the presence of tartaric esters as chiral ligands. The reagents for this asymmetric epoxidation of primary allylic alcohols are L-(+)- or D-(-)-diethyl (DET) or diisopropyl (DIPT) tartrate,[27] titanium tetraisopropoxide and water free solutions of *tert*-butyl hydroperoxide. The natural and unnatural diethyl tartrates, as well as titanium tetraisopropoxide are commercially available, and the required water-free solution of *tert*-butyl hydroperoxide is easily prepared from the commercially available isooctane solutions.

According to the *Science Citation Index*, reference [3] was cited 180 times in the period in between the years 1980 and 1984, and the reaction was used as the key step in almost a hundred "asymmetric syntheses". The method is not only of academic interest, but has also found application in industry and the Upjohn company uses it at the multikilogram scale in a reactor of more than 2000 L [4].

The full paper on titanium-catalysed asymmetric epoxidation appeared in 1987 [6], once the improved catalytic procedure in the presence of molecular sieves had already been fully developed [5]. On the other hand, excellent "autobiographic" accounts have also been published in which "Everything You Ever Wanted to Know About the Discovery of Asymmetric Epoxidation" is honestly and vividly exposed by K. Barry Sharpless [4] [7].

The paramount importance of Sharpless "asymmetric epoxidation" lies on the fact that the epoxide group is almost as versatile as the carbonyl group (in *Heading 5.2* we have referred to it as a "homocarbonyl" group). The method is of general applicability and is relatively indifferent to pre-existing chiral centres, so it may be used iteratively. Moreover, either of the two enantiomers may be obtained, usually

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[27] If optimal conditions are desired for a specific asymmetric epoxidation,variation of the tartrate ester is likely to be a useful exercise.

with optical yields higher than 90% (95% sometimes), so that the whole series of L-hexoses has been synthesised for the first time [8].

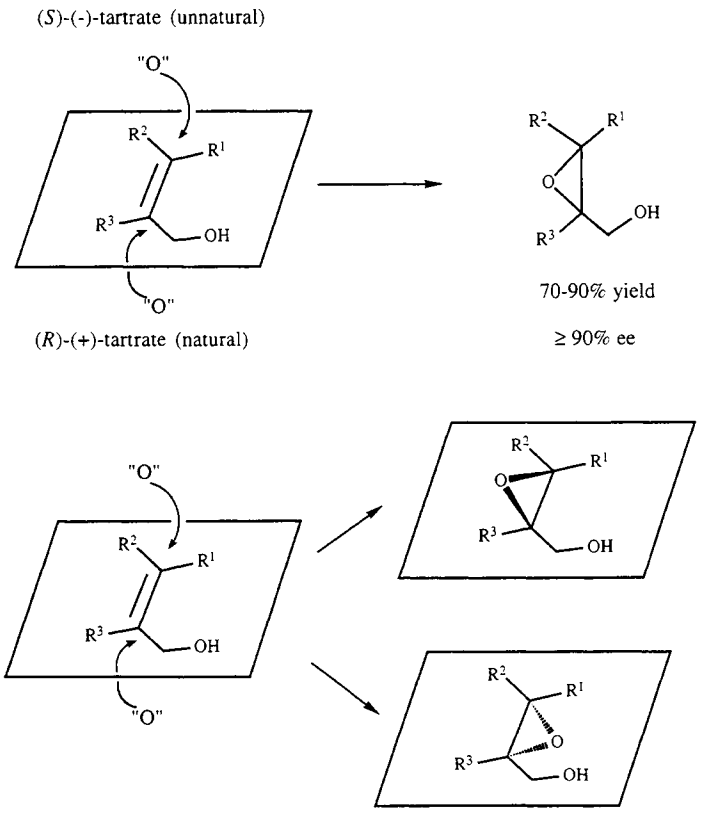
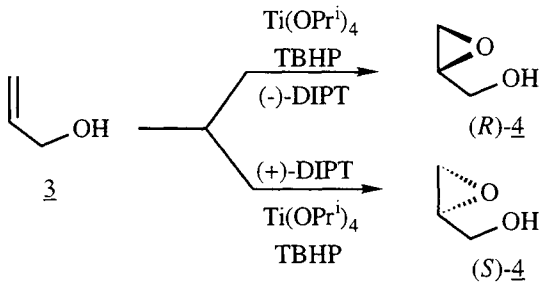


Fig. 10.1
Enantiofacial selectivity in the epoxidation of prochiral allylic alcohols
(allylic alcohol drawn as it is shown: OH down at the right side)

10.1.2. Asymmetric epoxidation by alcohol substitution pattern

R^1, R^2 and R^3 of the allylic alcohol (Fig.10.1) submitted to asymmetric epoxidation can be either hydrogen or groups other than hydrogen, a fact that provides a large number of different possible substrates, from the simple allylic alcohol (3) -which has open the way to the industrial production of optically active glycidol (4) (Scheme 10.2)- to all possible mono-, di- and trisubstituted regioisomers of allylic alcohols. The configuration of these regioisomers can be either *cis* (*Z*) or *trans* (*E*), all of which lead to a plethora of different substrates.

Although some substitution patterns -as the 2-substitution- can favour the nucleophilic opening of the resulting epoxide, the use of $Ti(OBu^t)_4$ in place of $Ti(OPr^i)_4$ has been proposed as a means to reduce this problem. However, the catalytic version of the reaction usually used nowadays precludes greatly the amount of epoxide ring opening.

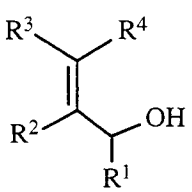


Scheme 10.2

More than a decade of experience on Sharpless asymmetric epoxidation has confirmed that the method allows a great structural diversity in allylic alcohols and no exceptions to the face-selectivity rules shown in Fig. 10.1 have been reported to date. The scheme can be used with absolute confidence to predict and assign absolute configurations to the epoxides obtained from prochiral allylic alcohols. However, when allylic alcohols have chiral substituents at C(1), C(2) and/or C(3), the assignment of stereochemistry to the newly introduced epoxide group must be done with considerably more care.

10.1.3. Kinetic resolution of allylic alcohols

A special case is the 1-substituted allylic alcohols 5:



5 ($R^1 \neq H$)

The presence of the stereogenic centre at C(1) introduces an additional factor in the asymmetric epoxidation: now, besides the enantiofacial selectivity, the diastereoselectivity must also be considered, and it is helpful to examine epoxidation of each enantiomer of the allylic alcohol separately. As shown in Fig. 10.2, epoxidation of an enantiomer proceeds normally (fast) and produces an *erythro* epoxy alcohol. Epoxidation of the other enantiomer proceeds at a reduced rate (slow) because the steric effects between the C(1) substituent and the catalyst. The rates of epoxidation are sufficiently significative to achieve the kinetic resolution and either the epoxy alcohol or the recovered allylic alcohol can be obtained with high enantiomeric purity [9].

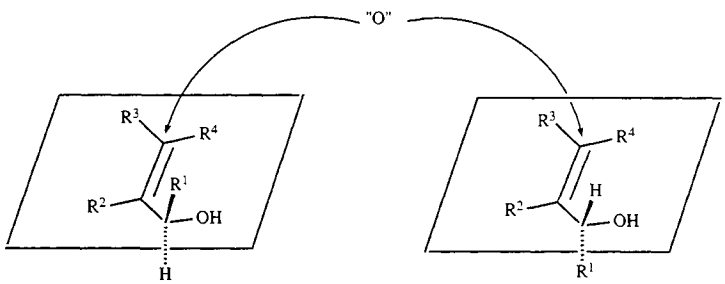


Fig. 10.2
Diastereofacial selectivity in Sharpless' epoxidation
of 1-substituted allylic alcohols

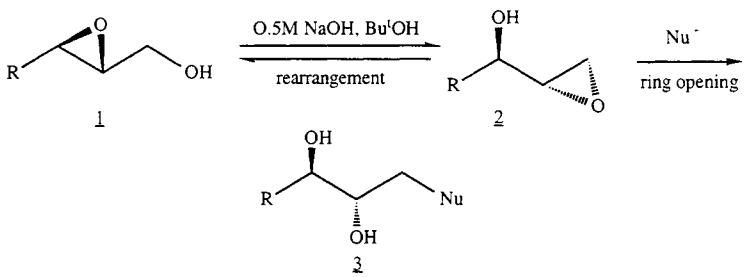
10.1.4. Nucleophilic ring opening of epoxy alcohols

The 2,3-epoxy alcohols resulting from epoxidation of allylic alcohols may be submitted to several selective transformations since there are, in principle, three possible reactive sites for nucleophilic substitution [10]. Thus, the "Payne rearrangement-opening reactions", which are usually not only stereospecific but highly regioselective [at C(1)], proceed with inversion of configuration at the site of ring opening via an SN2 mechanism, as shown in Scheme 10.3 [10a].[28]

Nucleophilic substitutions at C(2) and C(3) positions are not always as regioselective as the Payne rearrangement-opening reactions [10b] and the chemist may then utilise the C(1) hydroxyl group as a control element for inducing a

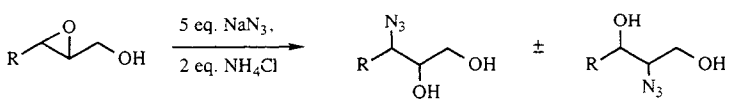
[28] Although the Payne rearrangement usually produces mixtures of epoxy alcohols, because the rate of reaction of 2 with any given nucleophile is faster than that of 1, the 1,2-epoxy-3-alcohols generated in situ can be selectively and irreversibly captured by a nucleophile to afford 3.

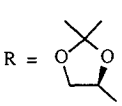
regioselective intramolecular attack at C(2) (see Table 10.1). However, even in bimolecular nucleophilic ring-opening reactions, there are cases in which unusual regioselectivities are observed as, for example, in the reaction of 2,3-epoxy alcohols with cuprates. Although the reaction takes place usually at the least hindered position, in the absence of a significant steric bias for ring-opening at either C(3) or C(2) a high regioselectivity is observed. In contrast with cuprates, organoaluminium reagents reliably open the epoxides at C(3). However, more complete studies have demonstrated that, in addition to steric effects, electronic effects may also play an important role in the opening of epoxides.



Scheme 10.3

TABLE 10.1. Ring-opening reaction of 2,3-epoxy alcohols with NH_4N_3



R = alkyl	3.5	:	1
R = $PhCH_2$	4	:	1
R = cyclo-C_6H_{11}	1.7	:	1
R = Bu^t	0	:	1
R = alkyl, OMe	1	:	2
R = 	1	:	10

10.1.5 Application of asymmetric epoxidation to multistep synthesis of natural products

Sharpless "asymmetric epoxidation" has been used in the enantioselective synthesis of several natural products, including the kinetic resolution of allylic alcohols [11] and the creation of:

One -

leukotriene B_4, [12]; (*R*)-(2-$^2H_1$)-cyclopentanone, [13]; aleuriaxanthin, [14]; (+)-*cis*-2-methyl-4-propyl-1,3-oxathiane, [15],

Two -

(+)-disparlure, [16] and; aklavinone, [17]; *exo*-brevicomin, [18]; *erythro*-6-acetoxy-5-hexadecanolide, [19]; lipoxin A, [20]; taxol side-chain, [21]; Darvon alcohol, [22]; ceramide, [23]; (+)-desepoxyasperdiol, [24],

Four -

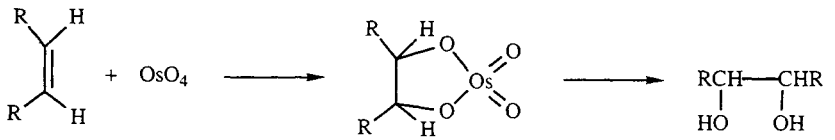
L-hexoses, [8]; iomycin (I), [25].; swainsonine, [26], or

Six - chiral centres:

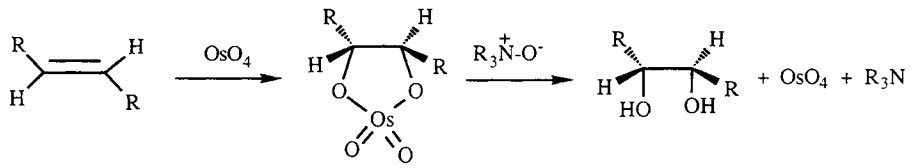
rifamycin, [27].

10.2. Asymmetric dihydroxylation of alkenes using osmium tetroxide

Osmium tetroxide is also a highly selective oxidant which gives glycols by a stereospecific *syn* addition [28]. The reaction occurs through a cyclic osmate ester:



Since the reagent is quite expensive, different catalytic procedures have been developed. A very useful procedure involves an amine oxide, such as morpholine-*N*-oxide, as the stoichiometric secondary oxidant (Scheme 10.4) [29].



Scheme 10.4

After the "asymmetric epoxidation" of allylic alcohols at the very beginning of the 80's, at the end of the same decade (1988) Sharpless again surprised the chemical community with a new procedure for the "asymmetric dihydroxylation" of alkenes [30]. The procedure involves the dihydroxylation of simple alkenes with *N*-methylmorpholine *N*-oxide and catalytic amounts of osmium tetroxide in acetone-water as solvent at 0 to 4 °C, in the presence of either dihydroquinine or dihydroquinidine *p*-chlorobenzoate (DHQ-pClBz or DHQD-pClBz) as the chiral ligands (Scheme 10.3).

Although the original procedure of catalytic asymmetric dihydroxylation (ADH) of *trans*-disubstituted alkenes was greatly improved, thanks to Sharpless's mechanistic insight, by just a slight change in the experimental conditions (slow addition of the alkene, [31]) and its scope highly enlarged (Table 10.2), there was still room for further improvements, mainly in the case of dialkyl substituted olefins. A great improvement was the finding that substitution of potassium hexacyanoferrate(III) (potassium ferricyanide) as the secondary oxidant for *N*-methylmorpholine *N*-oxide, affords the highest enantioselectivities obtained so far [32].

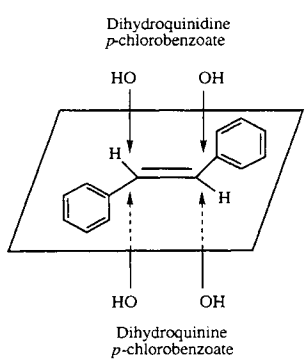
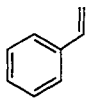
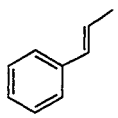
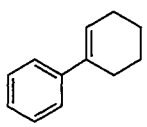
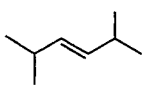
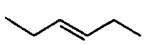


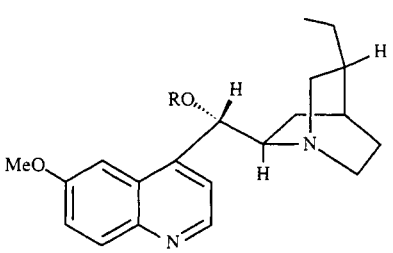
Fig 10.3

TABLE 10.2. Enantiomeric excesses obtained under different experimental conditions[a]

olefin	stoichiometric	catalytic		
		original	acetate	slow addition
	61	56	61	60 (5 h)
	87	65	73	86 (5 h)
	79	8	52	78 (26 h)
	80	12	61	46 (24 h) 76 (24 h + OAc)
	69	20	64	70 (10 h)

[a] in all cases the isolated yield was 85-95%

Moreover, looking for more effective ligands, Sharpless and his group prepared and tested a number of cinchona alkaloid derivatives, first in the stoichiometric ADH process [33] and then in the catalytic process. They found that aryl ethers of dihydroquinidine, as 4a and 4b, are excellent ligands for ADH of dialkyl substituted olefins (Table 10.3).



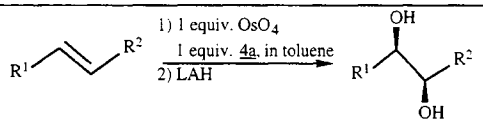
a, R = phenyl

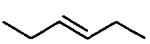
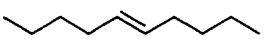
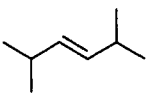
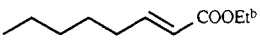
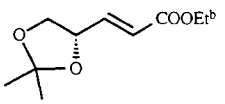
b, R = *o*-methoxyphenyl

c, R = *p*-chlorobenzoate

4

TABLE 10.3. Stoichiometric ADH using 4a.[29]



Entry	Olefins	Temp (°C)	%ee[a]	%ee[a] with 4c
1		0	85	71
2		-78	95	
3		0	88	73
4		-78	93	
5		0	89	79
6		-78	94	
7		0	90	67
8		0	97	77[c]

[a] Enantiomeric excess was determined by GLC or HPLC analysis of the bis-Mosher ester derivative. [b] The reaction was worked up with $NaHSO_3$ in H_2O/THF. [c] Diastereomeric excess.

It is noteworthy that ADH of α,β-unsaturated esters with this new ligand proceeds in excellent ee (≥90%, entries 7 and 8). By lowering the reaction temperature to -78 °C, the reaction with straight chain dialkyl substituted olefins takes place also with very high ee (≥93%, entries 2, 4 and 6).

In the stoichiometric ADH of (*E*)-3-hexene the highest ee was achieved using the ligand 4b (88% ee). On the other hand, the catalytic process (Table 10.4, entries 1-3) was carried out by slow addition of (*E*)-3-hexene (1 equiv.) to a mixture of 4a (0.25 equiv.), *N*-methylmorpholine *N*-oxide (NMO, 1.5 equiv.) and OsO_4 (0.004 equiv.) in acetone-water (10/1, v/v) at 0 °C, followed by working-up with $Na_2S_2O_5$. Although the catalytic reaction was slow and required a slower addition

[29] The stoichiometric ADH of olefins was performed by adding 1 equiv. of olefin to a 1:1 mixture of OsO_4 and 4a in dry toluene (0.1M in 4a), followed by reductive working-up with LAH to give the (*R,R*)-diol in 60-95% yield and good to excellent ee.

of the olefin than in the case of using 4c, it could be accelerated by addition of Et_4NOAc (2 equiv.) to the reaction mixture (Table 10.4, entry 4).

TABLE 10.4. Catalytic ADH of (*E*)-3-hexene.

Entry	Ligand	OsO_4	Secondary oxidant	Additive	Temp. (°C)	Time (hr)	%ee
1	4a	0.4 mol%	NMO		0	16	70
2	4a	0.4	NMO		0	30	75
3	4a	0.4	NMO		0	120	85
4	4a	0.4	NMO	Et_4NOAc	0	16	82
5	4a	1.25	$K_3Fe(CN)_6$	K_2CO_3	rt	20	83
6	4b	1.25	$K_3Fe(CN)_6$	K_2CO_3	rt	20	89

A further improvement resulted when potassium hexacyanoferrate(III) was used as secondary oxidant (Table 10.4, entries 5 and 6), in which case the slow addition of olefin was not necessary.[30] Chemical yields of 85-90% and ee of 89% were obtained by adding at room temperature 0.0025 equiv. of OsO_4 to a mixture of 1 equiv. of (*E*)-3-hexene, 0.25 eq of 4a or 4b, 3 equiv. of $K_3Fe(CN)_6$ and 3 equiv. of K_2CO_3 in *tert*-butyl alcohol-water (1/1, v/v), followed by reductive working-up with Na_2SO_3.

Sharpless concludes that ligand 4c is preferable for the ADH of arylsubstituted olefins, whereas the aryl ethers 4a or 4b are better ligands for the reaction of dialkyl or alkylcarboalkoxy substituted olefins.

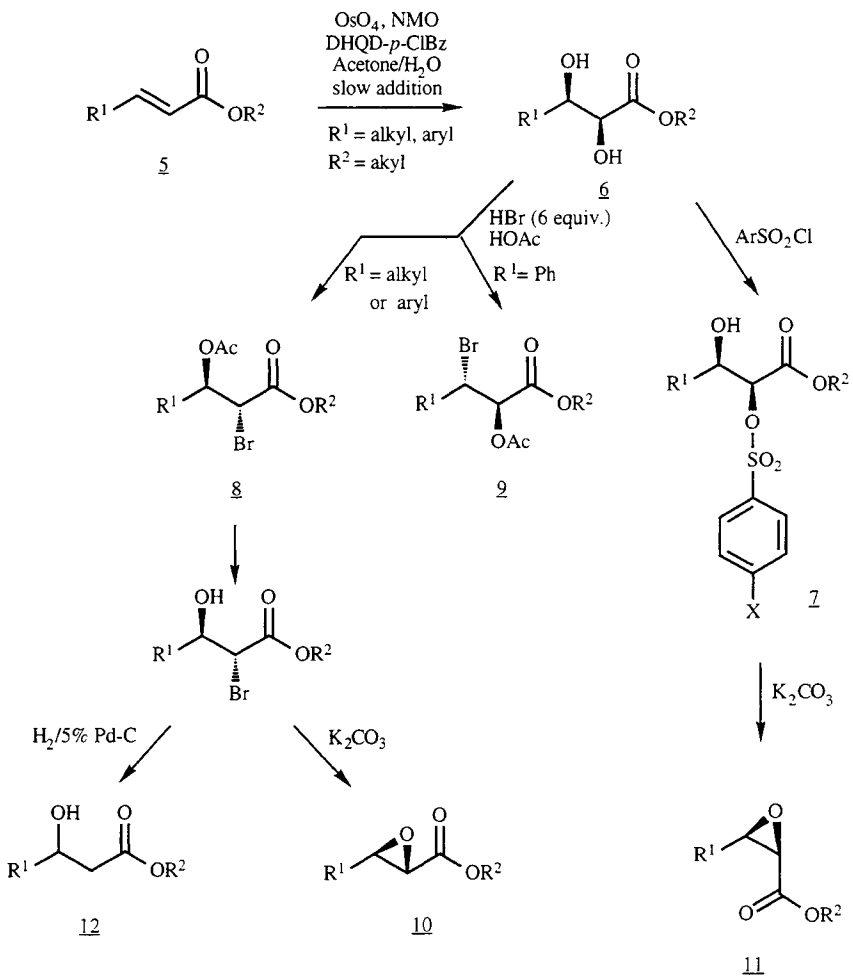
In fact, although good enantioselectivities in ADH of dialkyl substituted olefins could be previously obtained through the use of stoichiometric reagents at low temperature [34], the catalytic ADH developed by Sharpless is by far the best method that the synthetic organic chemist has presently at his hands.[31]

---

[30] Sharpless points out that this is apparently a direct consequence of the complete suppression of the catalytic "second cycle" [32].

[31] Sharpless and his group have also prepared polymer-bound alkaloid derivatives which allow the use of heterogenous catalytic ADH. The reactions proceed in good to excellent enantioselectivities in the case of *trans*-stilbene, and the OsO_4-polymer complex can be used for iterative processes [35].

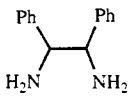
Sharpless and his group have also studied a series of selective transformations of *threo*-2,3-dihydroxy esters (6) -prepared by catalytic ADH of α,β-unsaturated esters 5- which lead to very useful and highly elaborated synthetic intermediates [36], such as α-(sulfonyloxy)-β-hydroxyesters (7), β-acetoxy-α-bromo esters or α-acetoxy-β-bromo esters (8 and 9), *threo*- and *erythro*-glycidic esters (10 and 11) and β-hydroxy esters (12). The substituent at the β-position plays an important role in determining the regiochemistry of the bromination of the 2,3-dihydroxy esters: whereas a β-alkyl substituent leads to β-acetoxy-α-bromo esters, a phenyl group directs formation of the α-acetoxy-β-bromo esters (Scheme 10.5).



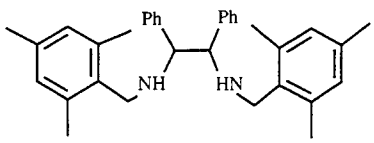
Scheme 10.5

The work by E.J. Corey [37], M. Hirama [38] and K. Tomioka [39], and their associates, on asymmetric dihydroxylation of alkenes with chiral diamine-osmium tetroxide complexes also deserves to be mentioned.

Whereas E.J. Corey uses the derivative (*S,S*)-14[32] of 1,2-diphenyl-1,2-diaminoethane (13), M. Hirama and K. Tomioka use chiral *N,N'*-dialkyl-2,2'-bipyrrolidines 15 and bis(3,4-diphenilpyrrolidines) 16, respectively. The method of E.J. Corey is by far the superior one, the chemical yields and the ee excesses usually being in the range of, respectively, 80-95% and 92-98%.



13



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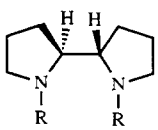
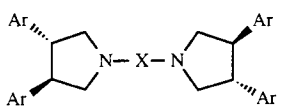


15, a. R = alkyl
b. R = H



16. a. Ar = Ph; X = $-(CH_2)_2-$
b. Ar = 3,5-Xylyl; X = $-(CH_2)_2-$
c. Ar = Ph; X = $-(CH_2)_3-$
d. Ar = Ph; X = 1,2-phenyl
e. Ar = Ph; X = 2,2'-biphenyl

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11. CHIRALITY IN NATURE AND INDUSTRY: THE PRESENT AND THE FUTURE. ENZYMES AND ANTIBODIES

11.1. Enantioselectivity in industry. An overview

In Chapter 9 we have already referred to the paramount importance of enantioselective syntheses for the preparation of optically active compounds.

The aim of this chapter is to give a general overview of the methods available for producing "industrial" quantities -*i.e.* amounts of at least some kilograms- of enantiomerically pure substances which can be used as "active" materials in commercial preparations (pharmaceuticals, drugs or medicines, pesticides, etc.).

To be of practical large-scale use, the methods must afford enantiomeric excesses (*ees*) of, at least, 70-80% for the crude material.

Approaches which may be applied are:

1) starting from optically active natural products -the so called "chiral pool"-, such as amino acids, hydroxy acids, terpenes and carbohydrates which can be used as building blocks for the synthesis of more complex chiral compounds. Table 11.1 shows some representative substances from the chiral pool;

2) resolution of racemates (either classical or kinetic resolution); and

3) asymmetric synthesis, *i.e.* converting prochiral precursors into homochiral compounds, either by

i) chemical catalysis or non-enzymatic chemical methods, which include the so-called *chemzymes*, or by

ii) enzymatic methods, and the newly developed technique of generating monoclonal catalytic antibodies or *abzymes*.

Since the first two approaches are very well known and exploited, and excellent reviews and books on the topic are available [1], we will deal only with some of the most recent findings in chemical catalysis -excluding the Sharpless asymmetric epoxidation and dihydroxylation, to which the whole of Chapter 10 is devoted. Synthetic catalysts which mimic the catalytic action of enzymes, known as *chemzymes*, will be also considered.

Finally, after a brief look at the structure and mechanism of action of enzymes, most of the chapter will be devoted to the innovative and promising field of catalytic antibodies or *abzymes*, which will probably be the method of choice for preparing optically active compounds in the future.

TABLE 11.1. Representative substances from the chiral pool[a]

Compound	Approx. price (US dollars/kg)
Ascorbic acid	13
(+)-Calcium pantothenate	16
(-)-Carvone	23
Anhydrous dextrose	1.2
Ephedrine hydrochloride	62
(+)-Limonene	3
L-Lysine	3.2
Mannitol	7.5
Monosodium glutamate	2
Norephedrine hydrochloride	24
Quinidine sulphate	130
Quinine sulphate	75
Sorbitol	1.7
L-Threonine	12-50[b]
L-Tryptophan	68

[a] Data from *Chemical Marketing Reporter*, Schnell Publishing, New York, 13 April (1990), cited in reference 1a; [b] depending on grade.

11.2. Asymmetric synthesis

Asymmetric synthesis [2] [3], which involves the conversion of prochiral precursors into homochiral compounds, can be attained by means of:

i) chiral auxiliaries -an example of which is the enantioselective aldol condensations using Evans' chiral oxazolidone auxiliaries (see page 239),

ii) chiral reagents -in this methodology a chiral reagent is treated with a prochiral substrate to deliver the optically enriched product, and

iii) chiral catalysts -which can be either chemical, or non-enzymatic catalysts (*chemzymes*), or natural *enzymes*, including monoclonal catalytic antibodies or *abzymes*.

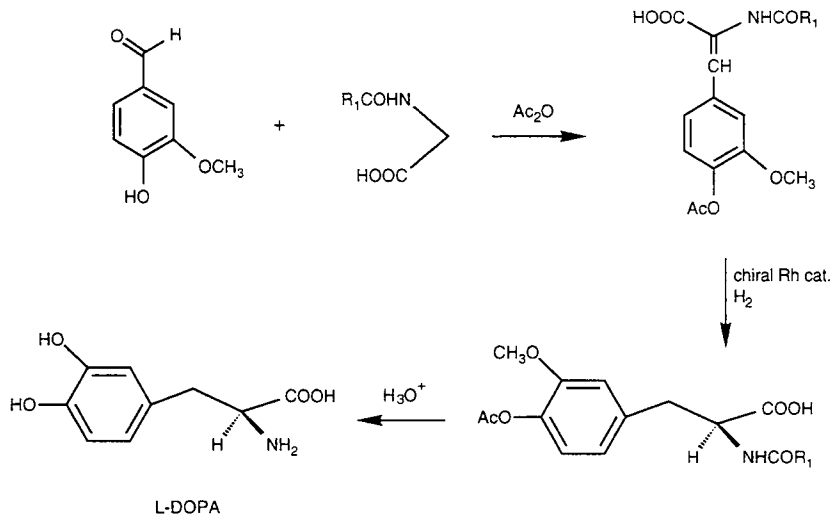
From the point of view of efficiency and application to the industrial production of optically pure compounds the chiral catalyst procedure is the methodology of choice. In this context, Sharpless' asymmetric epoxidation and dihydroxylation, Noyori-Takaya's second generation asymmetric hydrogenations and Jacobsen's epoxidation [3] have had a tremendous impact in the last few years and they constitute the basis of the newly spawned "chirotechnology" firms, as well as of the pharmaceutical, fine chemical and agriculture industries.

Asymmetric syntheses *via* transition metal mediated chiral catalysts are very useful since they offer two main advantages:

i) it is possible to produce large amounts of chiral compounds with the use of very small quantities of a chiral source, and ii) it is also possible to improve the efficiency of the catalyst by modification of the ligands.

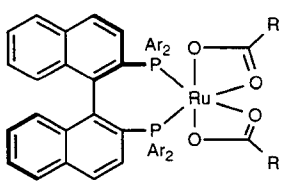
A classical example is the development of soluble chiral catalysts for homogenous asymmetric hydrogenation. The story began with the discovery of Wilkinson's catalyst [4]. In 1968, Horner [5] and Knowles [6], independently, reported the feasibility of asymmetric hydrogenations in the presence of optically active Wilkinson-type catalyst. Although the optical yields were rather low, further studies in this direction were the basis of the success of Monsanto's asymmetric synthesis of the anti-Parkinson's drug L-DOPA. The key steps of the synthesis are outlined in Scheme 11.1.

Later on, Kagan [7] reported an important result with DIOP bisdentate ligand, the first ligand with a C_2-symmetry axis, in which the stereoselectivity is improved by restricting the mobility around the metal atom; and Morrison [8] reported the interesting neomenthyl diphenylphosphine ligand, which is devoid of any chiral phosphorus atom. As stated by Kotha [1b]: "Early lessons learned in asymmetric hydrogenation paved the way to some of the new asymmetric catalytic processes".



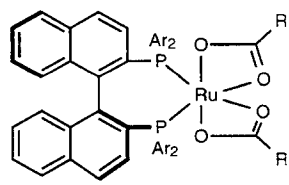
Scheme 11.1

More recently, Noyori [2] [9] has developed a "second generation" of soluble chiral catalysts of Wilkinson-type, such as the Ru-BINAP dicarboxylate complexes which greatly extended the utility and applications of asymmetric hydrogenation.



1a

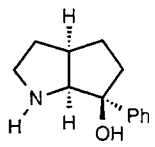
D-(*R*)-BINAP-Ru dicarboxylate



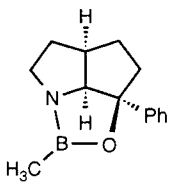
1b

D-(*S*)-BINAP-Ru dicarboxylate

As an example of non-enzymatic catalyst using oxazaborolidines [10], Corey and his associates have described an efficient synthesis of (+)-1(S),5(R),8(S)-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol (2) and its enantiomer. The *B*-methyloxazaborolidine derivatives (3) of these amino alcohols are excellent catalysts -or *chemzymes*- for the enantioselective reduction of a variety of achiral ketones to chiral secondary alcohols [11].



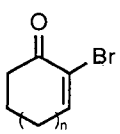
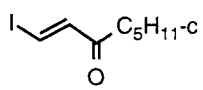
2



3

Table 11.2 summarises a number of examples of the enantioselective reduction of achiral ketones with borane in the presence of 0.1-0.2 equiv. of catalyst 3.

TABLE 11.2. Reduction of ketones by BH_3 with chiral catalyst 3 (derived from (+)-2)

ketone	equiv. BH_3.THF	equiv. catal.	reaction temp, °C	config. sec. alcohol (*%ee*)
$C_6H_5COCH_3$	0.6	0.1	0	*R* (97.5)
Bu^tCOCH_3	0.6	0.1	0	*R* (98.3)
α-tetralone	0.6	0.1	-22	*R* (95.3)
α-tetralone	0.6	0.2	-22	*R* (97.0)
c-$C_6H_{11}COCH_3$	0.6	0.1	-22	*R* (91.8)
 n=1	0.6	0.1	-23	*R* (97.5)
n=0	0.6	0.1	+23	*R* (95.0)
	0.6	0.1	-23	*R* (87.6)

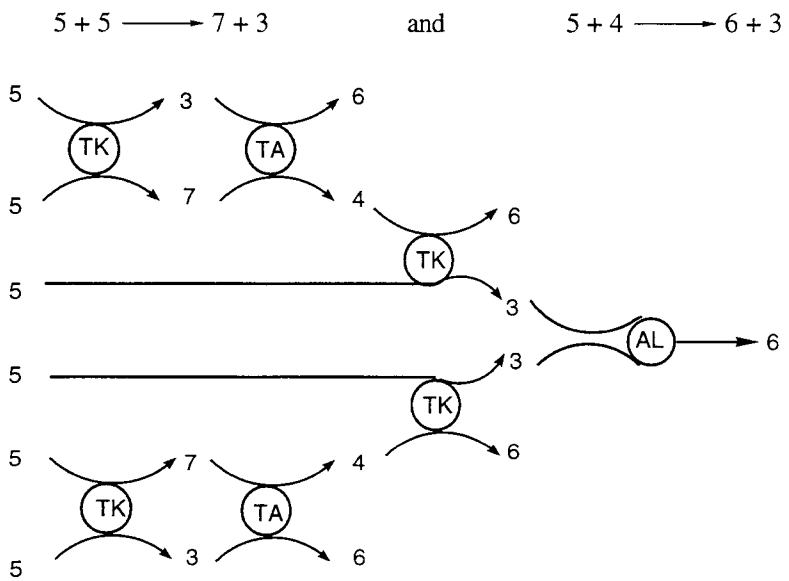
11.3. Enzymatic methods

11.3.1. Enzymes

Enzymes can be defined as polypeptides, either as simple chains or as an ensemble of them, possessing catalytic activity.

In discussing enzyme action two different aspects should be considered: i) *catalysis, i.e.* , the ability to accelerate a given reaction and to govern its mechanism properly, and ii) *specificity*, i.e., the capacity to discriminate among several reagents. However, since the evolution of enzymes has been a process of selection there is a limit in such a specificity [12].

The *transketolase* of the pentose cycle, for instance, is a good example of such limitation. This enzyme catalyses two different reactions (see Fig. 11.1), which also operate in Calvin's cycle.



TK =transketolase; TA = transaldolase; AL = aldolase
Simplest solution to the problem of pentoses
(only reactions of carbon transfer are indicated).

Fig. 11.1

The *transketolase specificity* could not be restricted further because, as it can be mathematically demonstrated, if a certain enzyme catalyses one of the two reactions, it must necessarily catalyse the other one. There cannot exist any enzyme which catalyses one of them without being able at the same time to catalyse the other one.

The catalysis takes place in a specific region of the enzyme named the *active site* or *catalytic cavity*. This active site involves those amino acid residues (i.e., side chains) directly implicated in the mode of binding and the specificity of the substrate, as well as in the catalytic process itself.

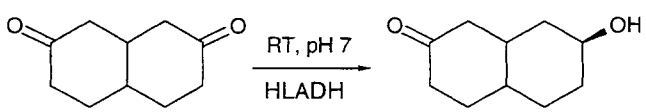
On the other hand, three kinds of *specificity* should be considered: one refers to the *specificity* towards the substrate or *structural specificity*; the second one refers to the *regiospecificity*; and the last one, which is always strictly operating, refers to the *stereospecificity* for a given substrate (or, much better, *enantiospecificity*, since chirality[33] is a *conditio sine qua non* for life to prosper).

The "lock-and-key" description of the catalytic action of enzymes given by Emil Fischer [13] one hundred years ago, put more emphasis on the enzyme-substrate specificity than on stereospecificity, suggesting the idea of:

"one-enzyme (lock), one substratum (key)".

It is worthwhile to remember here that baker's yeast, for instance, largely used by the experimentalist chemist to reduce *in vitro* a broad range of double bonds containing substrates, such as ketones and olefins (Table 11.3), is not a pure enzyme, but a cell containing hundreds of enzymes.

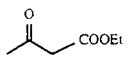
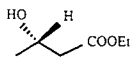
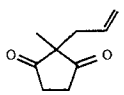
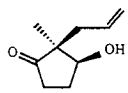
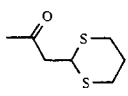
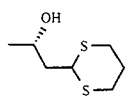
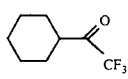
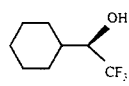
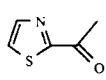
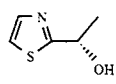
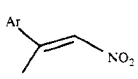
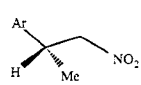
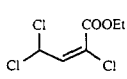
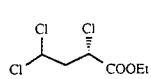
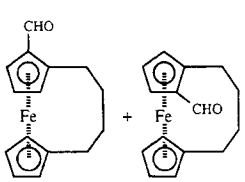
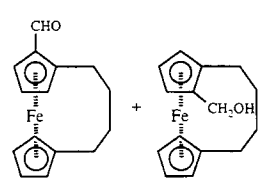
However, a pure enzyme, like horse liver alcohol dehydrogenase (HLADH), shows not only high stereoselectivity but regioselectivity as well, affording, for example, 89% yield of monoalcohol 5 from dione 4 with *ee* higher than 99% [14].



4 5

[33] Since chirality means "handness" it is quite pertinent to talk of homochiral molecules when referring to enantiomerically pure substances. Any natural sugar or amino acid is a homochiral product which belongs to the D or L-series, respectively.

TABLE 11.3. Diversity of substrates (ketones and olefins) accepted in yeast reductions[a]

Substrate	product	*ee*(%)
		97
		>98
		99
		99
		95
		89-98
		84-98
		89% *ee* 80% *ee*

[a] Taken from ref. 1a

11.3.2. Structure of enzymes and mechanism of action. Stereospecificity

The ability to form a complex having a transition state with a greater potential energy than either the reactants or the products is a fundamental requirement for enzyme catalysis (Pauling's postulate).

When an enzyme combines with a substrate, both the enzyme and substrate undergo conformational changes that increase the sensibility of the substrate to the attack by H^+, OH^- or some other specific functional groups of the enzyme. By this process, the substrate is transformed into its products, which separate from the *active site*. The enzyme recovers then its original conformation, combines with another molecule of substrate and the cycle is repeated. It is worthwhile to emphasise here that enzymatic reactions occur at very mild "physiological conditions", i.e., room temperature and pH near 7, and with rate accelerations of 10^8-10^{10} greater than the uncatalysed reaction.

Compared to the substrates on which they act, enzymes are huge molecules. This seems to be required for an efficient (i.e., error-free) functioning of the metabolic machinery, thus ensuring optimal results. A parallel could be drawn here with some mechanical tools: the greater the precision, the larger the tool. According to Srere [15], the big size of enzymes must be related to their need for sufficient surface area to provide specific binding sites for their mobilisation and localisation in the living cell, as well as for their integration into specific metabolic pathways.

Concerning the *stereospecificity* of enzymes, we must remember (see page 218) that stereospecificity means *order*; and order means "negative entropy" which, in turn, means *rigidity*, "lack of flexibility" or "absence of degrees of freedom". This leads organic chemists to view enzymes mainly as "entropy traps", in which the binding energy is used to freeze out the rotational and translational degrees of freedom necessary to form the activated complex. A direct consequence of this is the high stereospecificity observed in enzymatic reactions (see Table 11.2). Since changes in entropy are a complex mixture of changes in solvation, conformation, molecularity, etc., it is understandable [16] that enzymologists are much more concerned with structure than with thermodynamics.

In this context, time, speed and distances (space) are important parameters to be kept in mind, leading to the so-called "spatiotemporal" or "proximity theory". This theory states that "the reaction rate (speed) is a sensitive inverse function of distance and time".

The best way to combine all these parameters is to trace back the catalytic action of enzymes to *intramolecularity*. It is generally accepted that when van der Waals distances (contact distances) are imposed for definite times upon reactive groups, intramolecular reactions occur then at enzyme-like rates (accelerations of 10^8 to 10^{10} are associated to enzyme-catalysed reactions). On the other hand, according to the Page-Jencks theory [17] the fast rates of intramolecular reaction "are merely an entropic consequence of converting a bimolecular reaction into a unimolecular reaction".

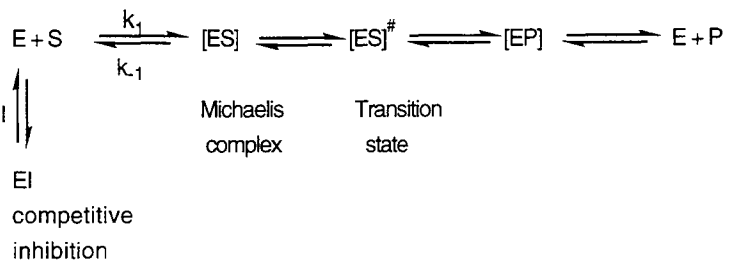
11.3.3. Reversible inhibitors: transition state analogs[34]

Compounds having a structure similar to a substrate for a given enzyme will not be transformed but will act as enzyme inhibitors.

Some of these inhibitors are reversible since they can easily be removed from the binding site, so the enzyme regains its activity. But in some instances a covalent bond is formed between the enzyme and the inhibitor, in which case the catalytic activity is not restored when the enzyme is separated from the solution containing the inhibitor. Such inhibitors are called irreversible.

In our context, an important class of reversible inhibitors are the transition state analogs [18], which are stable compounds designed to mimic the structure of an intermediate in the path of substrate's transformation by the enzyme. Such analogs are based in Pauling's postulate [19], which states that "an enzyme recognises and binds more tightly to the transition state than to the ground state of the substrate".

If E = enzyme, S = substrate, P = product and I = inhibitor, we will have:



[34] As usual in the field, "transition state" is also loosely used as equivalent to "reactive intermediate."

the fundamental equation based on Michaelis-Menten kinetics being:

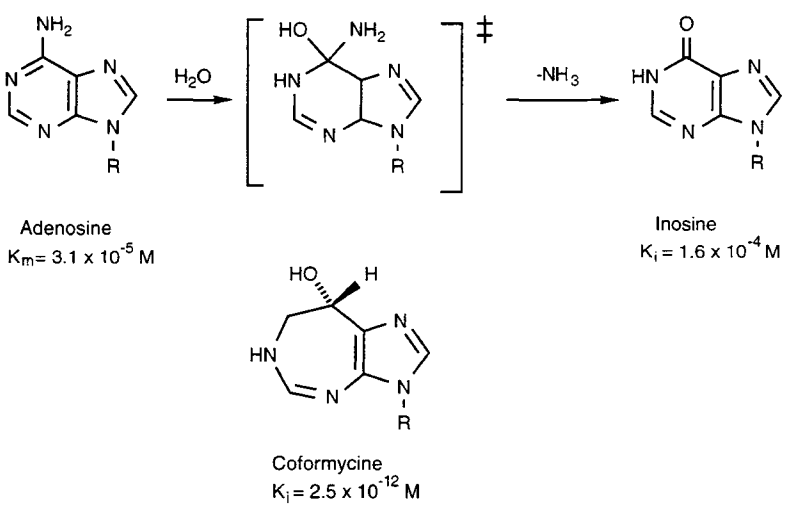
$$V = \frac{k_c [E]_0 [S]_0}{K_m + [S]_0}$$

The speed V of an enzymatic reaction is governed by two important constants, charateristic of a given substrate: the catalytic constant k_c and the Michaelis constant K_m.

A good substrate must have a k_c/K_m ratio as large as possible; that is, K_m should be small. On the other hand, a good inhibitor will have a small K_i where

$$K_i = \frac{[E][I]}{[EI]}$$

A good example to illustrate these points is the antibiotic coformycin which inhibits the enzyme adenosine deaminase (Scheme 11.2):

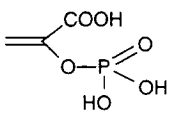


Scheme 11.2

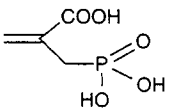
Inosine is a good inhibitor of the enzyme, but coformycine, which resembles more closely the transition state, is many orders of magnitude superior as an inhibitor.

Inhibition of enzymatic reactions by transition state analogs has been an extremely important approach for drug design [20], the principle underlying this is that "nature has developed enzymes for binding efficiently to the transition states of the reactions they catalyse".

Phosphonates, for example, have been used as analogs of biological phosphates [21].



phosphoenolpyruvate



2-phosphonomethylacrylate analog

11.4. At the crossroad of chemistry and biology: catalytic antibodies

11.4.1. Chemistry and immunology. Antibodies

Interaction between chemistry and immunology has led to the development of the impressive field of catalytic antibodies [22].

Whereas chemistry offers scientific explanations about molecular structures and mechanisms of the molecular interactions -which provide the basis for immunological responses, whatever their complexity could be-, the more important contribution of immunology to chemistry is opening the possibility of designing the *binding sites* of the immunoglobulins (antibodies) with respect to a given ligand or *antigen*. The highly specific sites created naturally within the immunoglobulins, in order to destroy foreign invaders, can be induced to recognise a great number of chemical structures, thus providing an opportunity to emulate nature's synthetic skills and to explore the noncovalent interactions of folded polypeptides that allow the three dimensional complementarity with a ligand.

The immune system of vertebrates is composed of a great number of interacting cellular and molecular species whose responsability is to detect, identify and destroy foreign invaders such as infective microorganisms and their concomitant macromolecular constituents [23].

B lymphocytes, white blood cells originating in the bone marrow, are widely distributed throughout the body and are the essential elements of the immune system, which is responsible for synthesising antibodies against foreign *antigens*.

It is important to realise that when B cells of the immune system are stimulated by a given *antigen*, they produce a huge number of antibodies which interact with different portions of the *antigen*, a process that identifies it as a foreign invader and induces its elimination. However, each B cell produces only a single structurally unique antibody, a fact that is important in the production of monoclonal antibodies.

The basic structure of an immunoglobulin molecule, such as the major serum antibody IgG, consists of four polypeptide chains: two identical light chains (molecular weight around 25 000 daltons) and two identical heavy chains (with a molecular weight around 50 000 daltons), cross-linked by disulfide bonds to form Y-shaped molecules with two flexible arms (Fig.11.2). The binding sites are located on the arms and vary from one molecule to another (variable region) [22b].

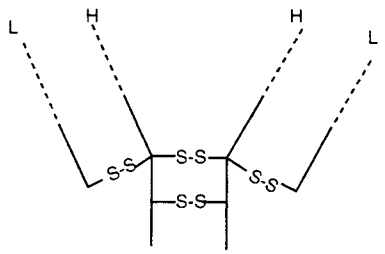


Fig. 11.2

There are different classes and subclasses of immunoglobulins which are determined by the amino acid sequence of the light and heavy chains.

Although small molecules do not usually stimulate antibody formation, antibodies against them can usually be raised if the small molecule, or *hapten,* is covalently attached to a large immunologically active carrier protein.

11.4.2. Polyclonal antibodies

Polyclonal antibodies are produced by injecting an *antigen* into an animal in the presence of an adjuvant containing bacterial lipopolysaccharides that stimulate the immune system. *Serum* prepared from the blood contains several different classes of antibodies that interact with different domains in the *antigen* molecule, each of

these antibodies originating from a distinct B cell. This *serum* is referred to as a *polyclonal antiserum.*

Polyclonal antisera are usually prepared either from isolated *antigens*, such as proteins or from synthetic peptides derived from the protein sequence. The *antisera* derived from small synthetic peptides are regio-specific with respect to the cognate protein and resemble in some way the monoclonal antibodies, but they are much easier to prepare.

11.4.3. Monoclonal antibodies. Hybridoma technology

In 1975 G. Kohler and C. Milstein [24] demonstrated that it was possible to generate monoclonal antibodies *in vitro.* The technique involves cloning a single antibody-secreting B lymphocyte so that uniform antibodies can be obtained in large quantities.

The preparation of monoclonal antibodies is a perfectly standardised but quite a long process [25], which is outlined in Fig. 11.3.

The process involves: i) immunisation of a mouse with an *antigen* against which antibodies are desired; after the immune response has been detected and antibodies are observed in the mouse *serum*, the animal is sacrificed and the spleen removed; ii) the spleen cells containing high concentration of B cells, including the ones stimulated to produce antibodies against the immunising *antigen*, are prepared and placed in culture with myeloma cells which are "immortal" bone-marrow-derived tumor cells; iii) hybridisation-immortalisation: the cells are induced to fuse by addition of polyethylene glycol (when a spleen cell and a *myeloma* cell fuse, the nuclei also fuse and the genetic material from each cell is recombined and the resulting *hybridoma* cells are thus endowed with genes from each progenitor cell.) Under ideal circumstances, cells will result that contain the *myeloma* genes responsible for immortalisation and the B cells genes capable to generate the derived antibody); iv) selection and purification of separate antibody-producing cell lines afford pure clonal populations of cells that grow indefinitely in culture, to produce virtually unlimited quantities of a single monoclonal antibody. Notice, however, that not all the antibodies generated possess the exact complementarity required for recognition. Only 100 or so, out of the many thousands of cell lines secreting antibodies, will be positive to binding in a *hapten* binding assay. In this selected group probably only 1-10 per cent will recognise the desired structural feature and their detection usually requires relatively large quantities of antibody.

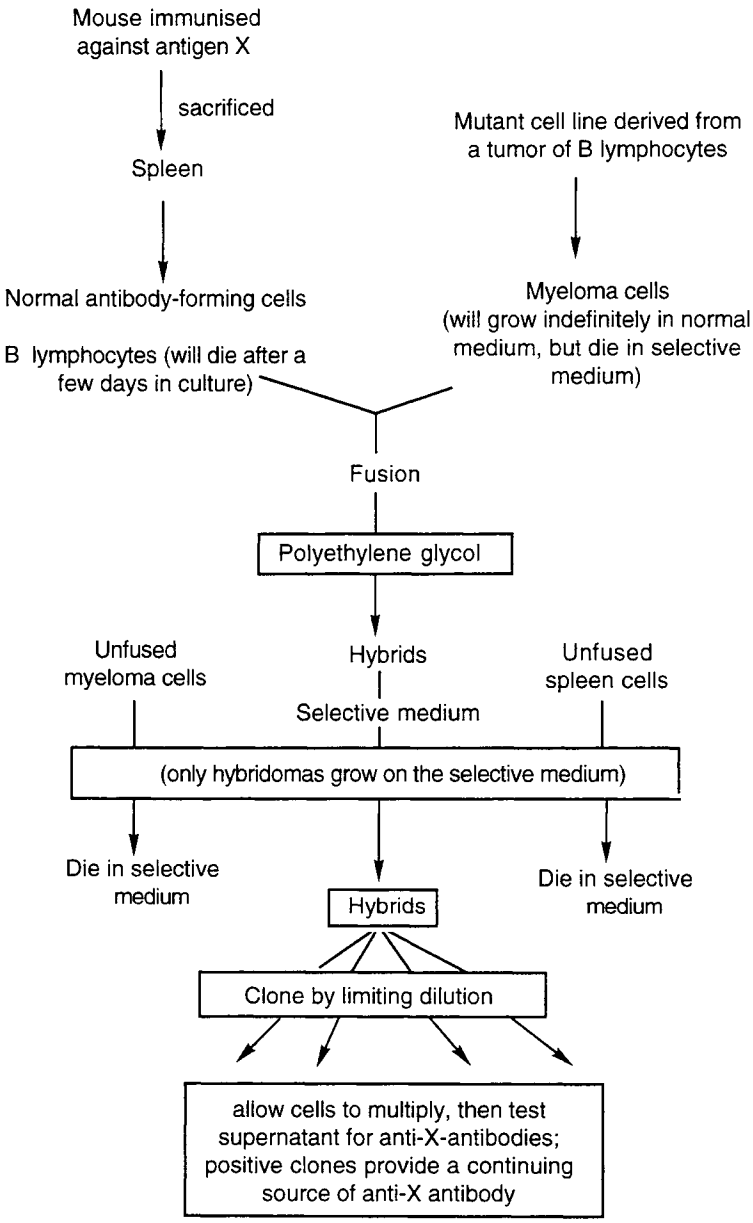


Fig. 11.3

Outline for the production of monoclonal antibodies

11.4.4. Catalytic antibodies (antibodies as enzymes)

Like enzymes, antibodies have the capacity to recognise complementary molecular structures and form very specific complexes with high association constants. One basic difference between antibodies and enzymes is that the former bind molecules in the ground states, whereas enzymes bind substrates in higher energy states. Furthermore, Pauling [19] -and also Jenks some years later- had predicted that stable analogs of the transition state of a given enzymatic reaction would bind tightly to the enzyme and increase its activity.

The question P.G. Schultz, from Berkeley, and R.A.Lerner , from Scripps, set forth was: "How to associate the prodigious capacity of molecular recognition of antibodies with potential enzymatic (catalytic) activity?" [22a] [26]. In 1986, they succeeded developing the first antibodies with catalytic activity [27]. Lerner called them *abzymes*. In fact, their strategy is quite simple: based on Pauling's hypothesis, Lerner's and Schultz's groups looked for antibodies that could stabilise the transition state of a given reaction, such as ester and carbonate hydrolysis.

Since then, catalytic antibodies which catalyze different chemical reactions have been described. The reactions range from ester or carbonate hydrolysis to carbon-carbon bond forming reactions, bimolecular amide formation or peptide bond cleavage, so the application of catalytic antibodies to general synthetic organic chemistry seems to be very promising [22].

It is clear that stabilisation of the transition state alone is not sufficient to reach reaction rates rivalling those of enzymes. Although a few examples of rate accelerations of *ca.* 1,000,000 fold have been described, most of the known antibodies enhance the reaction rates only some 1000 to 10,000 fold relative to the rates of the spontaneous reactions, values which are well below the usual accelerations observed with enzymes. Several factors can account for these differences. First, enzymes have functional groups in their *active* or *binding sites* capable of either adding or withdrawing protons or acting as nucleophiles. Moreover, in some instances, enzymes have *cofactors* or *coenzymes* which can promote a given reaction.

For all these reasons, some chemical or genetical modifications have been applied into the *binding sites* of antibodies in order to improve their reactivity [22]. Antibodies can be modified by the incorporation of natural or synthetic catalysts into the antibody recognition site, as for instance transition metal complexes, cofactors, and bases or nucleophiles, to carry other catalytic functions, which open the way to

the production of "semisynthetic" catalytic antibodies. In this context one can imagine, for instance, the generation of antibodies that can not only hydrolyse peptide bonds with a degree of specificity but can also be sequence specific. This would make possible to produce antibodies which would allow to cut and paste proteins, opening up new strategies for protein engineering.

Designing *haptens* in order to stimulate the production of catalytic antibodies depends on a variety of strategies based on transition state analogs, *entropy traps* and opportunistic chemistry.

11.4.5. Protocol for immunological activation of small haptens

Since small *haptens* are not immunogenic -*i.e.* do not usually stimulate the formation of antibodies-, they must be coupled to a carrier protein. For instance, Schultz [22b] described the coupling of the *hapten* to the carrier proteins bovine serum albumin (BSA) and keyhole limpet hemocyanin (KLH), in order to generate antibodies for his specific studies.

The spacer arm length between the *hapten* and the carrier is in the range of 6 to 8 Å, which should eliminate any steric interference with carrier side chains. According to the protocol described by Schultz the *haptens* were coupled to BSA and KLH via *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide or the *N*-hydroxysuccinimide ester at pH 5.5 in water. Other coupling strategies include substitution with diazonium salts and reductive amination. The ratio of *hapten*-carrier range between 8 and 15 *haptens* per carrier.

Mice were immunised with the KLH-*hapten* conjugate emulsified in complete Freund's adjuvant and the hybridoma technology applied in order to generate monoclonal antibodies from the polyclonal antiserum. For this, the hybridomas are cloned or separated in colonies of cells which produce a single antibody. The resulting cells are screened by an ELISA (**E**nzyme-**L**inked **I**mmuno**S**orbent **A**ssay) [28] for their ability to generate antibodies that bind selectively and with high affinity to the desired ligand. The purity of monoclonal antibodies is essential for highly effective catalytic activity.

11.4.6. Transition state analogs and entropy traps

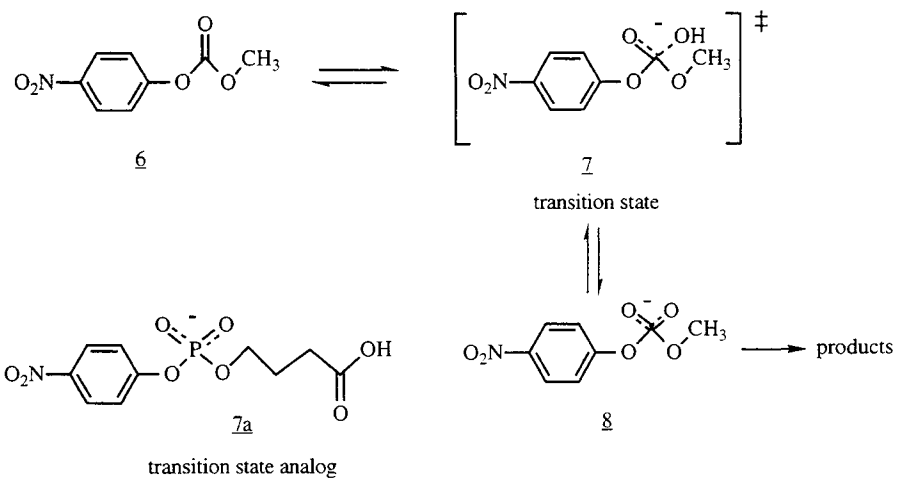
As stated above, an antibody generated for a *hapten* group resembling the transition-state configuration of a given reaction should lower the free energy of activation of the reaction by stabilising the corresponding transition-state, relative to

reactants or products, and increase the reaction rate. Antibodies to *haptens* that mimic stabilised transition states are able to catalyse a variety of reactions, including carbonate, ester and amide hydrolysis (see below).

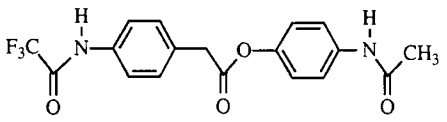
Furthermore, antibodies should be capable of efficiently catalyze reactions with unfavorable entropies of activation by acting as *entropy traps*: the binding energy of the antibody being used to freeze out the rotational and translational degrees of freedom necessary to form the activated complex. This principle has been applied to the design of antibodies that catalyze both unimolecular and bimolecular reactions (see below).

11.4.7. Carbonate, ester and amide hydrolysis

In order to generate antibodies which catalyse the hydrolysis of carbonates (6, 10), carboxylic esters (9) and amides with a certain degree of specificity, the phosphates (7a, 10a) and phosphonates 9a were used as *haptens* that mimic the tetrahedral negatively charged transition state of the spontaneous hydrolysis reaction (see Scheme 11.3) [27] [29].



Scheme 11.3



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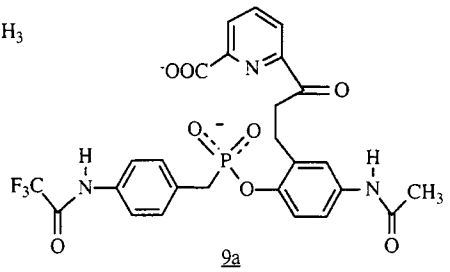
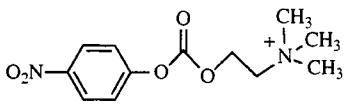
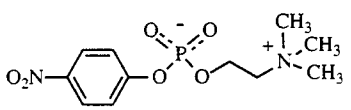


9a

transition state analog



10



10a

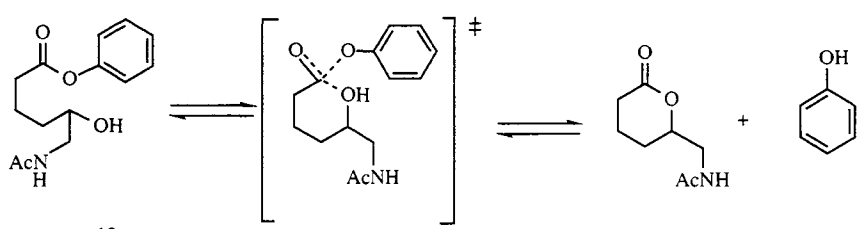
transition state analog

Scheme 11.3 (cont.)

More recently, antibodies have also been generated against the KLH conjugate of arylphosphonamide (a transition state analog).

11.4.8. Cyclisation reactions

Lerner and Benkovic examined the possibility of performing an intramolecular cyclisation reaction [30]. They chose the formation of a six-membered lactone ring from a hydroxy ester (12) and observed that only one single enantiomer of the δ-lactone (14) in 94% *ee* was formed from the corresponding δ-hydroxy ester. Moreover, the stereospecific ring closure reaction was accelerated by the antibody -elicited from the transition-state analog 15- by about a factor of 170.



12

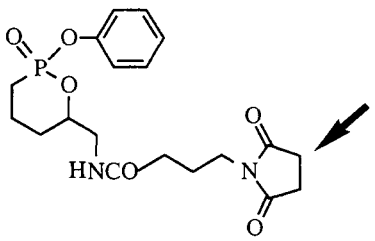
racemic mixture

13

transition state

14

δ-lactone
(optically pure)



via an immunogenic conjugate on a carrier protein to raise the antibody.

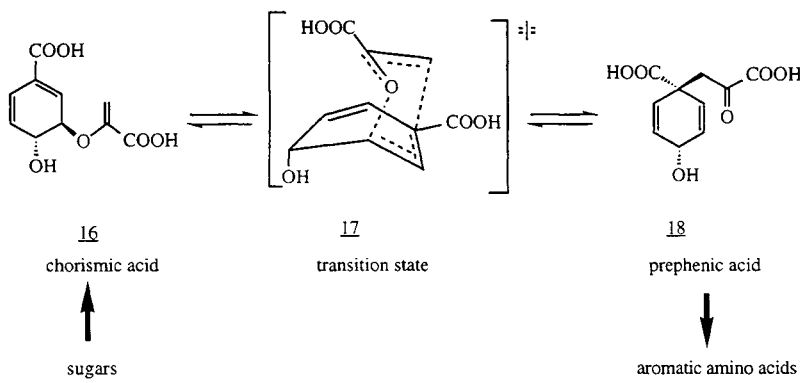
15

cyclic phosphonate ester analog

Scheme 11.4

11.4.9. Claisen rearrangement: chorismic acid to prephenic acid

An interesting application of the transition state analog strategy is the design of molecules that could mimic the transition state of the chorismate (16) to prephenate (18) conversion [31]. Biologically this conversion links a family of sugars with aromatic amino acids. The conversion takes place via a Claisen rearrangement in a [3,3]-suprafacial manner. This 3,3-sigmatropic rearrangement occurs through an asymmetric chairlike transition state (see Scheme 11.5).



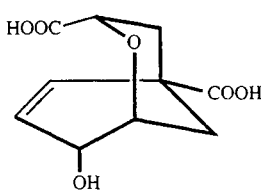
16 chorismic acid

17 transition state

18 prephenic acid

sugars

aromatic amino acids



19 *endo*-isomer

Scheme 11.5

Monoclonal antibodies were elicited to the *endo* bicyclic transition state analog 19, the most potent known inhibitor of chorismate mutase, an enzyme from *Escherichia coli* that catalyses the above reaction [32]. One out of the eight antibodies generated to the KLH conjugate of 19 was found by Bartlett and Schultz [31] to catalyse the Claisen rearrangement with a rate enhancement of around 10^4. It is argued that the transition state analogue induces a complementary combining site in the abzyme that constrains the reactants into the correct geometry for the [3,3]-electrocyclic reaction, a process that constitutes an *entropy trap.*

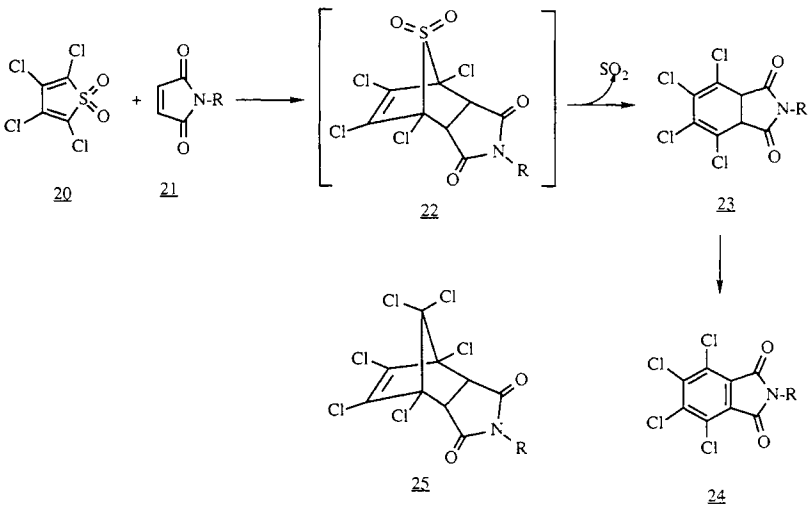
11.4.10. Diels-Alder reactions

The Diels-Alder reaction is one of the most powerful and versatile carbon-carbon bond-forming methods available to synthetic organic chemists; attempts to isolate enzymes that catalyze such a process have been unsuccessful. Therefore, the acceleration of this reaction by an *abzyme* has been an important landmark in the field of catalytic antibodies and of considerable potential for chemical synthesis.

Reactions with highly unfavourable entropy of activation ($\Delta S^{\ddagger}$ in the range of -30 to -40 $calK^{-1}mol^{-1}$), such as Diels-Alder reactions, can be catalysed by antibodies generated against properly designed *haptens*. These *haptens* mimic the boatlike conformation of the uncharged, highly ordered Diels-Alder transition state. However, these products are poor candidates, given the likelihood of severe product inhibition in the induced binding pockets, and a new strategy should be developed to facilitate catalyst turnover. One way to minimise product inhibition draws on chemical or conformational change to drive product release.

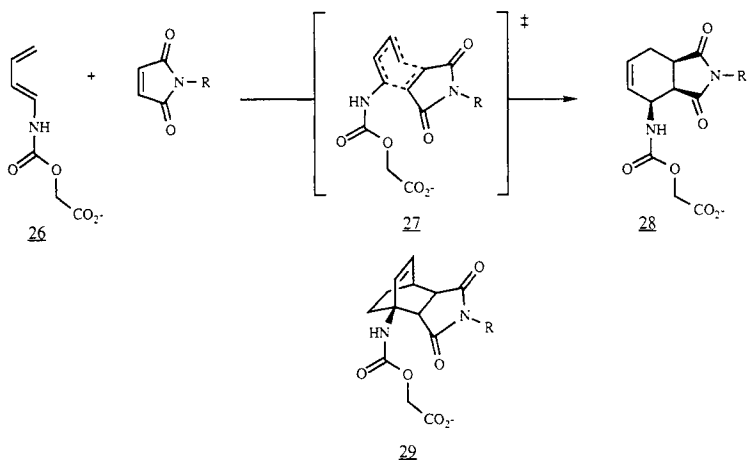
Hilvert [33] has recently used this approach to catalyse the Diels-Alder reaction between tetrachlorothiophene dioxide (20) and *N*-alkylmaleimides (21), a reaction that takes place in two steps: i) initial formation of tricyclic adduct 22; and ii) cheletropic extrusion of sulfur dioxide to give dihydrophtalimide 23, which is spontaneously oxidised under the reaction conditions to 24 (see Scheme 11.6).

A suitable stable transition state analog is hexachloronorbornene derivative 25, which mimics most of the geometrical features of the transition state, including the boat conformation of the cyclohexene ring. It was used to poduce antibodies that catalyse the reaction between 20 and 21 efficiently, with substantial rate acceleration and multiple turnovers.



Scheme 11.6

A similar strategy adopted by Braisted and Schultz [34] to catalyze de Diels-Alder reaction between the acyclic diene 26 and *N*-phenylmaleimide involved the synthesis of a *hapten* 29 that contains an ethano bridge that locks the cyclohexene ring into a boat conformation resembling the transition state 27 (see Scheme 11.7). In this case, the product's tendency to undergo an energetically favorable conformational change was expected to reduce its affinity for the active site. However, the low activity showed by the catalyst will require a more extensive screening of the immunological response to *haptens* like 29.



Scheme 11.7

The development of tailored "Diels-Alderase" antibodies could therefore provide a complete control of the stereochemical outcome of this cycloaddition reaction. Another possibility would be the use of antibodies to reverse the normally observed Diels-Alder endo/exo selectivity [35].

The ability to design at will highly efficient catalytic antibodies for any given reaction opens a promising future for this new technology both in chemistry and medicine.

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Chapter 12

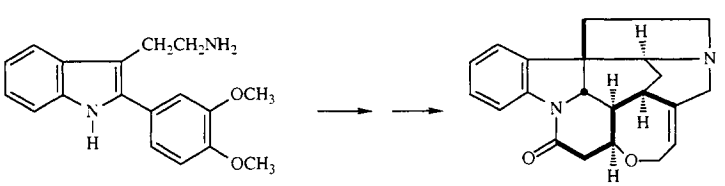
12. CONTROL ELEMENTS. SUMMARY

12.1. Control elements

In practice, whatever the methodology used, the retrosynthetic process always leads to sequences of intermediate precursors which go from the target to commercially available starting materials, but they do not say anything about the "control elements" which it may be necessary to introduce in order to carry out the synthesis in the laboratory so that the reactions proceed as required.

A "control element" may be *an atom or a group of atoms which are introduced in some stage of the synthesis so that a given reaction can be carried out selectively* [1]. The purpose of such "control elements" is to secure an efficient conversion of the starting materials to the target molecule. It should be remembered here that the yield R^i of compound i is the product of the conversion C by the selectivity S^i of the compound under consideration (see *Heading 1.4*).

Since the use of a control element usually requires two extra steps -one to introduce it and another one to remove it after the selectivity has been achieved- this methodology is rather inefficient. It is always more elegant and efficient if the atom or the group of atoms, which play the role of a control element, may be used subsequently in one of the steps of the synthetic sequence to elaborate the carbon skeleton and so becoming an integral part of the target molecule. Such is the case, for instance, of the synthesis of strychnine by Woodward [2]. Starting from 2-veratryltryptamine (1), in which the dimethoxybenzene ring originally had the purpose of protecting the α-position of the indole ring, its six carbon atoms become afterwards an integral part of the carbon skeleton of strychnine shown in structure 2 with heavy lines:

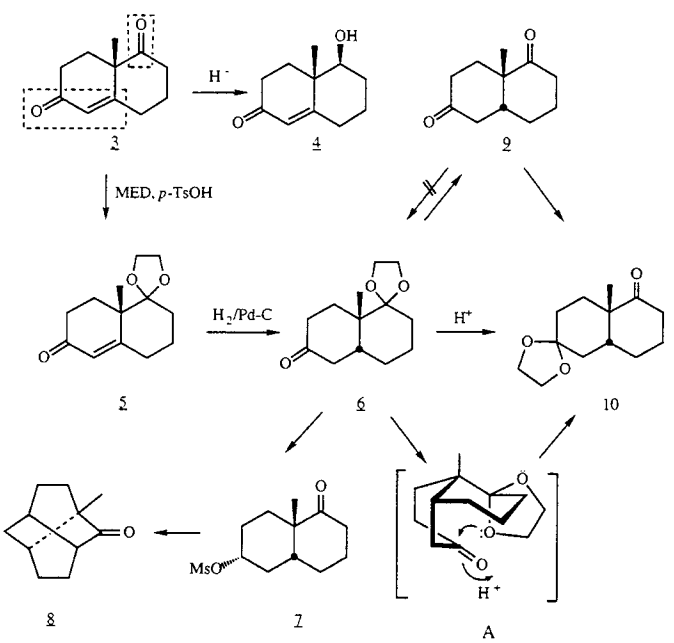


1 2

In *Heading 1.4* we have already seen that three different kinds of control elements [3] may be considered: 1) *chemoselective* control elements (controlling chemical reactivity), 2) *regioselective* control elements (controlling the orientation of reactants) and 3) *stereoselective* control elements (controlling the spatial arrangement of atoms within the molecule), which may control either the relative (*diastereoselective*) or the absolute spatial arrangement (*enantioselective* control elements).

12.1.1. Chemoselective control elements: protecting and activating groups. Latent functional groups

The achievement of a more or less efficient chemoselective control depends upon the similarity of two or more functional groups. Even if the functional groups are identical, but not their electronic or steric environment, the difference may be great enough to achieve directly a practically absolute chemoselectivity. For instance, in the Wieland-Miescher ketone (3), with two carbonyl groups, the non-conjugated carbonyl group can be chemo- and stereoselectively reduced by the hydride ion [4] to give 4 without affecting the α,β-unsaturated ketone which is a poorer electrophile (Scheme 12.1).

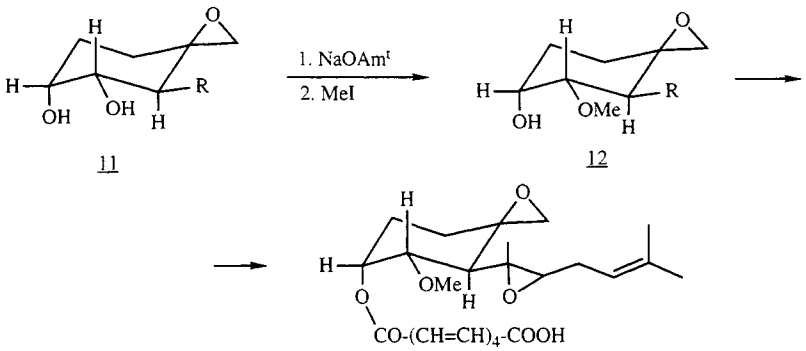


Scheme 12.1

In such cases it is also possible to achieve chemoselectivity in favour of the less reactive group by using *protecting groups* as control elements. In the Wieland-Miescher ketone it is possible to protect selectively the non-conjugated carbonyl as an acetal (5) so that the conjugated group remains free to be submitted to further transformations [5]. For instance, the less reactive carbonyl group can be converted, after catalytic hydrogenation of acetal 5 to the *cis*-decalone 6, into a good leaving group with the correct stereochemistry (as in 7) to arrive finally at methyltwistanone 8 [6].

An example of identical functional groups with a different steric environment is found in the related dione 9, from which would not be possible to prepare the monoacetal 6 since the less hindered carbonyl group at C(6) is more reactive and leads to monoacetal 10. In fact, monoacetal 6 -prepared from 5- undergoes a smooth and clean acid-catalysed isomerisation to 10 through an intramolecular transacetalisation process (A) [7].

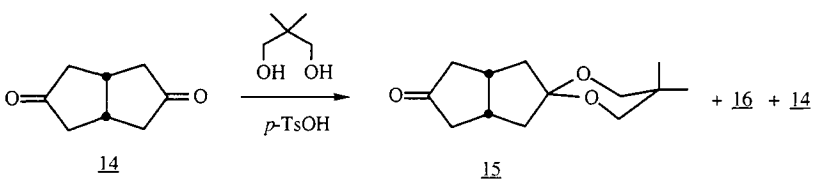
A more subtle example of identical functional groups with different steric enviroment is found in the intermediate 11 which Corey [8] uses in the synthesis of fumagillin (13). The two identical secondary hydroxyl groups in the cyclohexane derivative 11 can be differentiated by using a *bulky reagent* since the axially disposed hydroxyl group is less accesible than the one which is equatorially disposed and can be chemoselectively methylated (12) in the presence of sodium *tert*-amylate (Scheme 12.2).



11 12 13

Scheme 12.2

However, when not only the functional groups but also the electronic and steric environment are identical then chemoselectivity can only be achieved by introducing the appropriate protecting groups by means of reactions which are essentially reversible and working under equilibrating conditions in order to arrive at statistical mixtures of all possible reaction products. *cis*-Bicyclo[3.3.0]octane-3,7-dione (14) may be monoprotected as an acetal by reacting it with one equivalent of 2,2-dimethyl-1,3-propanediol, in the presence of *p*-toluenesulphonic acid, to give a 2:1:1 mixture of monoacetal (15), the corresponding diacetal (16) and the starting diketone (Scheme 12.3). However, the yields may be substantially increased if the diacetal and the diketone -after chromatographic separation- are equilibrated to the statistical mixture in the presence of acid and separated again by chromatography. By this procedure it is possible, in principle, to obtain almost quantitative yields if the equilibrating/separation process is repeated once and again [9]. Sometimes monoprotection may be achieved by direct equilibration of a 1:1 mixture of the unprotected and the diprotected compound.



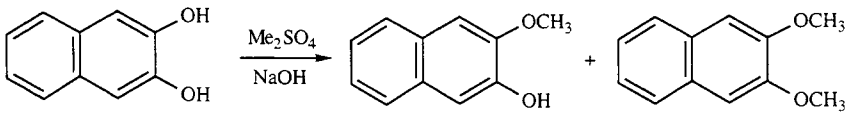
14 15

Scheme 12.3

From these and other similar examples it is clear that the presence of symmetry either in the starting materials or in some of the synthetic intermediates may be very often a complicating factor and the *symmetry must be broken* in some way in order to proceed along the planned synthetic sequence [10]. This is in contrast with the fact that the presence of symmetry in the target molecule is usually a simplifying factor as we have seen, for example, in the synthesis of indigo discussed in *Heading 4.1.*

If the introduction of the protecting group takes place through an irreversible reaction, then the chemoselective protection of one of two identical mutually interacting groups may be a critical step in the synthetic sequence. For instance, the monoprotection of 2,3-dihydroxynaphthalene (17) as the corresponding methyl

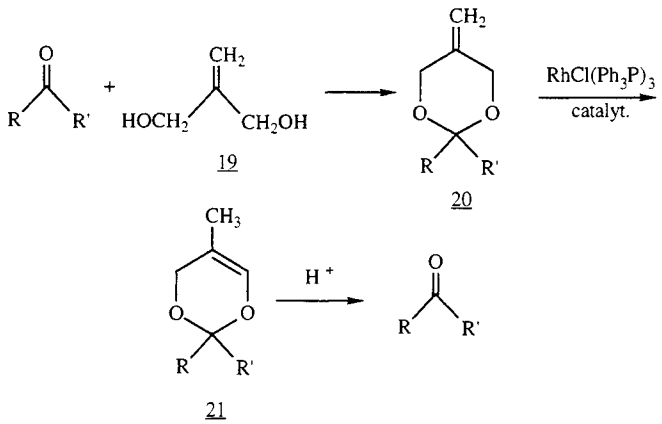
ether according to a Schotten-Baumann reaction leads to a mixture in which the product 18 is present only in a 23% yield [11]:



17 18 (23%)

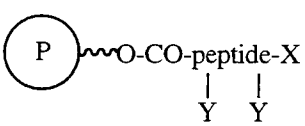
Scheme 12.4

In fact, several protecting groups are presently available for the most common functional groups found in organic molecules, and which are sensitive to different reaction conditions [12]. This provides great versatility in the experimental fulfilment of an organic synthesis in the laboratory since it allows the protecting groups to be chosen according to the required reaction conditions in each one of the different steps of a synthetic sequence. Thus, whereas the protection of a hydroxy group as an acetate restricts the reaction conditions to a practically neutral pH medium, the protection of this group as a tetrahydropyranyl acetal, for instance, is compatible with reactions proceeding in strongly basic reaction conditions but excludes the use of any reaction which takes place in acid medium. Following this philosophy, in recent years more and more selective protecting groups have been developed which offer different possibilities at the moment of making the choice. In this context, we must mention the protecting groups which are sensitive to light [13] or to hydrogenolysis [14], as well as the transition-metal complexes which being stable at any pH are, however, easily demetallated under oxidative conditions [Ce(IV), *N*-amine oxides or electrochemically] [15]. Of some interest is the design of protecting groups in which a bond becomes labile at the appropriate moment in such a manner that it allows the elimination of the protecting group under very mild conditions. An example is the sequence outlined in Scheme 12.5 in which a carbonyl group is protected as an acetal with diol 19. If in the later steps of the synthesis the exocyclic double bond of 20 is isomerised at the endocyclic position an extremely acid-sensitive enolether 21 results which can be easily hydrolysed by shaking the product with a 10:1 mixture of THF:1N HCl for 1.5 h at room temperature [16].



Scheme 12.5

With respect to the synthesis of peptide fragments in solid-phase in which several protecting groups are used, Barany and Merrifield introduced in 1977 [17] the concept of "orthogonality". According to this concept all the protecting groups of the peptide chain -the group X of the N-terminal end and the group Y of the side-chains of trifunctional aminoacids, as well as the polymeric support P, which acts also as a protecting group of the C-terminal carboxylic end- must be independent, each one from all the others; i.e., each one of the different protecting groups may be eliminated in the presence of all the other groups in any order one may choose according to the requirements of the synthesis:

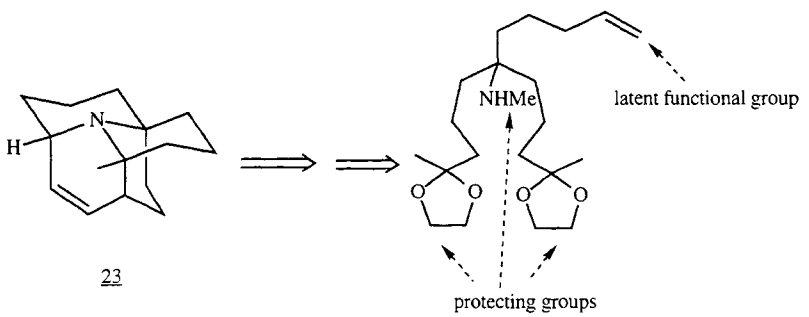


The conditions of "orthogonality" require that the deprotection of the α-amino functional group, that of the side-chains of trifunctional aminoacids and the cleavage of the peptide-resin bond take place in completely different conditions, such as in acid medium, basic medium and photolysis, respectively. When the conditions are only slightly different so that they require, for instance, the presence of acids of different strength such as TFA in dichloromethane or HF, then the condition of orthogonality, properly speaking, is not fulfilled since the order in which they are used is important, the weaker acid of course being used first. This situation in

which there is not strictly speaking "orthogonality" is usually found in most of the synthesis of complex organic compounds.

An alternative solution to protecting groups is the use of *latent functional groups* [18], which are conveniently unmasked when necessary by the pertinent chemical transformations. An example of a latent functional group is found in the abovementioned syntesis of strychnine (2) in which the veratryl group of intermediate 1, besides blocking the α-position of the indole ring, plays the role of a "latent muconic ester" which is then unmasked by ozonolysis of the dimethoxybenzene ring.

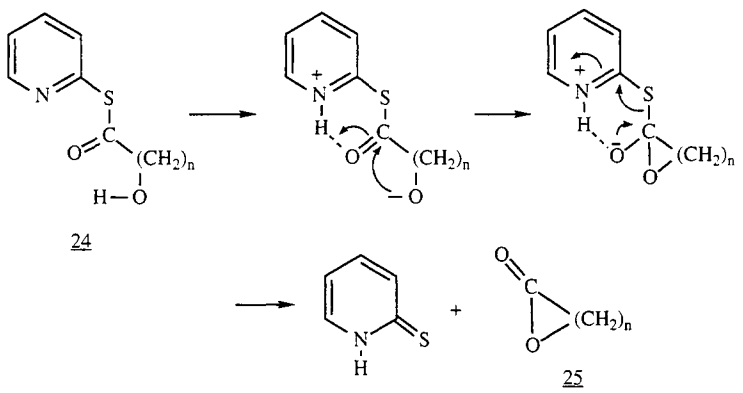
Another example of using "latent functional groups" is provided by Corey's synthesis of porantherine (23) [19] in which the starting material 22 has two identical keto groups, conveniently protected as acetals, an amino group protected as the *N*-methyl derivative and a vinyl group which plays the role of a "latent aldehyde group" and will be unmasked later on in the synthetic sequence by oxidative cleavage of the double bond (Scheme 12.6).



23 22

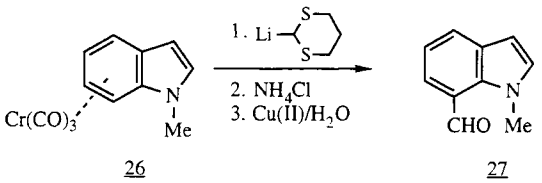
Scheme 12.6

Sometimes, instead of using protecting groups as chemoselective control elements it may be more convenient to resort to *activating groups* as, for instance, the *S*-2-pyridylcarboxylic esters (24) which react intramolecularly to give macrolides 25 in excellent yields [20] (Scheme 12.7).

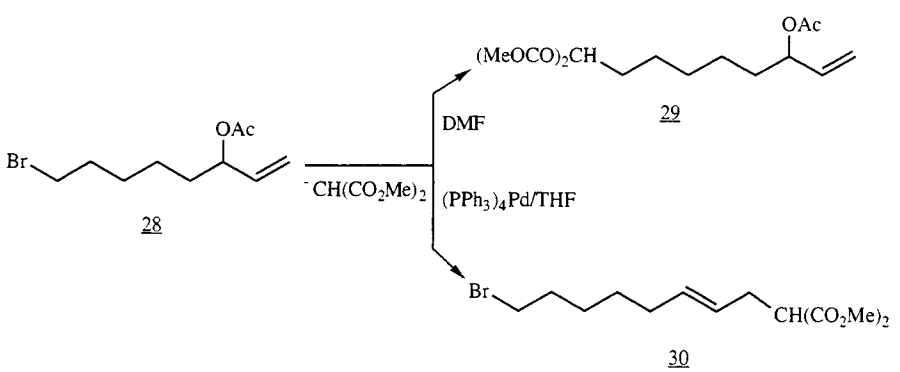


Scheme 12.7

One may also resort here to organotransition metal complexes. For example, benzene rings can be selectively activated to nucleophilic attack by complexation to chromium tricarbonyl (Scheme 12.8) [21]. Similarly, an allylic acetate can also be selectively activated in the presence of a bromide (29 *versus* 30) by addition of a palladium(0) catalyst in THF, which coordinates with the double bond [22] (Scheme 12.9).



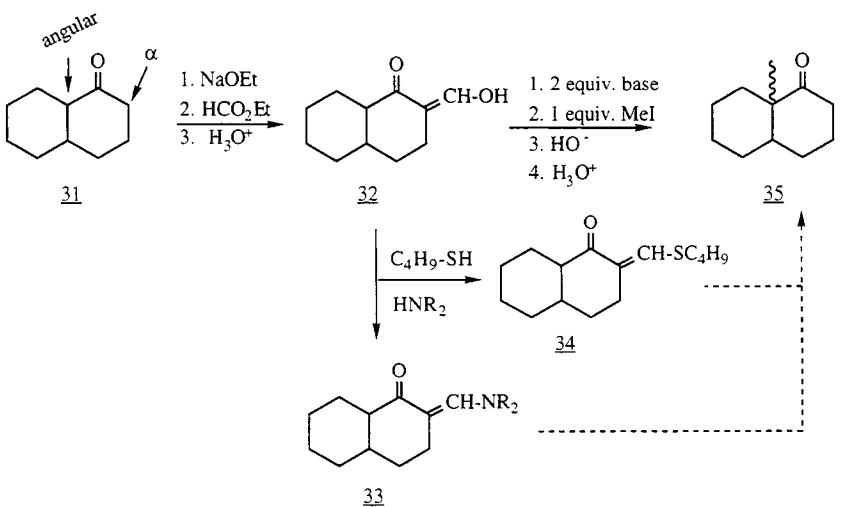
Scheme 12.8



Scheme 12.9

12.1.2. Regioselective control elements: blocking and activating groups. Bridging elements

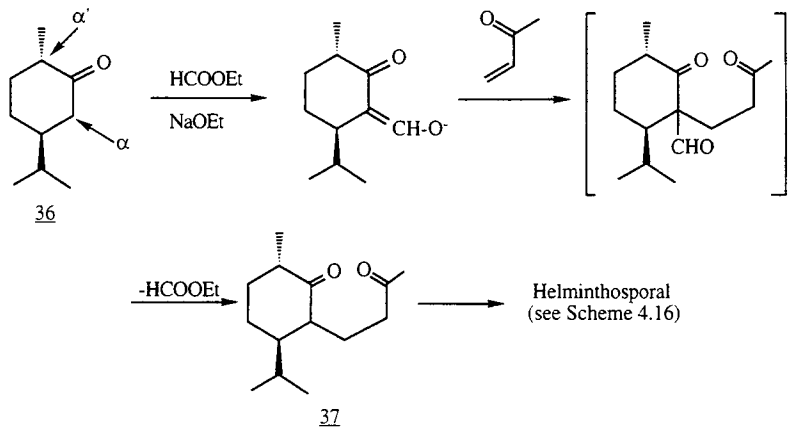
As in the case of chemoselective control elements, we can consider also different kinds of *regioselective control elements*. In the first place, we must consider *blocking groups* which block a specific activated site or region of a molecule. A classical example is the so-called "angular methylation", one of the first problems which chemists engaged in the total synthesis of steroids had to confront [23]. Considering the most simple case of a 2-decalone (31), the methylation of the α-methylene group competes favourably with the "angular methylation" of the vicinal fused atom (35). A way to overcome this difficulty is to block the free methylene group by means of a hydroxymethylene group (32), -followed (or not) by a further condensation with a secondary amine (33) or an alkyl sulfide (34)-, then carrying out the methylation and finally eliminating the blocking group (Scheme 12.10).



Scheme 12.10

An alternative solution to blocking groups, is the introduction of an *activating group* at the less reactive position in order to favour the attack of the reagent at this site of the molecule. Such is the case, for instance, in the synthesis of helminthosporal by Corey [24]. In the first step of the synthesis, which involves a Michael condensation of carvomenthone (36) with methyl vinyl ketone to give the

adduct 37, the unsubstituted α-position is activated by introducing a formyl group which is then spontaneously eliminated under the same basic conditions of the reaction (Scheme12.11).

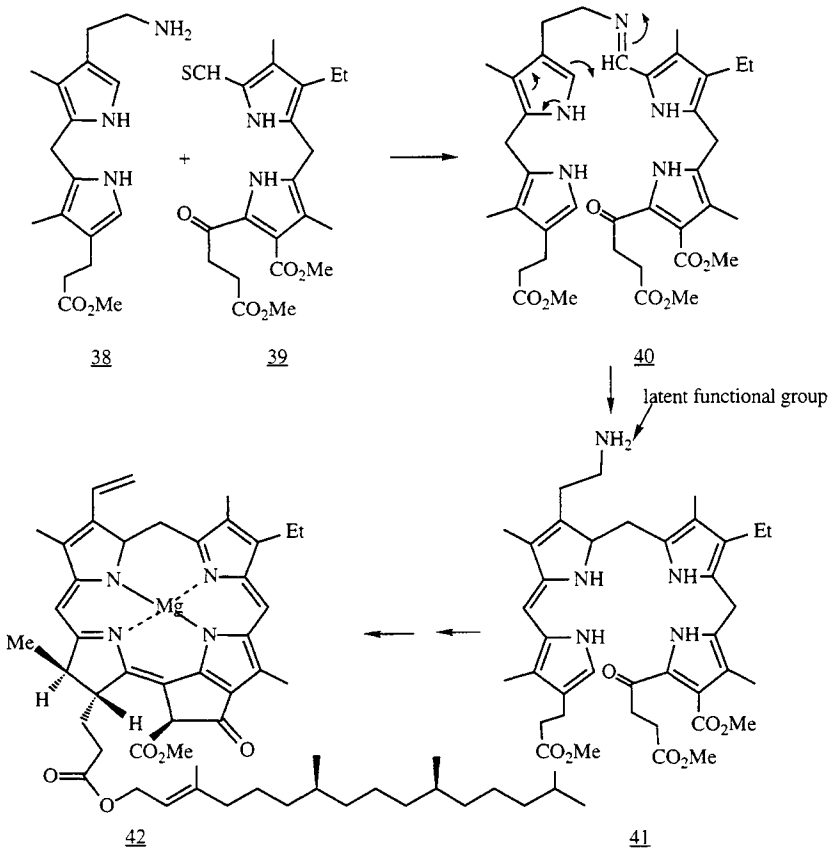


36 37

Scheme 12.11

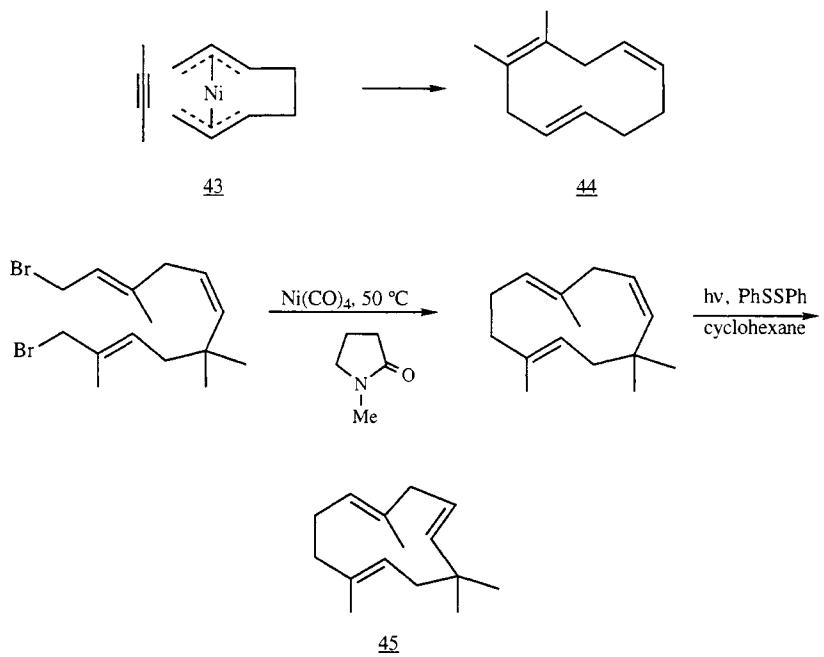
It should be noted here that a regioselective control may also be exerted by just controlling the experimental conditions. Thus, working under strictly kinetic conditions (low temperature, absence of oxygen and slow addition of the ketone to an excess of a solution of an aprotic base) the less substituted enolate of carvomenthone can also be selectively generated and may be then submitted to different kind of reactions. However, reversible reactions like the Michael addition would equilibrate the reaction mixture to the thermodynamically more stable enolate.

Finally, a third type of regioselective control elements are bridging groups: in this case a flexible carbon-chain, with free rotation around a σ bond, may be "frozen" in a given conformation by means of a temporary bridge, a double bond or simply by a metal atom, so that it can react in a regioselective fashion. A good example of the use of a bridging group to exert regioselective control is found in the synthesis of chlorophyll by Woodward [25]. As shown in Scheme 12.12 a temporary C=N double bond, which is formed by reaction of a primary amine (38) with a thioaldehyde (39) acts as a bridging element that holds the two dipyrrolylmethanes in the correct orientation. After the condensation has been carried out, the bridging element is used to generate the vinyl group present in the target molecule 42.



Scheme 12.12

Metal atoms have also been used as bridging elements to fix the molecular geometry and favour intramolecular cyclisations (43 ⟶ 44). The method has been applied to the synthesis of corrins [26], α-santelene [27], humulene (45) [28] and other macrocyclic alkenes [29] (Scheme 12.13).



Scheme 12.13

12.1.3. Stereoselective control elements

Regarding *stereoselective control elements*, some of the most important and updated methods and strategies, have been already discussed in Chapters 8 and 9 (see also the *Summary* given below).

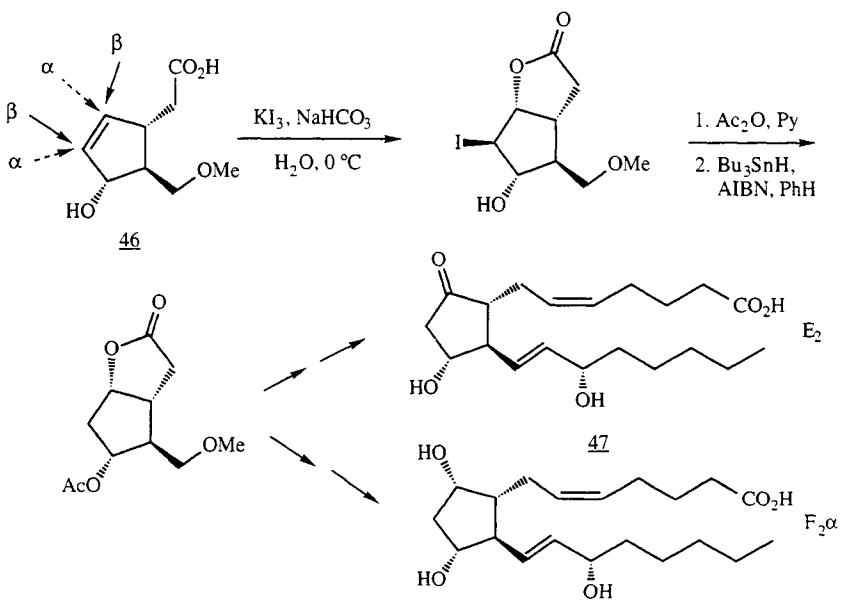
12.1.4. On the use of control elements in organic synthesis: Summary

In fact, there are three levels of refinement or sophistication in using control elements in organic synthesis:

Level 1: The different control elements -whether they are *chemo-*, *regio-* or *stereoselective-* are introduced *ad hoc* (expressly) and they are then eliminated once the control has been exerted. This requires at least two extra steps in the synthetic sequence with the concomitant lowering of overall yields.

Level 2: The atoms or groups of atoms of the different control elements, once the control has been exerted, are used in subsequent stages of the synthesis to build up the carbon skeleton of the target molecule, so that they become an integral part of it. This is the case in Woodward's synthesis of strychnine.

Level 3: This level represents the most efficient and elegant strategy, which is based on the *principle of mutual internal protection of functional groups*. This means that the functional groups themselves, which are present in the synthetic intermediates, act as the control elements. A classical example is found in the synthesis of prostaglandins (47), by Corey and his associates (Scheme 12.14) [30], in which the carboxylic acid group present in intermediate 46 acts, through a iodolactonisation reaction, as a *regioselective* control element (attack on the sp^2 carbon atom at the α-position to the acetic acid chain), as well as a *stereoselective* control element (attack from the same face on which the acetic acid chain is attached).



Scheme 12.14

12.2. Logic-centred synthetic analysis methodology: Summary

1) Structural synthetic analysis of the target molecule:

i) Symmetry, either real or potential.

ii) Functional groups:

HP-1: Eliminate or modify (FGI) the highly unstable groups.

HP-2: Determine all the bifunctional relationships in order to detect:

a) the source of possible instabilities (the β-hydroxyketone group, for instance, which is present in all the prostaglandins of the E series, and is responsible for their instability and sensitivity to either acids or bases, giving the corresponding secondary prostaglandins of the A and/or B series),

b) all the consonant bifunctional relationships which can be logically disconnected or, at least, for which a reasonable mechanism exists:

HP-3: FGI, in order to introduce a C=O group, modify a double bond or to proceed to a "reactivity inversion" operation (*Umpolung*) in dissonant bifunctional relationships (see below iii-a).

HP-4: FGA, in order to functionalise or create new consonant bifunctional relationships (new dissonances *must be* avoided): sometimes, introduce a double bond prior to disconnection of bonds (conjugated if a C=O group is already present).

HP-5: Reconnection of functional groups, such as carbonyl groups which are separated by 2, 3, 4 or 5 carbon atoms, to give 4-, 5-, 6 or 7-membered rings. Of special interest is the reconnection of 1,4-D and 1,6-D systems to the corresponding consonant rings (see below iii-d).

HP-6: Reference to aromatic systems: stability, orientation rules and their relationship with more or less unsaturated cyclohexane rings and decalin systems.

iii) Carbon skeleton: chains, rings and appendages:

MONOFUNCTIONAL SYSTEMS:

HP-7: Heterolytic disconnection of the appendages directly attached to sp^3 carbon atoms bearing functional groups of type E and eventually of type A.

HP-8: Heterolytic disconnection of carbon-carbon bonds of the carbon skeleton at the *ipso*-, α- or β-position to the functional group.

HP-9: Systematic disconnection of substituted nucleophilic heteroatoms (OR, SR, NR_2) directly bound to the carbon skeleton, especially to primary sp^3 carbon atoms.

BIFUNCTIONAL SYSTEMS:

Consonant bifunctional systems: see ii-b.

Dissonant bifunctional systems:

a) illogical disconnections (proceed to FGI in order to invert the reactivity of the resulting fragments),

b) plausible disconnections (3-membered dissonant rings),

c) homolytic disconnections: radical reactions (electron transfer, oxidation, reduction),

d) reconnection to consonant rings (see HP-5),

e) sigmatropic rearrangements.

MONOCYCLIC and POLYCYCLIC SYSTEMS: reduce the *cyclic order* by:

a) retro-annulations,

b) pericyclic and cheletropic cycloreversions: Woodward-Hoffmann rules (FGA in order to introduce a double bond and/or an activating carbonyl group prior to disconnections).

UNUSUAL SYSTEMS: quaternary carbon atoms, medium-sized rings (from 7 to 10 atoms) and bridged systems:

a) pinacol rearrangement,

b) Grob and Wharton internal fragmentations,

c) strategic bonds (Corey's rules).

iv) Stereochemical features:

a) elimination of chiral centres ($sp^3 \Longrightarrow sp^2$)

b) stereoselective reactions: order, negative entropy, rigidity, absence of degrees of freedom,

c) pericyclic reactions,

d) acyclic stereoselection: auxiliary or temporary rings and bridges, highly ordered transition states.

e) Biogenetic considerations.

2) Simplification of the molecular magnitude and complexity.

3) Generation of the intermediate precursors of the synthesis tree.

4) Examination of the sequences in the synthetic direction, from the starting materials (I_0) to the target (T), in order:

a) to optimise the ordering of intermediates (iterative processing),

b) to apply the necessary control elements, and

c) to eliminate all the observed inconsistencies, as well as to identify unresolved problems.

5) Evaluation and election of an specific synthetic sequence: *subjectivity*.

6) Realisation of the synthesis in the laboratory: occasional modifications, surprises, opportunism, new discoveries, flexibility, alternative solutions, perseverance and FAITH.

12.3. General strategies

In the actual realisation of an organic synthesis chemists confront some *logistic* problems whose solutions involve not only the application of a given *strategy*, but the *tactical* use of all the resources that modern synthetic organic chemistry may offer. The demand of intermediate precursors, for instance, is more easily satisfied using *strategies* which involve *convergent* syntheses rather than *linear* ones. Although less general, other strategies [31] familiar to synthetic organic chemists with a minimum of experience are:

1) Strategies based on functional groups, either mono- (1FG) or bifunctional systems (2FG).

i) Monofunctional systems: which may be disconnected either directly or after a FGA operation. These strategies are applied, amongst others, to the synthesis design of amino (alkaloids) and amido compounds (peptides and proteins).

ii) Consonant bifunctional systems: which can be disconnected directly by a reasonable mechanism (especially efficient in the synthesis of alkaloids as, for instance, in the syntesis of luciduline and porantherine).

iii) Dissonant bifunctional systems: which require reactivity inversion (*Umpolung*) and apply, amongst others, to cyclopentanoid systems, such as polyquinanes, *cis*-jasmone, sesquiterpenes, prostaglandins, etc.

2) Strategies based on cycloeliminations (retro-annulations and cycloreversions) which apply mainly to fused polycyclohexane derivatives, such as steroids.

3) Strategies based on reconnections which have been applied succesfully to sesquiterpenes, such as caryophyllene, isocaryophyllene and hirsutic acid, as well as to *Cecropia* juvenile hormone.

4) Strategies based on rearrangements and internal fragmentations (see also "reconnections") which apply also to sesquiterpenes, polyunsaturated chains (such as squalene, jubavione, etc.).

5) Strategies based on very particular and specific reactions, such as Diels-Alder addition, either inter- or intramolecular (see also cycloeliminations), cationic cyclisations (important in the "biomimetic synthesis" of steroids), Pauson-

Khand annulations (extremely efficient in the synthesis of polyquinanes and cyclopentanoid sesquiterpenes -triquinacene, coriolin, etc.-, among many others).

6) Strategies based on two consecutive specific reactions or the so-called "tandem methodologies" very useful for the synthesis of polycyclic compounds. Classical examples of such a strategy are the "Robinson annulation" which involves the "tandem Michael/aldol condensation" [32] and the "tandem cyclobutene electrocyclic opening/Diels-Alder addition" [33] so useful in the synthesis of steroids. To cite a few new methodologies developed more recently we may refer to the stereoselective "tandem Mannich/Michael reaction" for the synthesis of piperidine alkaloids [34], the "tandem cycloaddition/radical cyclisation" [35] which allows a quick assembly of a variety of ring systems in a completely intramolecular manner or the "tandem anionic cyclisation approach" of polycarbocyclic compounds [36].

7) Strategies based on some special topological features, such as the presence of "strategic bonds" and/or "common atoms" which apply preferentially to sesquiterpene compounds (as, for instance, longifolene, patchouli alcohol, seychellene, sativene, etc.) and non-natural compounds with a high degree of internal connectivity as, for example, twistane, bullvalene, etc.

8) Strategies based on known, highly elaborated, but nevertheless readily accesible, starting materials with a "complexity index" as near as possible to the "complexity index" of the target molecule. This strategy has also been applied to non-natural compounds as, for instance, in the synthesis of triquinacene by Woodward [37] and in the syntheses of dodecahedrane by Paquette (Domino Diels-Alder adduct) [38] and Prinzbach ("pagodane") and their associates [39].

9) Strategies based on biogenetic pathways which apply only to natural products as in, for instance, usnic acid, tropinone, thebaine, strychnine, steroids etc.

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Chapter 13

13. SELECTED ORGANIC SYNTHESES

Since we have dealt with several partial aspects of a great number of syntheses throughout the book and, on the other hand, excellent books where total syntheses are exhaustively and critically examined are available, in this last chapter only a few ones will be discussed in full.

Some of these reference books that, in the author's opinion, every synthetic organic chemist should always have at hand are:

a) I. Fleming, "Selected Organic Syntheses", John Wiley & Sons, London, 1973.

b) J.S. Bindra and R. Bindra, "Creativity in Organic Synthesis", Vol. 1, Academic Press, Inc., New York, 1975

c) N. Anand, J.S. Bindra, and S. Ranganathan, "Art in Organic Synthesis" Holden-Day, Inc., San Francisco, 1970; 2nd. Edition, John Wiley & Sons, New York, 1988.

d) N. Nakanishi, T. Goto, S. Itô, S. Natori, and S. Nozoe, "Natural Products Chemistry", Oxford University Press, Oxford-Kodansha Ltd., Tokyo-University Science Books, Mill Valley, California, 3 Vol. (1974-1983).

e) J. ApSimon, "The Total Synthesis of Natural Products", Wiley-Interscience, New York, 9 Vol. up to now (1992).

f) T. Lindberg (Editor), "Strategies and Tactics in Organic Synthesis", Academic Press, Inc., Orlando, 3 Vol. up to now (1991).

g) E.J. Corey and X.-M. Cheng, "The Logic of Chemical Synthesis", John Wiley & Sons, New York, 1989.

The compounds whose syntheses are described below comprise:

1) Twistane, as an example of a non-natural product, which is a chiral, bridged polycyclic compound, completely deprived of functionality.

2) Luciduline, as an example of an alkaloid whose synthesis -either in its racemic form or as the natural optically pure *dextrorotatory* enantiomer-, has been accomplished by different research groups following essentially two different strategies. One of the strategies involves the disconnection of the 1,3-C bifunctional

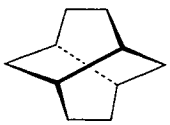
relationship present in the molecule, acccording to a retro-Mannich condensation; the second one involves the disconnection of a "strategic bond".

3) Caryophyllenes, as an example of two naturally occurring isomeric sesquiterpenes containing a medium-sized ring, in which the success of the total syntheses lies in the stereoselective control of a chiral centre, in a common synthetic key intermediate, which governs the configuration (*E* or *Z*) of the double bonds present in each one of the two isomers. In this context, a brief reference to *Cecropia* Juvenile Hormone synthesis by the Syntex group, as well as to Johnson's cationic cyclisation of unsaturated polyolefins to fused polycyclic compounds, is made.

4) As an example of the usefulness of the Sharpless asymmetric epoxidation the enantioselective synthesis of (-)-swainsonine and an early note by Nicolaou on the stereocontrolled synthesis of 1, 3, 5...(2n + 1) polyols, undertaken in connection with a programme directed towards the total synthesis of polyene macrolide antibiotics, such as amphotericin B and nystatin A_1, will be discussed.

5) Finally, two total syntheses of taxol, accomplished independently at the beginning of the year 1994 by Nicolaou and Holton, and their associates, will be discussed in detail as an example of a natural product, the disponibility in substantial amounts of which is of paramount importance for fighting against some types of cancer.

13.1. TWISTANE



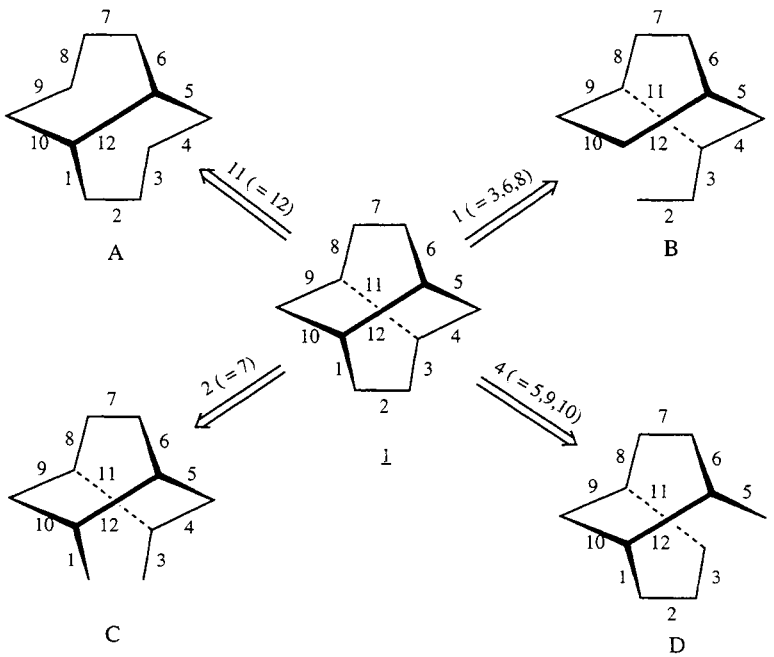
1

Twistane (1) is a polycyclic bridged hydrocarbon, the systematic name of which is tricyclo[4.4.0.$0^{3,8}$]decane. Twistane is a dissymmetric molecule which belongs to the D_2 point symmetry group and has three C_2 axis of symmetry. The name "twistane" goes back to the early 60's and was given by Howard Whitlock [1] because it is formed from two cyclohexane rings in a "twisted boat" conformation, in contrast to adamantane which holds the cyclohexane rings in the more stable chair-conformation. As with other $C_{10}H_{16}$ polycyclic hydrocarbons, twistane may easily be isomerised to adamantane by using Lewis acids.

As it is a bridged polycyclic system, twistane has "strategic bonds" (bonds 11 and 12 in the conventional numbering adopted in structure 1),[35] the disconnection of which leads to rather simple intermediate precursors.

However, as we will see below, twistane has been used as a model for testing the validity of the retrosynthetic analysis approach [2], as well as the soundness and/or limitations of the "strategic bond" concept.

Owing to the D_2 symmetry present in the structure of twistane only four "one single-bond" disconnections are possible[36] (Scheme 13.1.1):



Scheme 13.1.1

Since twistane is a molecule without functionality, the fragments or synthons resulting from bond disconnections must be properly functionalised in order to create, in the synthetic direction, the corresponding bond. Or alternatively, as stated

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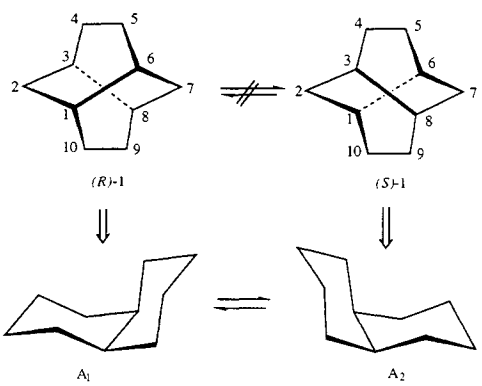
35 At this point, the student should be able to find the "strategic bonds", looking first for all the primary rings, the set of synthetically significant rings, the maximum bridging ring, etc., as explained in Chapter 7.

36 Altough no syntheses of twistane involving two-bond disconnections have been reported, there is a paper in which such an approach is used for constructing a highly substituted twistane [3].

in *Heading 3.3*, one may functionalise first the target molecule and proceed then to the disconnection according to the pertinent mechanism and the appropriate "heuristic principles" which may apply in this particular case. The functional groups must, of course, be removed (FGR) at the end of the synthesis once they have played the role of activating the corresponding position and the carbon framework has been constructed.

On the other hand, twistane is a chiral molecule and the disconnection of either one of the two identical strategic bonds, 11 and 12, in each one of two possible enantiomers leads to one of the two possible conformationally enantiomeric *cis*-decalins (A_1 and A_2), the resolution of which is indeed not possible since they rapidly interconvert into one another (Scheme 13.1.2). From this point of view, the two possible enantiomeric twistanes -to which we will refer as (*R*)- and (*S*)-twistane[37] - may be regarded as the corresponding "frozen" conformationally different enantiomeric *cis*-decalins, a fact that intuitively accounts for the chirality exhibited by the two "genetically" related systems.



Scheme 13.1.2

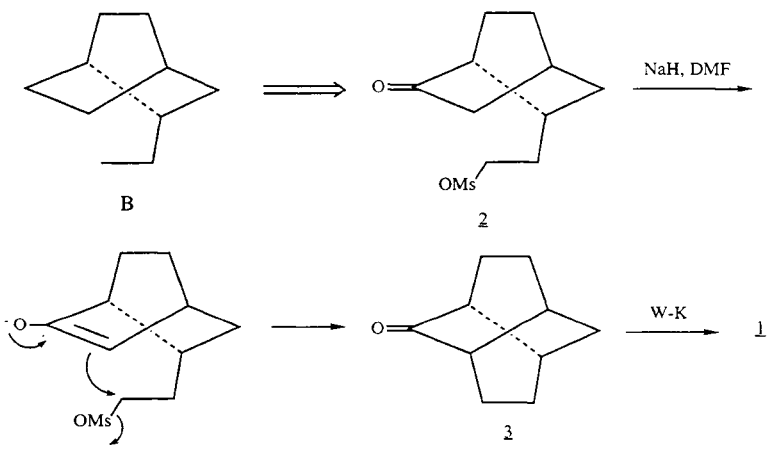
13.1.1. Synthesis of twistane from a bicyclo[2.2.2]octane precursor

Although the disconnection of the "strategic bonds" should be in principle the solution of choice in designing a rational synthesis of twistane (see below, *13.1.2*), syntheses based in the disconnection of bonds other than those have also been

[37] We refer to (*R*)- and (*S*)-twistane because the configuration of all four carbon atoms at the bridgeheads is, respectively, (1*R*, 3*R*, 6*R*, 8*R*) and (1*S*, 3*S*, 6*S*, 8*S*) (see Scheme 13.1.2). An alternative nomenclature is to use the symbols P (Plus) and M (Minus) as applied to helical structures [4].

accomplished successfully [2]. Of these alternative syntheses the first one, described by Whitlock in 1962 [1], involves the disconnection of bond 1 (or its equivalents 3, 6 or 8) to give the bridged system bicyclo[2.2.2]octane with a two-carbon atom side-chain at the *endo* position (B).

In the synthetic direction, the formation of the bond requires the reaction of an electrophilic centre with a nucleophilic one. Of the different possibilities, the addition of a carbonyl group (FGA) into the ring and the introduction of a leaving group at the side-chain appears the best solution (Scheme 13.1.3). On one hand, the carbonyl group will stabilise a negative charge at the α-position and, on the other, the leaving group at the free-rotating appendage will ensure the effectiveness of the S_N2 attack which proceeds in 89% yield (*Cf.* with the synthesis from a *cis*-decalin, described below, where the stereochemistry of the leaving group must be rigorously controlled). The carbonyl group of the resulting twistanone 3 is then removed by Wolff-Kishner reduction (52% yield).



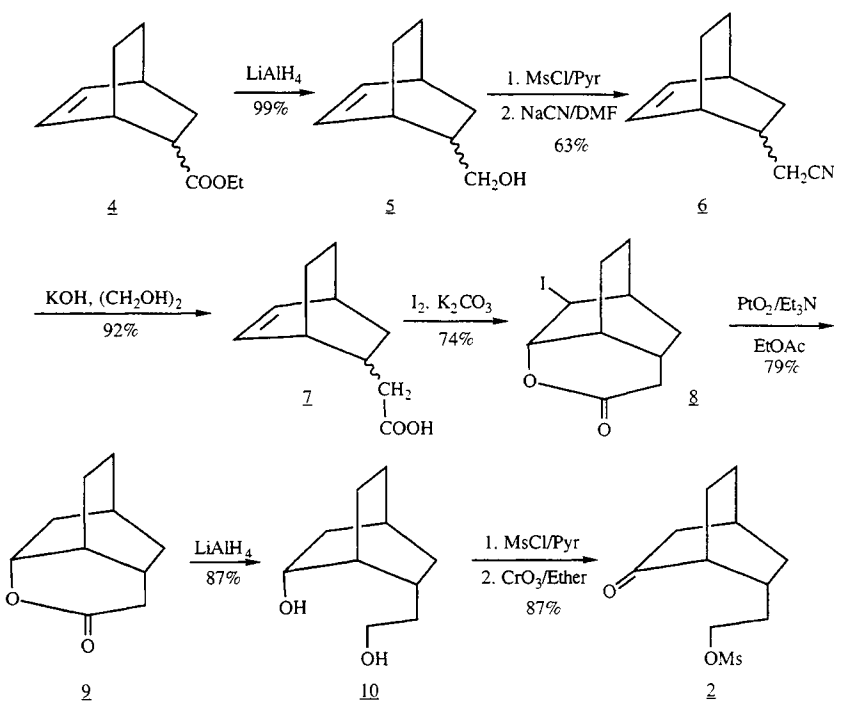
Scheme 13.1.3

The retrosynthetic analysis led to the bridged bicyclo[2.2.2]octanone 2 as the key intermediate which was synthesised from an epimeric mixture of ethyl bicyclo[2.2.2]oct-5-ene-2-carboxylate (4) as shown in Scheme 13.1.4.

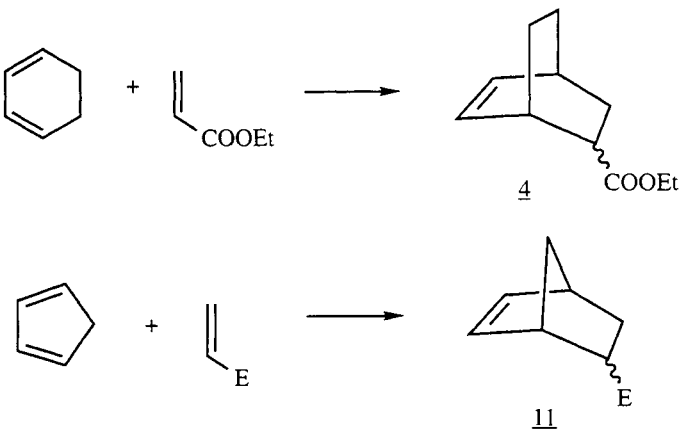
The starting material 4 is easily prepared in 88% yield by a Diels-Alder reaction of 1,3-cyclohexadiene and ethyl acrylate as described by Skeda and Tramposch [5] (Scheme 13.1.5). Whitlock found by v.p.c. that the *endo* derivative is by far the

predominant isomer (ratio *endo*:*exo* = 85:15) as might be expected from the Diels-Alder additions. Notice that the *endo* derivative is the synthetically significant epimer, and the homologation of the side-chain is carried out by a procedure which may be considered as an alternative to the classical Arndt-Eistert reaction.

Although the synthesis requires more steps than the synthesis involving "strategic bond" disconnection (see below), and starts from a compound such as 4 which already bears a bridge, the synthetic scheme is perfectly valid and the synthesis proceeds in excellent overall yield. This poses the question of whether or not Corey's rule number 3, referring to the maximum bridging ring, may sometimes be too restrictive, since the bridged compound bicyclo[2.2.2]octane (4) as well as bicyclo[2.2.1]heptane (11) are as "normal" as fused systems (as decalin, for instance) may be. In fact, both bridged systems are easily obtained by Diels-Alder additions of "normal-sized" six- and five-membered rings, respectively (Scheme 13.1.5).



Scheme 13.1.4



Scheme 13.1.5

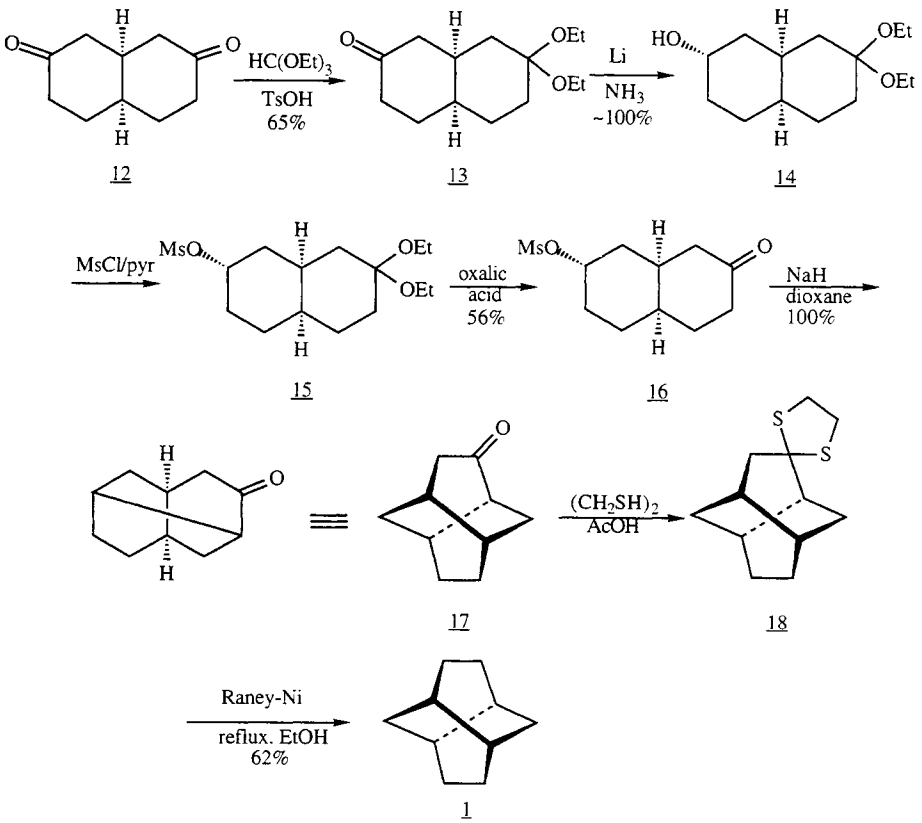
We must draw attention to the internal regio- and stereochemical control exerted in step 7 ⟶ 8, for the functionalisation of C(2) without resorting to control elements other than the functional groups themselves (Level 3, see *Heading 9.2.3*). For this, Whitlock uses the iodolactonisation of the double bond generated in the Diels-Alder reaction taking advantage of the *endo* side-chain at C(5).

The first synthesis of an optically pure enantiomeric twistane, reported in 1968 [6], also follows this synthetic route with only slight modifications.

13.1.2. Synthesis of twistane from cis*-decalins. Strategic bond disconnections*

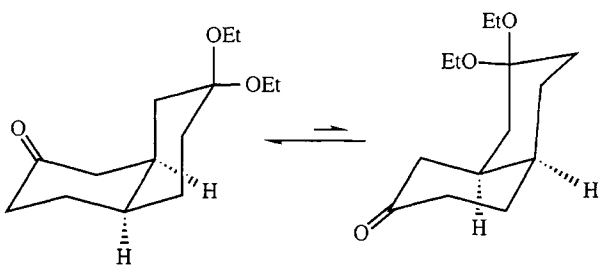
The first synthesis of twistane involving one of the strategic bonds (1 ⟹ A) was accomplished by Deslongchamps and Gauthier [7] in 1967 according to the synthetic sequence outlined in Scheme 13.1.6. The starting material is *cis*-decalin-2,7-dione 12 which was prepared by catalytic reduction of 2,7-dihydroxynaphthalene and oxidation of the resulting diol as described by Anderson and Barlow [8]. Acetalisation of diketone 12 with triethyl orthoformate, afforded a mixture of di- and monoacetal 13 which were separated by column chromatography on neutral alumina. Notice that the acetal group of 13 not only protects one of the two carbonyl groups present in 12, but also stabilises conformation 13a of the *cis*-decalin system (strong 1,3-diaxial interactions are present in the less favoured conformation 13b). Conformation 13a allows the necessary stereochemical control on the configuration of the leaving group in 15 and 16, which must be *exo* (*cis* with

respect to the two hydrogens of the ring junction). Since the reduction of carbonyl groups by an alkali metal in liquid ammonia leads to the most stable equatorial alcohols [9], conformation 13a assures that the hydroxyl group will have the *exo*-configuration (13a ⟶ 14).

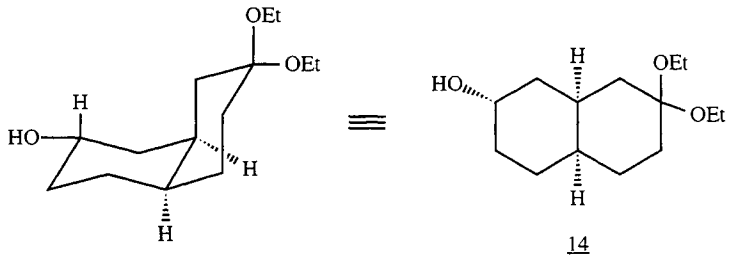


12 13 14 15 16 17 18 1

Scheme 13.1.6



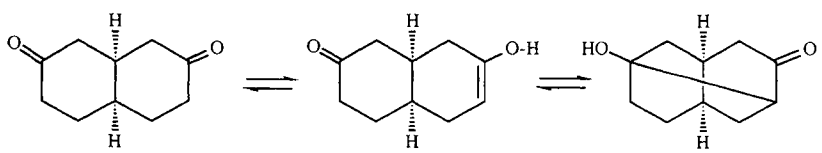
13a 13b



14

Mesylation of alcohol 14 and hydrolysis of the acetal with oxalic acid leads to the key decalone 16 which cyclises in the presence of NaH in dioxane to afford twistanone 17 in quantitative yields. The elimination of the carbonyl group was carried out by an alternative method to the Wolff-Kishner reduction, which involves the thioacetalisation of the twistanone (18) with ethane-1,2-dithiol and removal of the resulting thioacetal by Raney nickel in boiling ethanol (62% yield).

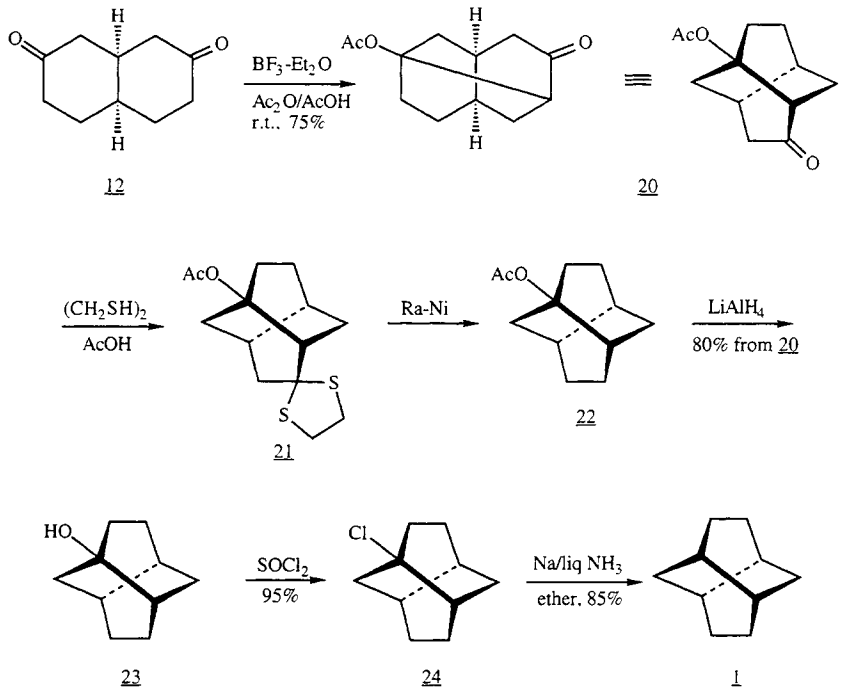
In a second synthesis of twistane reported by Deslongchamps two years later [10] the construction of the twistane structure is greatly simplified. The excellent yield found in the cyclisation step (16 ⟶ 17) of the preceeding synthesis, suggested that in strong acid medium the starting *cis*-decalin-2,7-dione (12) could be in equilibrium with 8-hydroxy-4-twistanone 19, through an acid-catalysed aldol condensation:



12 19

Even in the less favoured case that the aldol 19 was only present in minute amounts, it would be possible to shift the equilibrium by trapping it as a derivative (an acetate, for instance).

With this idea in mind, Deslongchamps treated the *cis*-decalin-2,7-dione (12) with a mixture of acetic anhydride-acetic acid in the presence of boron trifluoride ethyl etherate, at room temperature, and the twistanone 20 was isolated in 75% yield. The whole synthetic sequence is outlined in Scheme 13.1.7.



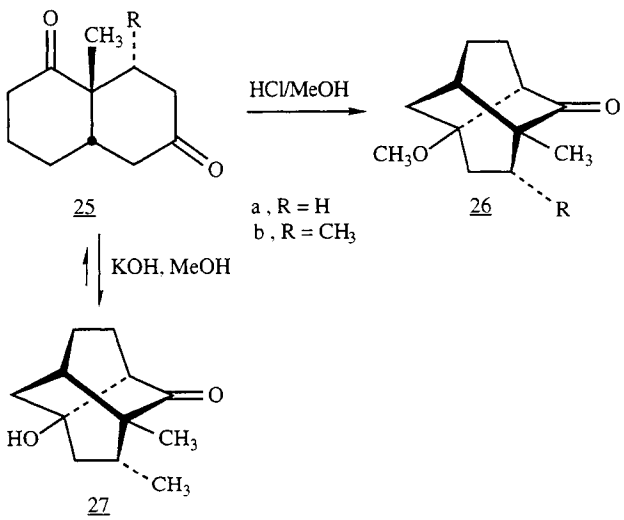
Scheme 13.1.7

Although this synthesis provides the most direct entry into the twistane polycyclic structure, the adequate balance between the problem of framework construction and the subsequent functional group manipulations, required by the "principle of maximum simplicity", is missed. However, the synthesis represents without doubt an outstanding contribution to the synthesis of polycyclic non-natural products.

In fact, a similar intramolecular cyclisation was studied by Reusch [11] and he found a remarkable methyl substituent effect on the aldol equilibrium. Starting from the cis-decalones 25 (easily prepared from the Wieland-Miescher ketone), in which the angular methyl group prevents isomerisation to the more stable *trans*-decalone,[38] it was found that other methyl groups may exert profound but less

[38] However, as already stated [12] this is probably unnecessary, since in the basic medium in which the cyclisation takes place the *trans*-decalone with no angular methyl group would be in equilibrium with the corresponding *cis*-decalone. Even in the less favoured case, the equilibrium would shift to the *cis*-isomer since this is the only isomer which can cyclise to twistanone. Should this be the case, then the stereochemical control in preparing the starting decalone would be unnecessary and the synthesis would be greatly simplified.

easily explained influences. Thus, whereas compound 25a (R = H) gave only 25% of twistanone 26 (R =H) on treatment with hydrogen chloride in anhydrous methanol solution, compound 25b (R = CH_3), in which a second methyl group at C(10) is present, gave almost quantitative yields of the twistanone 26 (R = CH_3) (Scheme 13.1.8). The second methyl group must be *trans*-oriented with respect to the angular methyl group, since no such influence is exerted when it is *cis*-oriented. As noted by Reusch, the influence is even more striking working under basic conditions in which case a mixture of 25b (29%) and its internal aldol isomer 27 (71%) is generated starting either from pure 25b or pure 27 in methanolic potassium hydroxide.



Scheme 13.1.8

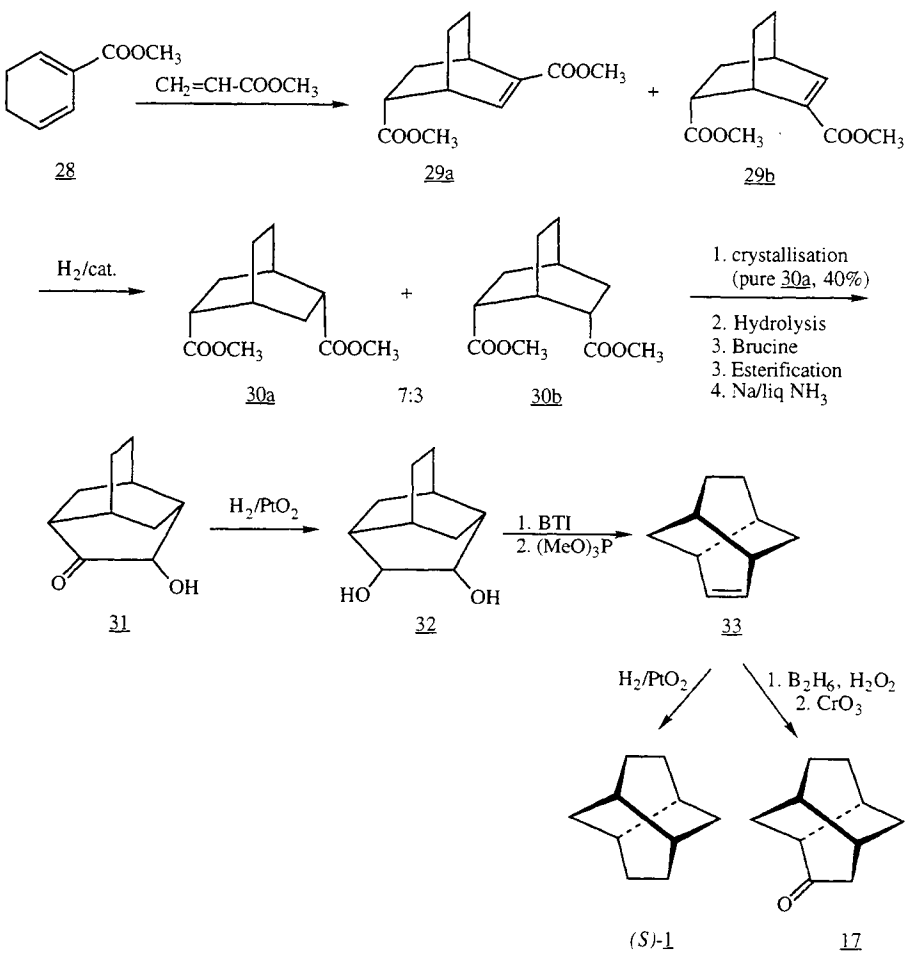
13.1.3. Synthesis of optically pure twistane from a bicyclo[2.2.2]octane precursor, via twistene

This synthetic route, reported in 1969 by Tichy and Sicher [13], differs from the Whitlock approach discussed earlier, because it involves a key synthetic intermediate of type C (Scheme 13.1.1). That is to say, the bicyclo[2.2.2]octane precursor bears two appendages in contrast to the intermediate of type B involved in Whitlock's synthesis.

This new approach is justified because the final aim of the authors was the synthesis of an optically active "twistene", otherwise it would be a violation of

Corey's rules number 2 and 3. Nevertheless, the synthesis is highly efficient and proceeds in only five steps.

The synthetic sequence is outlined in Scheme 13.1.9. The starting ester 29a was prepared by condensation of methyl 4,5-dihydrobenzoate (28) with methyl acrylate. Although the regioisomer 29b was also formed as the minor component, the mixture was hydrogenated and the desired diester 30a could be separated by crystallisation in 40% yield.



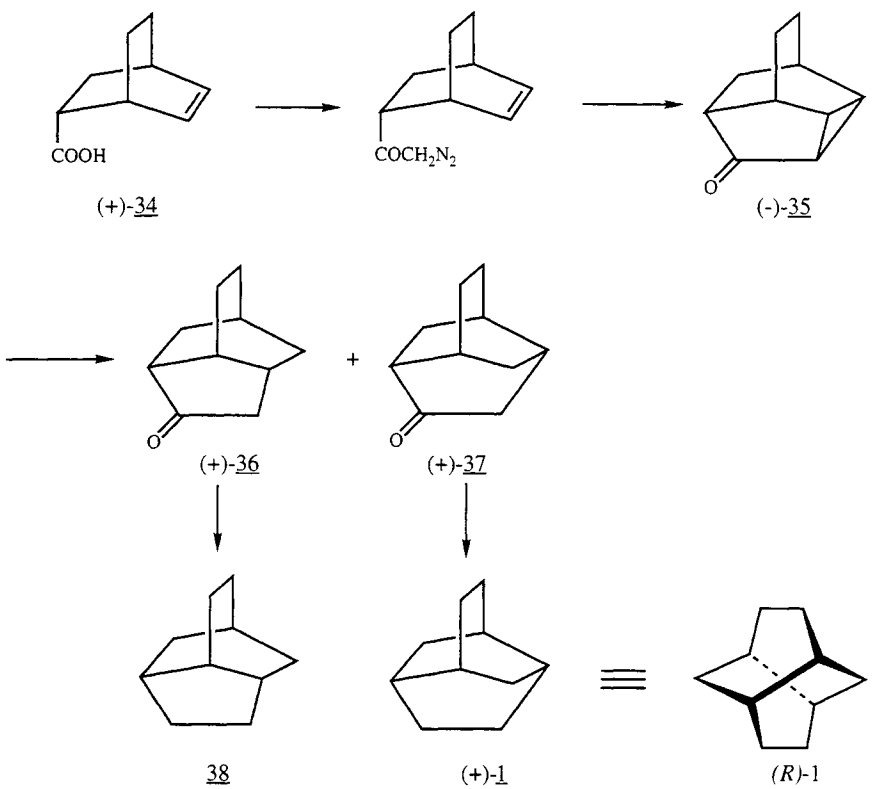
Scheme 13.1.9

The synthesis was then continued with both, the racemic diester and the pure enantiomer (-)-30a which was prepared by hydrolysis of the racemic diester, resolution of the corresponding acid via the brucine salt and reesterification.

Acyloin condensation of diester 30a with sodium in liquid ammonia, followed by direct hydrogenation in the presence of Adam's catalyst, furnished the diol 32 in 49% yield. Diol 32 was transformed into the cyclic thiocarbonyl derivative (80% yield) which after heating with trimethylphosphite [14] afforded twistene 33 in 50% yield. Hydrogenation of 33 gave a compound identical in all respects with twistane 1. From the diester (-)-30a (+)-twistene was obtained, m.p. 35.5-36.5 °C, $[\alpha]_D^{25}$ + 417° (c 0.438, EtOH), which after hydrogenation led to *(S)*-1, m.p. 161-163.5 °C, $[\alpha]_D^{25}$ +434° (c 0.482, EtOH). On the other hand, hydroboration of (+)-twistene afforded (+)-4-twistanone 17 which exhibits a positive Cotton effect, thus confirming the assigned (*S*)- configuration.

However, later on, in 1974, a full paper by Tichy describing an alternative approach to optically pure (+)-twistane was published [6b], in which the absolute configuration of twistane, twistene and some of their derivatives were determined in an unequivocal way, chemically. From this work it could be concluded that the absolute configuration was actually opposite to that inferred from CD-measurements. That is to say, the starting diester 30a has in fact the (*2R,5R*)-configuration and not the (*2S,5S*) as previously reported and (+)-twistane must have the configuration *(R)*-1 and not *(S)*-1 as concluded previously [13].

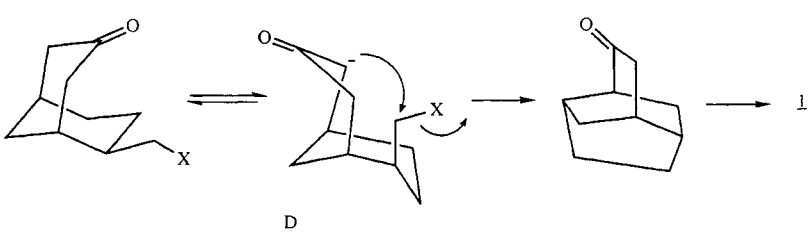
The new synthetic route (Scheme 13.1.10) starts from acid (+)-34 (94% optical purity) which was transformed into the tetracyclic ketone (-)-35 *via* the corresponding diazoketone. Hydrogenation over palladium gave a mixture of (+)-36 and (+)-37 (87.5% and 12.5%, repectively). Wolff-Kishner reduction of this mixture afforded a mixture of the two corresponding hydrocarbons: the optically inactive 38 and (+)-1, the specific optical rotation of which (calculated from the value given in ref. [12]) is in excellent agreement with the value found. Therefore, if the acid (+)-34 has the (*R*)-configuration as depicted in Scheme 13.1.10, the (+)-twistanone (+)-17 and (+)-twistane (+)-1 must have the *(R)*-configuration.

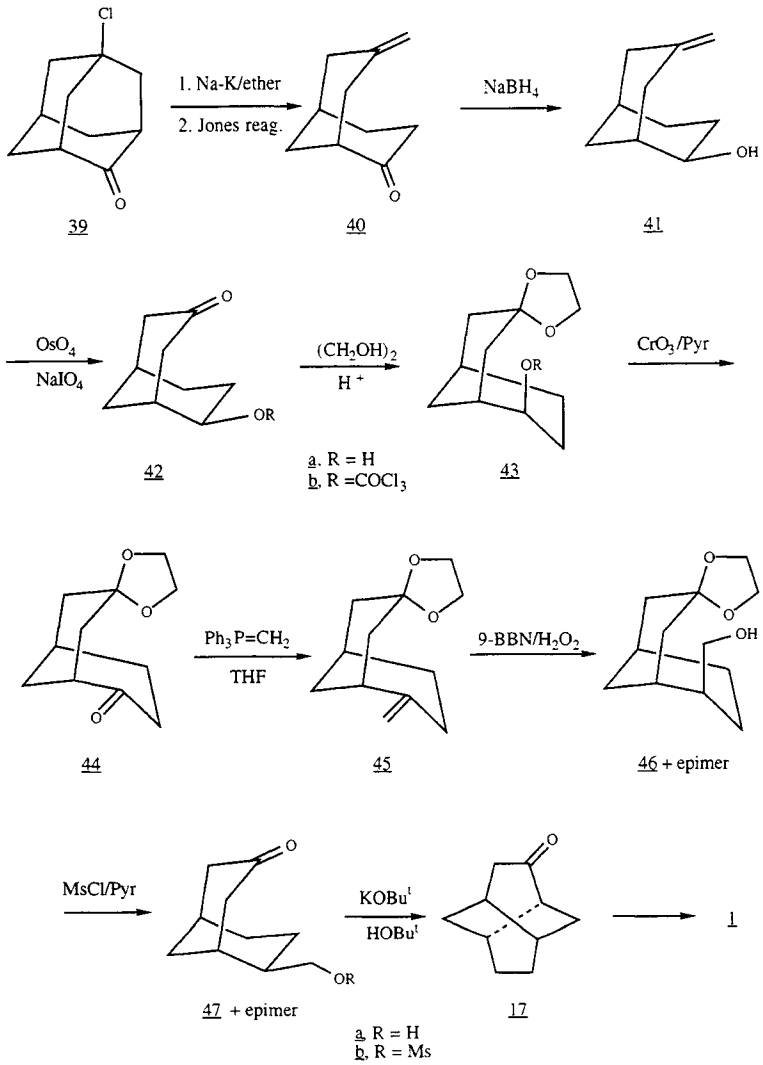


Scheme 13.1.10

13.1.4. Synthesis of twistane from a bicyclo[3.3.1]nonane precursor

The synthesis of twistane involving an intermediate of type D was reported in 1976 by Hamon and Young [2]. This synthetic approach constitutes a violation of Corey's rule number 4 (which refers to "perimeter" and "core bonds") and involves a bicyclo[3.3.1]nonane precursor in which the relative configuration of the C(6) side-chain is crucial if cyclisation is to occur. The cost of such a "violation" was relatively high and a great number of drawbacks are found in the original article.





Scheme 13.1.11

The synthetic sequence, which shows only the succesful solutions adopted in every step, is outlined in Scheme 13.1.11. Reaction of 1-chloroadamantan-4-one (39) [15] with sodium-potassium alloy in ether gave a mixture of ketonic and hydroxylated material which upon oxidation with Jones reagent gave 7-methylenebicyclo[3.3.1]nonan-2-one (40) in 75% yield. Reduction of 40 with sodium borohydride gave the alcohol 41 which could be also obtained in better yields from 1-chloroadamantan-4-one with a large excess of sodium-potassium

alloy, followed by a careful workup procedure. The crystalline alcohol, in which the side-chain must be equatorially oriented from the method of preparation, was treated with osmium tetraoxide/sodium perdiodate to give the ketol 42a in 75% yield. The ketol was converted into the trichloroacetate 42b and the carbonyl group was protected as an acetal 43b. Mild basic conditions afforded acetal alcohol 43a in 84% overall yield from ketol 42a. The acetal alcohol 43a was oxidised with Collins reagent and the resulting acetal ketone 44 was converted into the methylene acetal 45 in almost quantitative yield by a Wittig reaction. Hydroboration of the double bond with 9-borabicyclo[3.3.1]nonane gave a 85:15 mixture of alcohols in quantitative yields, in which the desired alcohol (46) was the predominant isomer (attack from the less hindered *exo* face). Hydrolysis of this mixture of acetal alcohols gave a mixture of the corresponding keto alcohols (47a + epimer) which were converted into a mixture of mesylates (47b + epimer) (95% yield). Treatment of this mixture with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gave, after purification and separation by preparative g.l.c., twistan-4-one (17) which was converted to twistane (1) as previously reported by Deslongchamps [7].

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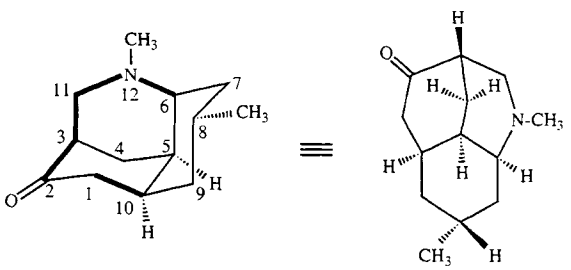
13.2. LUCIDULINE

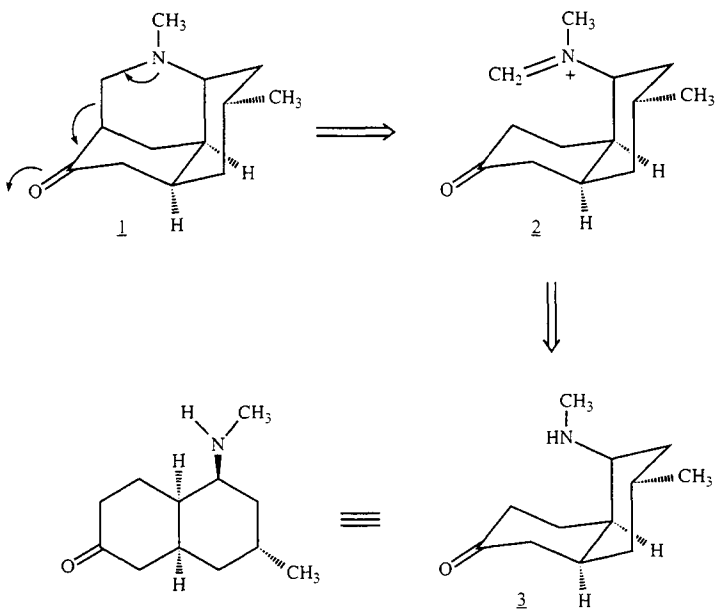


1a 1b

The structure of luciduline (1a) which is an alkaloid isolated from *Lycopodium lucidulum* and biogenetically related to lysine [1], was determined by chemical means and later on confirmed by X-ray analysis. Luciduline is a fully consonant polycyclic bridged system with five chiral centres and a 1,3-C bifunctional relationship. Since the backbone of the molecule has a plane of symmetry (see perspective 1b) -in fact a"broken symmetry" due to the presence of a nitrogen atom in one of the six-membered rings-, luciduline has two rings with the maximum number of bridging sites and a number of "strategic bonds" (five, indicated by heavy lines in drawing 1a) which is more than that expected for a tricyclic bridged structure. Disconnection of anyone of the five "strategic bonds" leads to *cis*-decalin systems or the equivalent octahydroquinolines.

13.2.1. The total synthesis of racemic luciduline

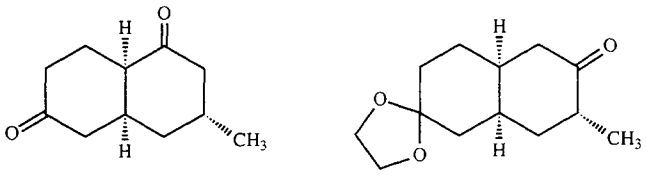
For the synthesis of luciduline one could, therefore, follow either a strategy based on the disconnection of a "strategic bond" or a strategy based on the 1,3-C bifunctional relationship. The last one is in fact the strategy of choice since the disconnection of the 1,3-C system, according to a retro-Mannich reaction (Scheme 13.2.1), implies also the disconnection of two "strategic bonds" and leads to the *cis*-decalone 3 with a methylamine at the *endo* position and a methyl group at the *exo*-configuration [2]. In the given conformation (3), which ought to be "frozen" in some way in order to exert the necessary streochemical control, the two groups are, respectively, axially and equatorially disposed.



Scheme 13.2.1

Although the *cis*-decalone 4, which is a 1,5-consonant dione, appears as a suitable starting material for the synthesis of the key intermediate 3, its easy isomerisation to the *trans*-configuration, as well as the problems associated to the stereochemical control in introducing the methyl and the *N*-methylamino groups at the right configuration, suggested that it could be better to start from the *cis*-decalone 5. Notice that the acetal group "freezes" the *cis*-decalin system in the

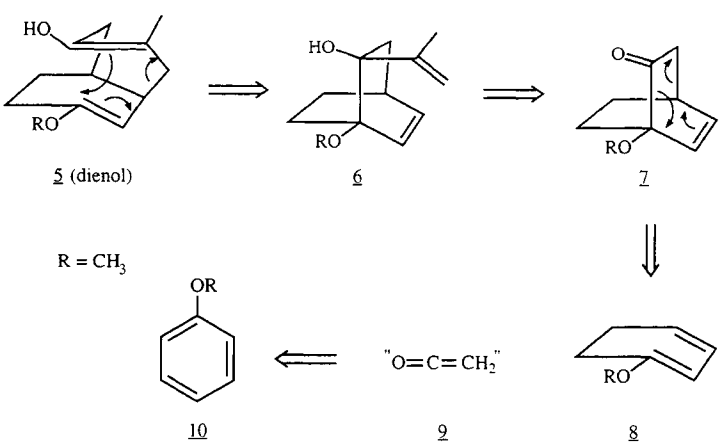
conformation in which the α-methyl group adopts the more stable equatorial position.



4 5

Since compound 5 is the monoacetal of a dissonant 1,6-dicarbonyl system it could be synthesised by an oxy-Cope rearrangement according to the method of Evans which we have discussed in Chapter 5 (see *Heading 5.3* on page 136).

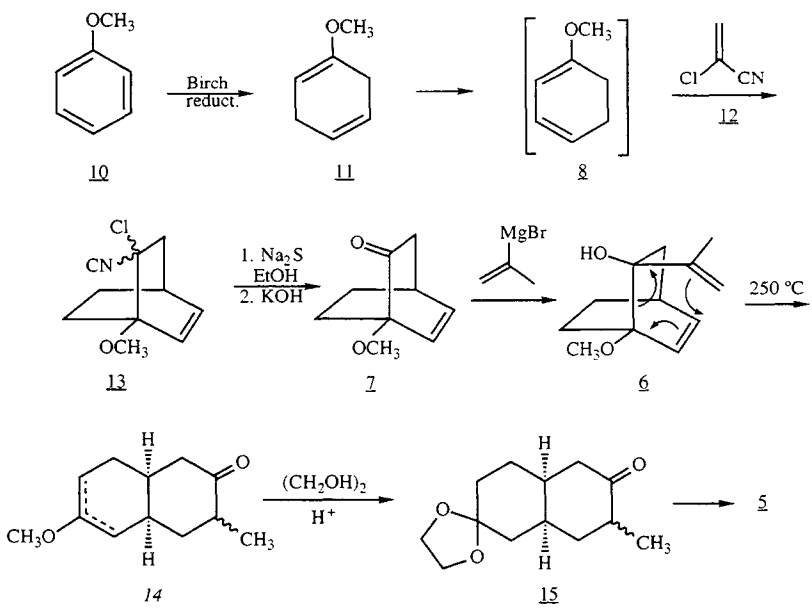
The complete retrosynthetic analysis is shown in Scheme 13.2.2. A [3,3]-sigmatropic rearrangement of the "dienol" form of the free diketone of acetal 5 (in which R may be a methyl group) leads to the bicyclo[2.2.2]octane system 6. Disconnection of the appendage attached to the carbon atom bearing the hydroxyl group affords the ketone 7 which is reduced, by a retro-Diels-Alder reaction, to fragments 8 and 9. Fragment 9 is in fact a "ketene equivalent" and the precursor of cyclohexadiene 8 must be a phenol ether 10.



Scheme 13.2.2

In the actual synthesis, Birch reduction of anisole (10, R = CH_3) affords the corresponding 2,5-dihydroderivative (11) which, under the Diels-Alder reaction conditions with 2-chloroacrylonitrile 12 [3], isomerises to the conjugated diene 8 and undergoes the [4 + 2] cycloaddition to give the adduct 13. Hydrolysis under the conditions shown in Scheme 13.2.3 and reaction of the resulting ketone 7 (R = CH_3) with isopropenylmagnesium bromide, from the less hindered side, affords compound 6 (R = CH_3) which on heating to 250 °C undergoes the [3,3]-sigmatropic rearrangement to the *cis*-decalin 14 (mixture of isomers). Finally, acetalisation of 14 affords the *cis*-decalone 15 in yields greater than 65%.

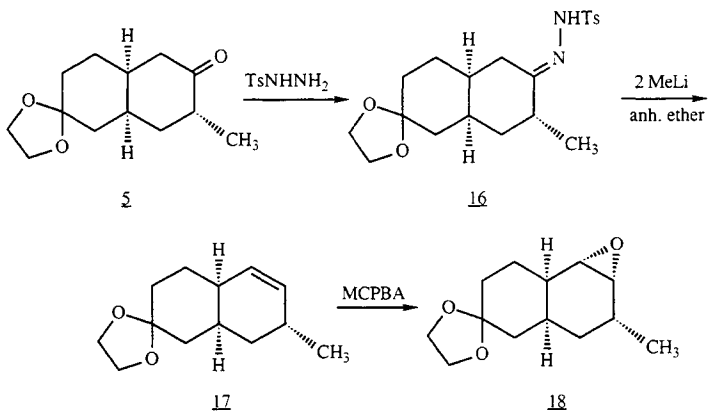
It is worthwhile emphasising here that the observed chemoselectivity is due to the fact that enolethers are better electrophiles than the free carbonyl groups. In fact, the ketoacetal 15, obtained by chromatography, is an equilibrium 60:40 mixture of methyl epimers at C(4) in which the desired α-epimer 5 is the predominant isomer. However, the pure compound 5 could be obtained in good yields by recrystallisation from hexane (m.p. 117-118 °C) and re-equilibration-crystallisation recycling of the remaining mixture 15 in the mother liquor.



Scheme 13.2.3

The next steps of the synthesis, which formally involves a 1,2-carbonyl transposition from C(3) to C(2) and its conversion to the desired *endo-N*-methyl group, followed by a Mannich condensation, are outlined in Schemes 13.2.4 - 13.2.6.

The 1,2-carbonyl transposition takes place through the *endo*-epoxide 18 easily prepared through the tosylhydrazone 16, followed by regioselective cleavage to the less substituted double bond (17) with 2 equivalents of methyllithium [4] and epoxidation with MCPBA in chloroform from the more accesible convex face of the decalin system.



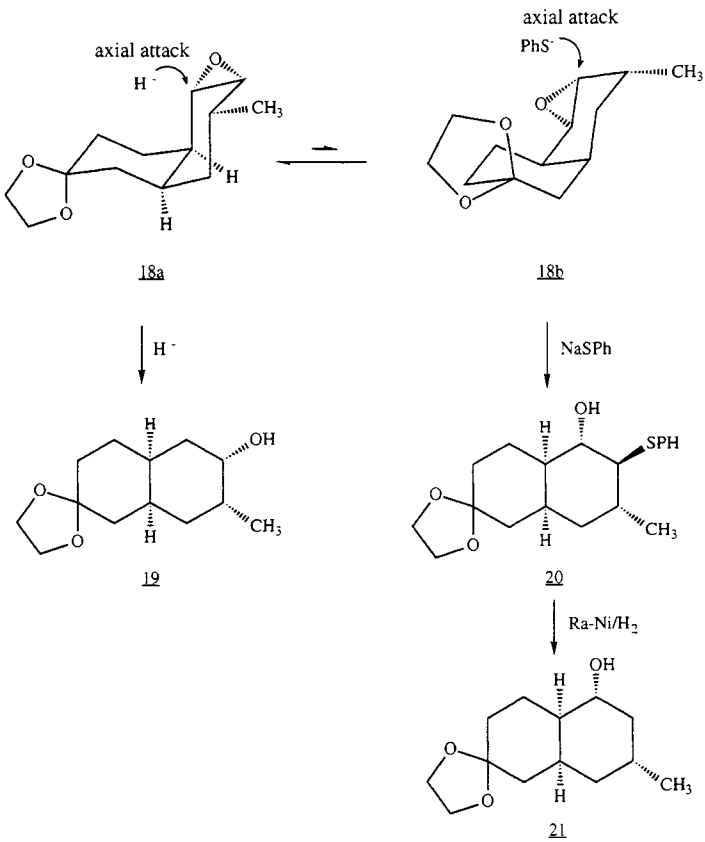
Scheme 13.2.4

The regioselective opening of epoxide 18 to the acetal-alcohol 21 deserves a brief comment. The decalin system of 18 is not a strictly rigid structure and both possible conformations, 18a and 18b, are in fact in an equilibrium in which the former is by far the predominant one (Scheme 13.2.5).[39] Since the opening of the epoxide takes place in a *trans*-diaxial fashion [5] (see Chapter 8, Scheme 8.6), a small anion like hydride will attack the epoxide in this conformation leading to the unwanted acetal-alcohol 19. However, a bulky nucleophile like sodium thiophenoxide can only attack the epoxide axially at the more accesible carbon atom in the less favoured conformation 18b to give regioselectively the desired alcohol 20 albeit with the extra phenylsulfide group which can easily be removed by Raney-

[39] See footnote 19 on page 223.

nickel in refluxing alcohol [6] to give 21 (the overall yield from 5 to 21 is 65% without purification of the intermediates).

Treatment of 21 with *p*-TsCl in pyridine, followed by acid hydrolysis of the acetal-tosylate 22 (HCl in acetone) afforded the keto tosylate 23 in 89% yield (Scheme 13.2.6). Although the introduction of the *endo*-*N*-methylamino group into the acetal-tosylate 22 by an S_N2 substitution is apparently an almost trivial operation, the fact that the attack must take place on the sterically congested concave face of the *cis*-decalin system and the tendency of secondary cyclohexyl tosylates to undergo elimination with amines [7], make it troublesome.

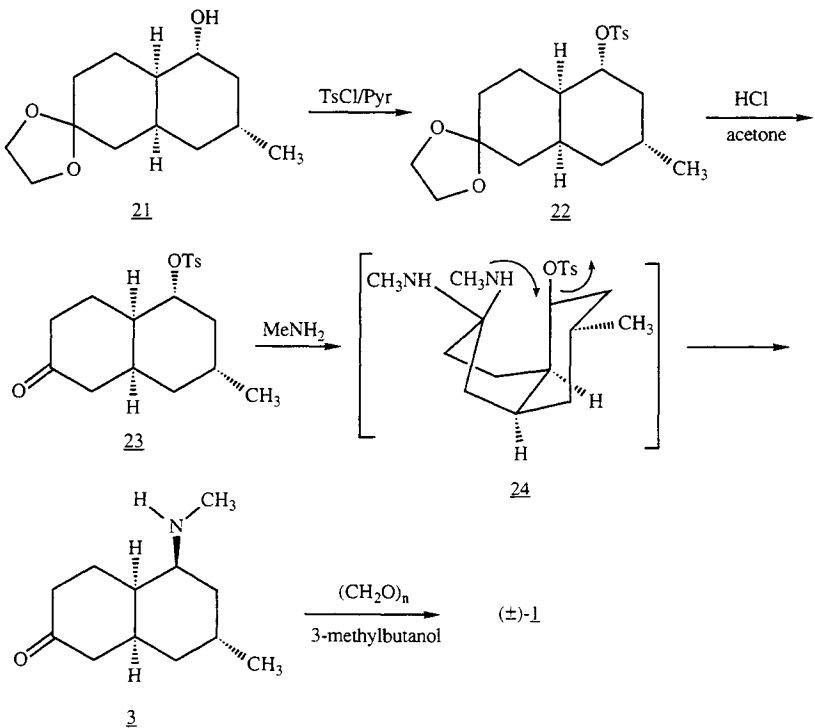


Scheme 13.2.5

As anticipated, the reaction of 22 with either *N*-methylamine or sodium azide under a variety of conditions afforded always the corresponding alkene as the main

reaction product. Evans and Scott finally circumvented this problem by working with the *cis*-decalone 23 and an excess of *N*-methylamine in a sealed tube at 75 °C, in which case the displacement of the tosylate takes place by an intramolecular transference, within the hindered concave face, of the *N*-methylamine. The reaction probably occurs through the intermediate bis-aminal derivative 24 in high yields (94%).

With the key intermediate 3 in hand, the Mannich condensation was accomplished by heating 3 with paraformaldehyde in refluxing 3-methylbutanol, to give (±)-luciduline 1, identical in all respects with an authentic sample of the natural alkaloid.



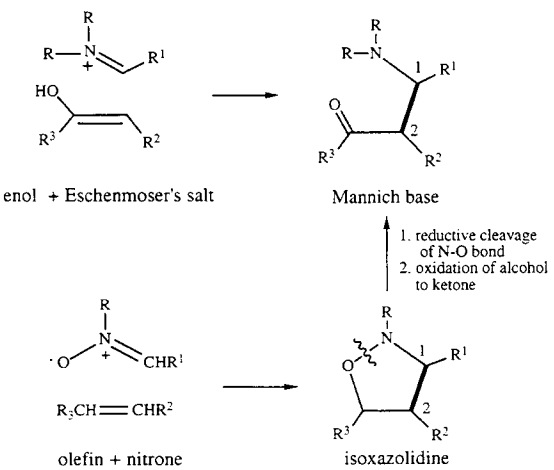
Scheme 13.2.6

Notice that although the $\Delta^{1(2)}$-enol is favoured over the $\Delta^{3(2)}$-enol in *cis*-decalin systems [8], the resulting product from the corresponding Mannich condensation would lead to a highly congested compound with two 1,3-diaxial interactions instead of only one 1,3-diaxial interaction in luciduline.

13.2.2. The enantioselective total synthesis of optically pure (+)-luciduline

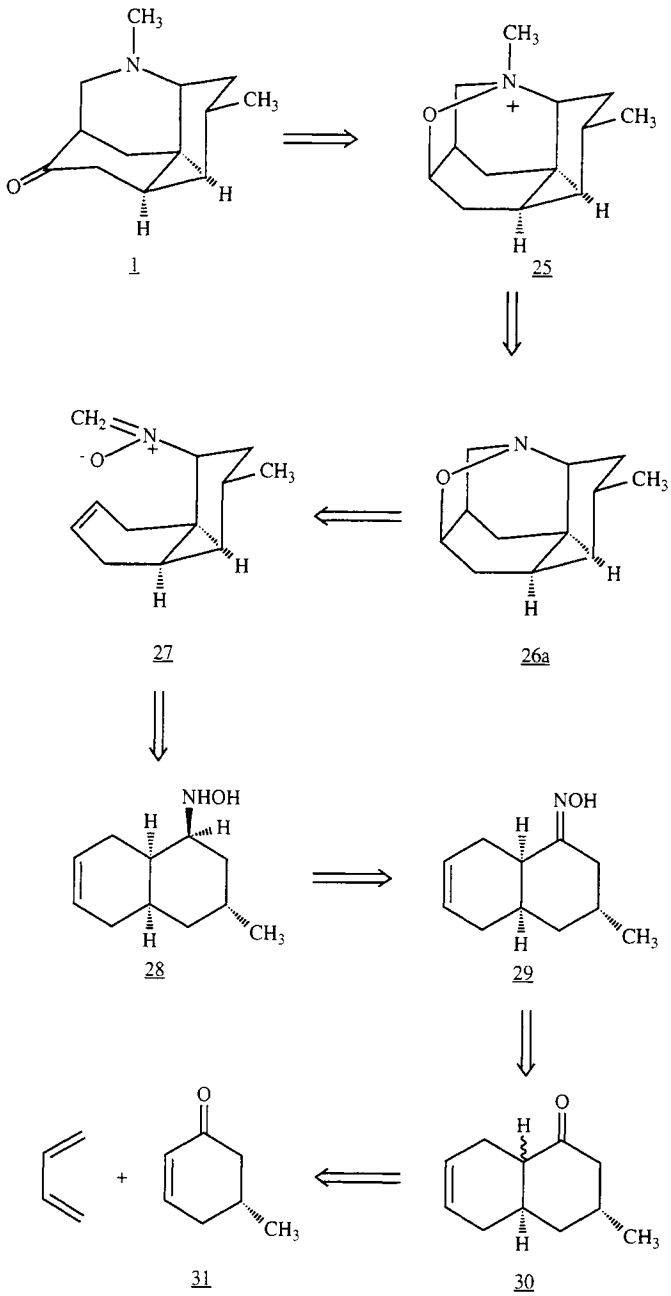
In 1978 Oppolzer and Petrzilka reported the first enantioselective total synthesis of natural (+)-luciduline from (*R*)-5-methyl-2-cyclohexenone (31) by a sequence of seven steps in 33% overall yield [9].

The key step of the synthesis, which involved a classical Mannich condensation in the synthesis by Evans and Scott (as well as in the biogenesis of alkaloids in general [10]), is substituted by a 1,3-dipolar cycloaddition of a nitrone to a carbon-carbon double bond [11] which provides an alternative route for the formation of a new C(1)-C(2) bond with the concomitant creation of a 1,3-consonant relationship between an oxygen atom and a dialkylamino group. In order to arrive at a typical Mannich base two more steps are, however, necessary. The similarity between the two processes is shown is Scheme 13.2.7:



Scheme 13.2.7

With this idea in mind, the retrosynthetic analysis (Scheme 13.2.8) leads now to unsaturated *cis*-decalin 28 which could be reduced to 5-methyl-2-cyclohexenone 31. In the synthetic direction there was initially the uncertainty of whether nitrone 27 would cyclise to 26b rather than to the desired adduct 26a (see below Scheme 13.2.9). However, the authors felt that in fact the risk was "less critical in view of the regioselectivity observed in intramolecular *N*-alkenylazomethinimine additions involving non-polarised olefinic bonds" [11][12].


CH3
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CH3
O
H
H
1
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N
+
O
CH3
H
H
25
CH2
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-O
CH3
H
H
27
N
O
CH3
H
H
26a
NHOH
H
H
H
CH3
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H
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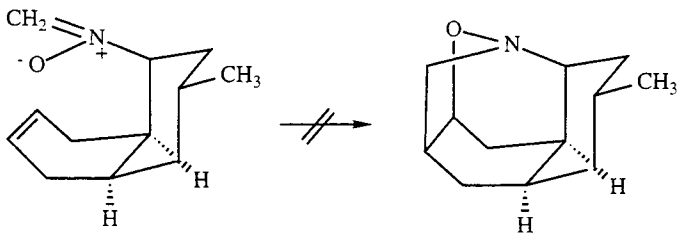
30

Scheme 13.2.8

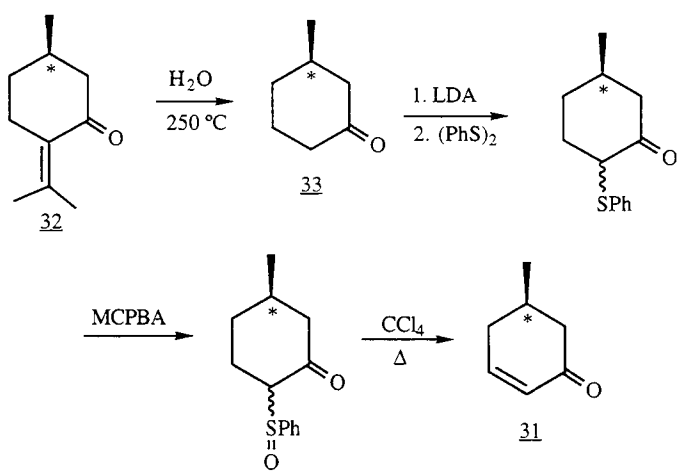


27 26b

Scheme 13.2.9

In order to arrive at optically pure (+)-luciduline, first of all it was necessary to prepare the starting cyclohexenone 31 with the correct absolute configuration. The natural and easily available monoterpene (+)-pulegone 32 was choosen as the source of optically pure (+)-(*R*)-5-methyl-2-cyclohexenone 31.

Retroaldolisation of (+)pulegone (32) afforded (*R*)-3-methylcyclohexanone 33 (see Chapter 3, page 72), which was dehydrogenated through the well known sulphoxide elimination process [13] furnishing optically pure 31 in 49% overall yield (Scheme 13.2.10).



Scheme 13.2.10

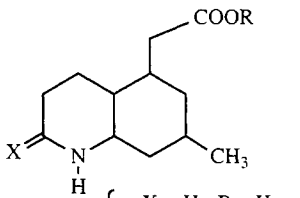
In practice, the synthesis was carried out as outlined in the retrosynthetic Scheme 13.2.8. The Diels-Alder reaction between butadiene and (+)-(*R*)-5-methyl-2-cyclohexenone (31), in the presence of $SnCl_4$ in anhydrous acetonitrile solution at 25 °C, gave 30 in 67% yield as a 2:5 mixture of *cis*:*trans* isomers. Therefore, in the presence of the Lewis acid the addition of butadiene took place exclusively from the opposite side of the methyl group of the dienophile. Although the desired but less predominant *cis*-isomer was difficult to separate from the more stable *trans*-isomer, it could be isolated as the corresponding oxime 29 since it reacts faster with $HONH_2 \cdot HCl$ than its *trans*-isomer. In fact, after finding the right conditions for effecting the rapid *cis* $\rightleftharpoons$ *trans* isomerisation the less stable *cis*-isomer was continously separated from the equilibrium mixture by transformation to the oxime 29. Under the proper experimental conditions the isolated yield was 60% of the cis-oxime. The reduction of oxime 29 with two equivalents of $NaBH_3CN$ afforded the hydroxylamine 28 in 98% yield, the attack of the hydride ion taking place from the more accesible convex face. Heating 28 with an excess of paraformaldehyde in the presence of molecular sieves in refluxing toluene gave *directly* the expected bridged isoxazolidine 26a in 87% yield, with no traces of 26b, indicating a highly regioselective addition of the intermediate nitrone 27 to the non-polarised olefinic double bond.

Finally, the remaining steps were accomplished by methylation of 26a with methyl fluorosulphonate in ether to give the methylammonium salt 25, reductive cleavage of the N-O bond with LAH and oxidation of the resulting alcohol with Jones' reagent. The yields of the last three steps are almost quantitative and the overall yield of the seven steps synthetic sequence leading to optically pure (+)-luciduline (1) is 33%.

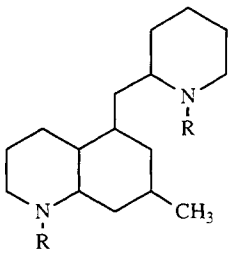
13.2.3. The synthesis of (±)-luciduline through a biogenetic key intermediate

A third total synthesis of luciduline in its racemic form was reported by Szychowski and MacLean in 1979 [14]. The final aim of the authors was to synthesise an intermediate which may be involved in the biosynthesis not only of luciduline itself but also of other members of the *Lycopodium* alkaloids family.

Nyembo *et al.* [15] proposed in 1978 that the amino acid 34 and other compounds of general structure 35, known as phlegmarines, the stereochemistry of which is not specified, may be intermediates involved in the biosynthesis of *Lycopodium* alkaloids.



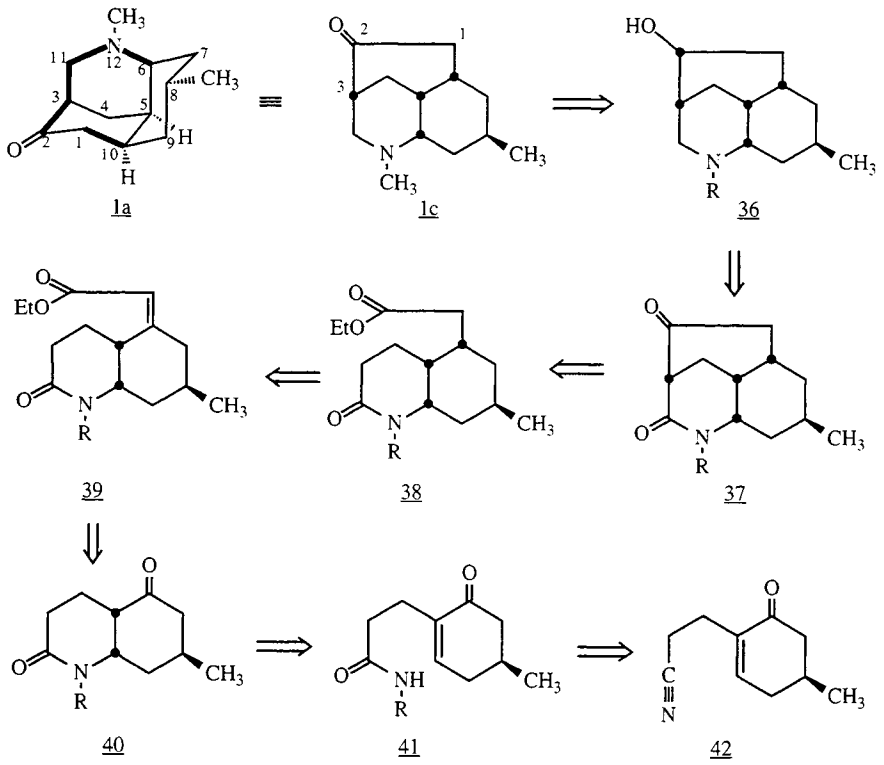
34 { a, X = H_2; R = H
b, X = O; R = C_2H_5



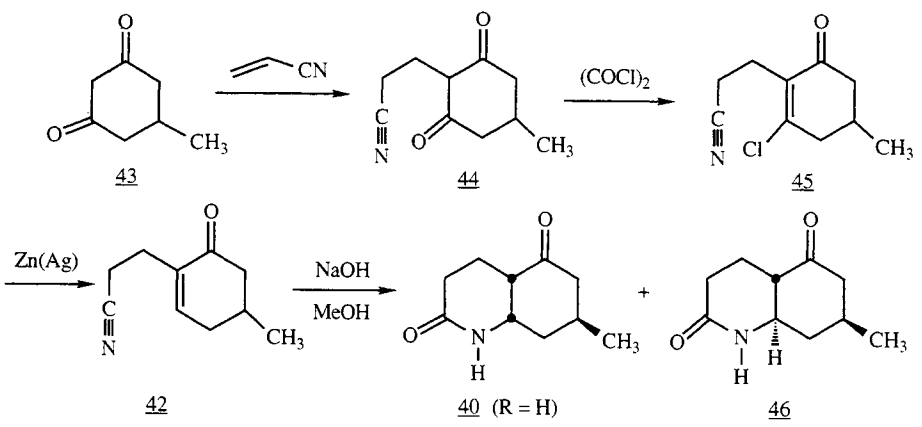
35, R = H or CH_3

The purpose of the work was to synthesise 34b and its conversion to (±)-luciduline. The retrosynthetic pathway is outlined in Scheme 13.2.11 and starts with the disconnection of the "strategic bond" C(2)-C(3). It is worthwhile emphasising here once more the importance of biogenetic considerations since they may be not only a source of inspiration but may also introduce great simplicity in the general plan of the synthesis. On the other hand, we must remember once more that a complex molecule has "thousand faces" and finding the right perspective may also be a simplifying factor (*Cf.* 1a and 1c).

The compound used as starting material was the cyano derivative 42 which was synthesised by addition of acrylonitrile to 5-methyl-1,3-cyclohexanedione (43). The resulting compound was treated with oxalyl chloride (44 ⟶ 45) and then reduced with Zn activated with Ag to furnish the desired cyano derivative 42 which was cyclised to a mixture of bicyclic keto lactams by a method developed by Nomura *et al.* [16] (Scheme 13.2.12). Thus, treatment of cyano compound 42 with methanolic NaOH gave a mixture of two lactams, 40 (R = H) and 46 which were separated by column chromatography on silica gel and the structures assigned on the bases of their n.m.r. spectra. The ratio was greater than 5:1 and did not change with the reaction time. The predominant compound was the *cis*-lactam 40 (R =H) which did not easily isomerise to the *trans*-isomer 46 in spite of having a carbonyl group at the α-position of the bridgehead.

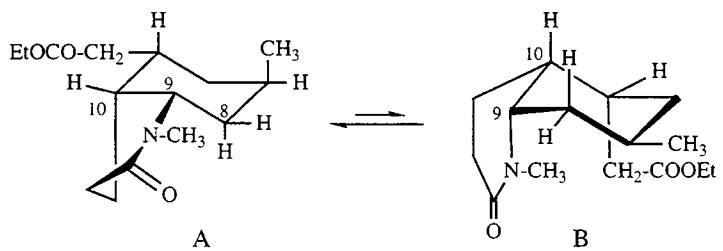


Scheme 13.2.11



Scheme 13.2.12

The next step was to introduce two more carbon atoms [40 (R =H) ⟶ 39 (R = H) ⟶ 38 (R=H)]. Although the Wittig-Horner reaction afforded some of the unsaturated ester 39 (R = H) the reaction gave a mixture of isomers in which the compounds with an endocyclic double bond predominated. However, the unsaturated ester 39 (R =H) could be obtained in good yield by the Peterson reaction [17] with ethyl trimethylsilylacetate.[40] The *N*-methyl group was introduced with dimethyl sulphate, before hydrogenation in order to prevent cyclisation of the ester group with the nitrogen atom, and the *N*-methylated derivative 39 (R = CH_3) was hydrogenated with Adam's catalyst to yield a 1:1 mixture of the corresponding *endo*- (38, R = CH_3) and *exo*-isomers which were separated by column chromatography on silica. Cyclisation of *endo*-38 (R = CH_3) to luciduline lactam 37 requires a conformation in which the ethoxycarbonylmethyl side-chain and the *N*-Me are axially disposed, as shown below:



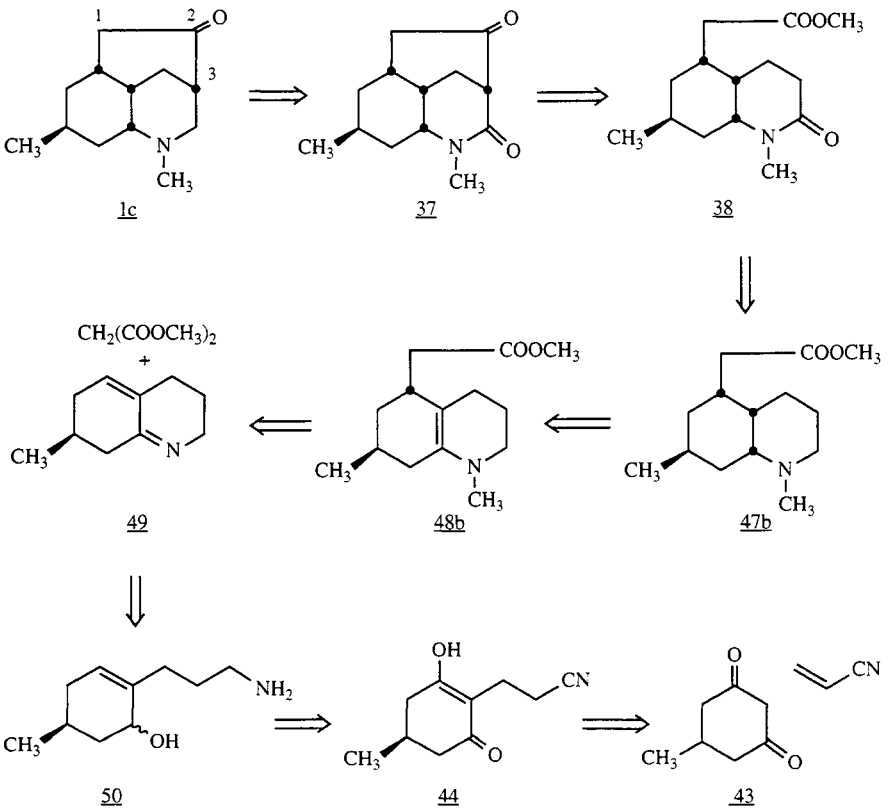
However, the interconversion barrier is not very high since 38 (R = CH_3) was successfully cyclised to luciduline lactam 37 (R = CH_3) with base (lithium *N*-isopropylcyclohexylamide at -60 °C) in high yield (90%). The reduction of lactam 37 (R = CH_3) with lithium aluminum hydride gave (±)-dihydroluciduline 36 (63% yield) identical with a sample prepared by reduction of an authentic sample of (±)-luciduline. Reoxidation of the alcohol at C(2) of (±)-dihydroluciduline 36 with Jones' reagent gave finally (±)-luciduline 1.

---

[40] The reaction was normally carried out with the mixture of lactams. Whereas the *trans*-isomer gave a mixture of two unsaturated esters (*E* and *Z*), the *cis*-isomer 39 (R = H) gave only one isomer to which the (*E*)-configuration was assigned on spectroscopic bases.

13.2.4. Synthesis of (±)-luciduline from 7-methyl-2,3,4,6,7,8-hexahydroquinoline

The last synthesis of luciduline in its racemic form was reported in 1984 by D. Schumann [18] and is based in a synthesis of (±)-lycopodine previously described in 1982 [19].

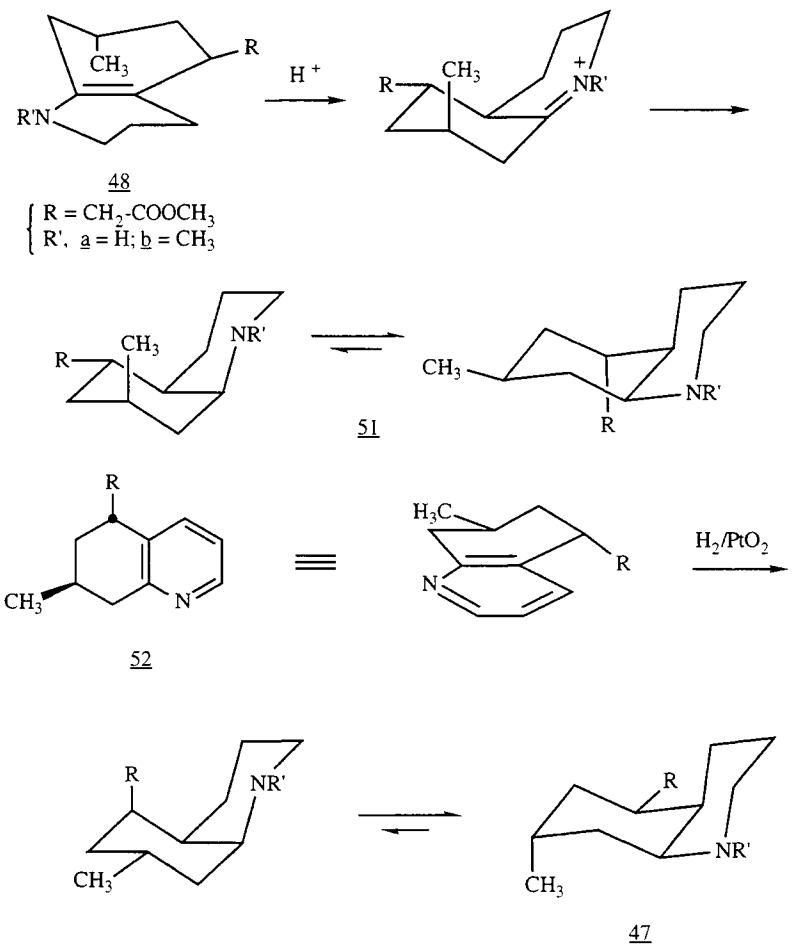


Scheme 13.2.13

The retrosynthetic analysis also involves disconnection of the "strategic bond" C(2)-C(3) and the sequence is very similar to that described above by Szychowski and MacLean (*Heading 13.2.3*).[41] The actual synthesis, however, rather than the intermediate 48b shown in Scheme 13.2.13 -whose hydrogenation leads to the wrong stereochemistry (51)- requires the tetrahydro derivative 52 from which ester 47b can be obtained stereoselectively by catalytic hydrogenation with Adam's

[41] Notice that compounds 1c, 37 and 38 (see Scheme 13.2.11) are now arbitrarily drawn as the enantiomers.

catalyst, followed by the Leuckart-Wallach *N*-methylation of the intermediate 47a (Scheme 13.2.14). Oxidation with potassium permanganate and crown ether of 47b yields the lactam 38 which was converted into (±)-luciduline as in the synthesis by MacLean. The tetrahydro derivative 52 is obtained in poor yields (14%) by disproportionation of the diastereomeric mixture of imines resulting from the 1,4-addition of malonic acid to the enimine 49 and the starting material for the preparation of the key intermediate 47b is also 5-methyl-1,3-cyclohexadione 43 as in the previous synthesis by MacLean.



Scheme 13.2.14

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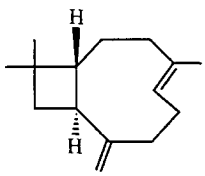
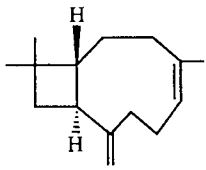
13.3. CARYOPHYLLENES

Caryophyllenes are a class of sesquiterpenes that protect plants against insects, and have a quite unusual structure: a four membered-ring fused to a medium-sized ring of nine carbon atoms. There are two isomers which only differ in the configuration of an endocyclic double bond: the so-called α-caryophyllene (*E*-isomer) (1a) and the corresponding (*Z*)-isomer: the β- or isocaryophyllene (1b).



1a



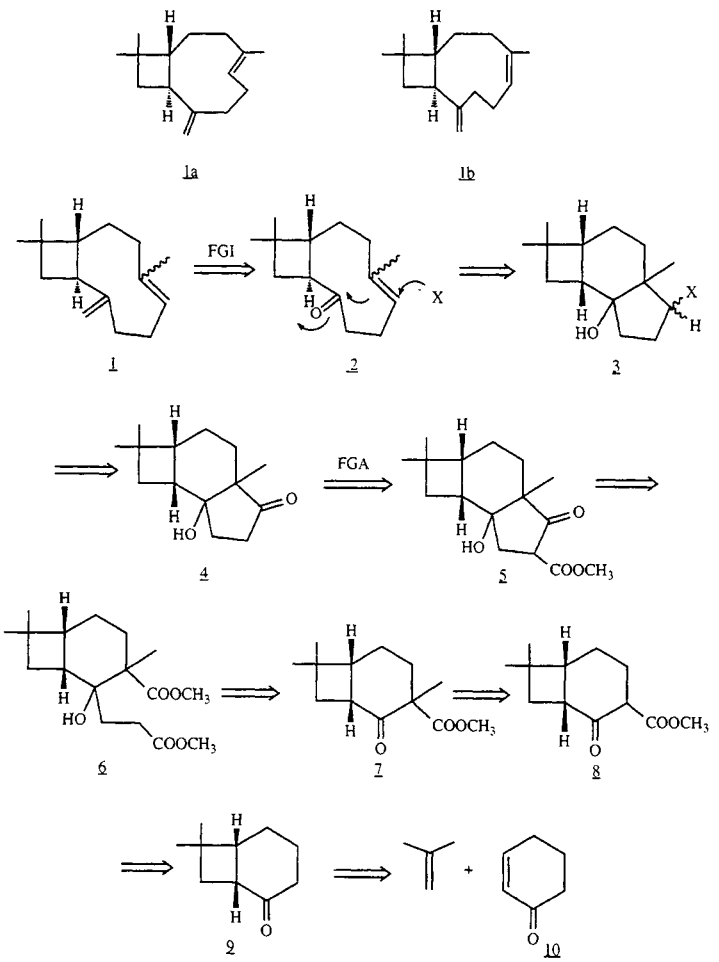
1b

Therefore, a rational synthesis of caryophyllenes should be designed in such a way that after proceeding through a series of common intermediates at a given step they may offer the opportunity to exert a stereochemical control in the formation of the endocyclic double bond. In this context, the synthesis reported by Corey as early as 1964 [1] is still more efficient than more recent syntheses in which only one isomer (isocaryophyllene, 1b) is formed [2] or that require parallel synthetic sequences which start from compounds which are only remotely related to each other [3].

13.3.1. Syntheses of caryophyllenes from a common key intermediate

The synthesis reported by Corey and his co-workers is based on the heuristic principle which refers to the convenience of reducing medium-sized rings of 7 to 10 carbon atoms to common-sized rings of 5 or 6 carbon atoms (HP-9) (see *Heading 7.1.1*). This heuristic principle, together with the first one (HP-1) referring to the modification or elimination of highly reactive or unstable functional groups leads, in the retrosynthetic sense (Scheme 13.3.1), to replace the exocyclic double bond by a

carbonyl group (1 ⟹ 2), followed by a "Wharton-Grob reconnection" of the 9-membered ring to the intermediate 3 with a six-membered ring fused to a five-membered ring. The functional group X must be a good leaving group derived from a hydroxyl group, such as OTs, and its stereochemistry -which will determine the configuration of the double bond in the intermediate 2- will be controlled in the actual synthesis by the reduction of a carbonyl group (4 ⟶ 3). The retrosynthetic analysis proceeds then by a FGA (5), followed by a retro-Dieckmann condensation and disconnection of the resulting intermediate precursor to the bicyclic ketone 7 and a three-carbon fragment with inverted reactivity , (-)CH_2-CH_2-$COOCH_3$.



Scheme 13.3.1

Finally, disconnection of the two appendages leads to bicyclic ketone 9 which can be disconnected into 2-cyclohexenone 10 and isobutylene, according to a -(2+2) cycloreversion.

The general strategy is thus decided and it only remains to choose at every step the most convenient tactics that modern organic chemistry offers to the synthetic organic chemist in order to achieve the final objective. In fact, as stated by Corey, the most problematical step is the first one since *a priori* it was difficult to foresee the favoured orientation of the reactants in the photochemical (2+2)-cycloaddition. However, the simplicity of the derived synthetic scheme and the fact that the risk is found in the first step justifies attempts in this direction. On the other hand, it seemed that the *trans*-junction of the bicyclic system present in caryophyllenes would be better attained in the last steps of the synthesis, once the medium sized-ring had been created, since the *cis*-configuration should be more stable for a fused system involving a four-membered ring and a "normal-sized ring".

In the synthesis, the photochemical cycloaddition gave the desired cycloadduct 9 as the predominant product (35-45%), but unexpectedly the unstable *trans*-isomer was formed in larger amounts than the *cis*-isomer.[42] However, isomerisation takes place easily either in the presence of an aqueous base or by heating the reaction mixture at 200 °C.

With the bicyclic ketone 9 in hand, the following steps were required to arrive at the intermediate 4: α-methoxycarbonylation and α-methylation, and construction of the cyclopentane ring . The reaction of bicyclic ketone 9 with NaH and dimethyl carbonate in dioxan gave the ketoester 8, which was then methylated to afford the intermediate 7 in excellent overall yield. The methylation, however, was not stereoselective and gave a 3:1 mixture of two diastereomers. Reaction of this mixture with the lithium derivative of the dimethylacetal of propargylaldehyde (11), which plays the role of the C_3-fragment with "inverted reactivity" (and so allowing the construction of a dissonant five-membered ring), took place from the more accesible convex face of the *cis*-bicyclic system to give compound 12 (Scheme 13.3.2).

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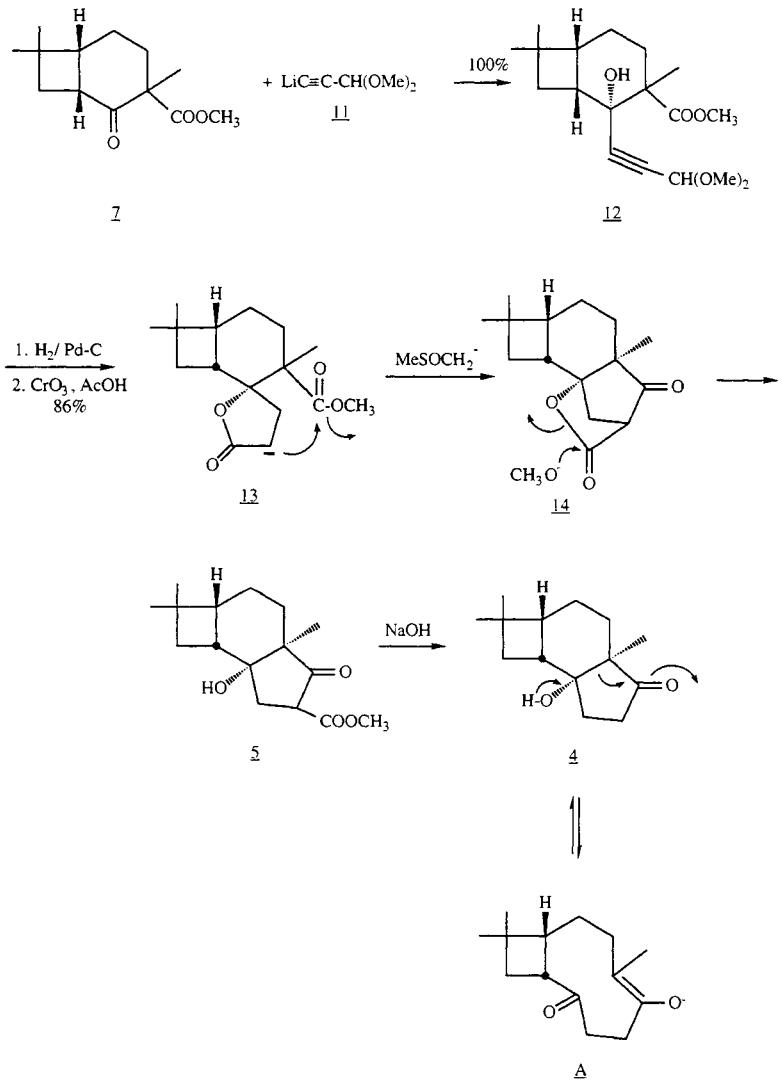
[42] In fact, the formation of the *trans*-isomer in the photoaddition of 2-cyclohexenone to isobutylene and the regiospecificity observed were unexpected on the basis of some earlier studies. However, isomerisation of 2-cyclohexenone to a distorted *trans*-isomer could account for the observed results [4].

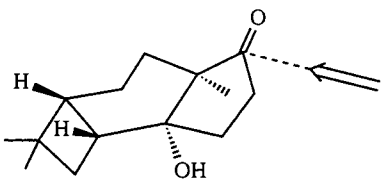
Catalytic hydrogenation of the triple bond (Pd/C) and oxidation of the acetal in acid medium led to lactone 13 which could be cyclised directly to the tricyclic intermediate 5 according to a Dieckmann condensation induced by sodium methylsulphinylmethylide in DMSO. The cyclisation takes place through intermediate 14. Compound 5 was a diastereomeric mixture still, but on treatment with aqueous alkali, at room temperature, gave a crystalline compound in about 30-35% yield, to which the *cis-anti-cis-* configuration was assigned (in fact an equilibration through the intermediate A may take place).



Scheme 13.3.2

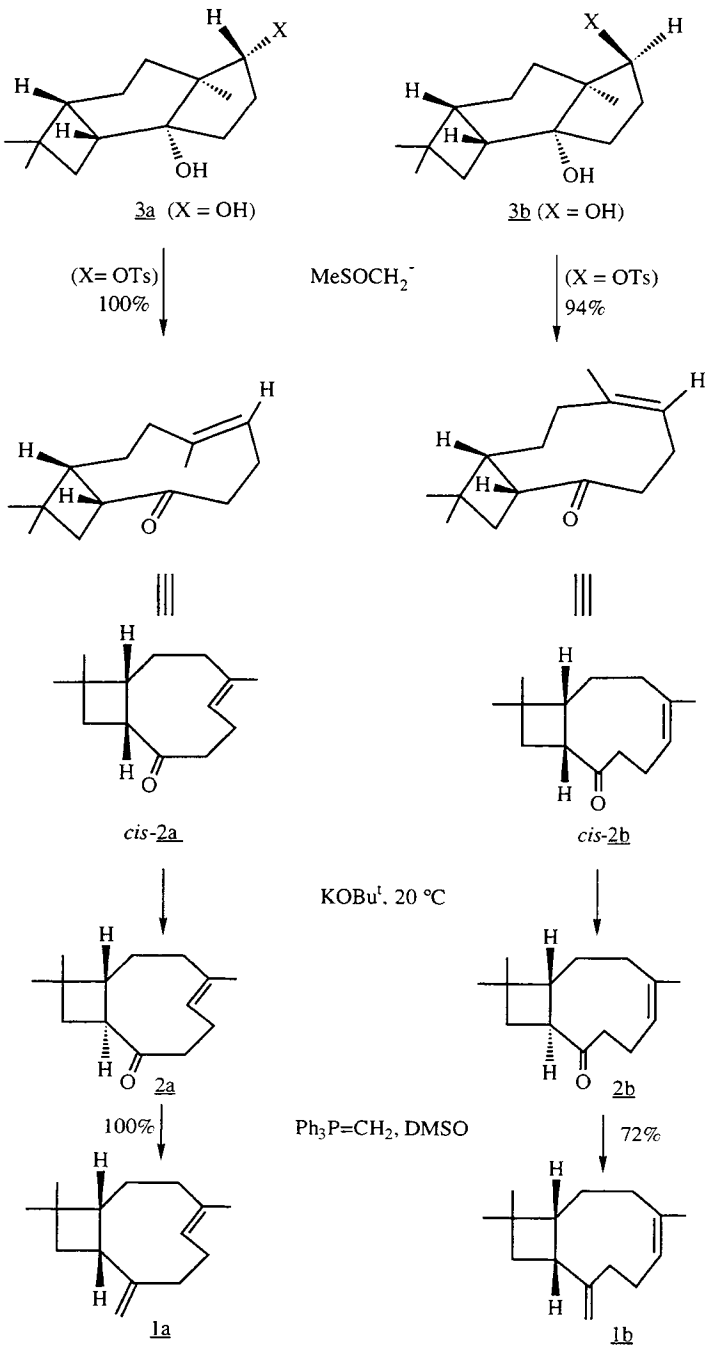
As noted by Corey, the relative configuration of the two carbon atoms joining the six- and the five-membered rings is not relevant for the synthesis, since what will determine the stereochemistry of the double bond is the relative configuration of the angular methyl group and the secondary hydroxyl group in 3 (X = OH).

In practice (Scheme 13.3.3), the reduction of hydroxyketone 4 with either metal hydrides or sodium in wet ether gave only one compound to which the structure 3b (X = OH) was assigned (attack on the convex face of the tricyclic system).



On the other hand, reduction with Raney nickel led to a 1:1 mixture of diols. Since one of them was identical to the diol obtained before, the second diol should be the corresponding isomer in which the angular methyl and the hydroxyl group are cis (3a, X = OH).

Preferential chemoselective tosylation of the secondary hydroxyl groups (3a and 3b, X = OTs), followed by Wharton-Grob fragmentation induced by sodium methylsulphinylmethylide in DMSO, afforded the corresponding *cis*-bicyclic ketones which were easily isomerised to the thermodynamically more stable *trans*-isomers 2a and 2b. Assuming that the internal elimination is concerted and that the stereoelectronically favourable *coplanar* mode of elimination will prevail, the control of the configuration of the double bond is determined -as stated above- by the relative configuration of the angular methyl group and the vicinal leaving group. Treatment of the *cis*-bicyclic ketones with methylenetriphenylphosphorane gave finally racemic α-caryophyllene (1a) and isocaryophyllene (1b), respectively, identical with samples of natural caryophyllenes.


3a (X = OH)
3b (X = OH)
(X= OTs)
100%
MeSOCH2-
(X = OTs)
94%
cis-2a
cis-2b
KOBut, 20 °C
2a
2b
100%
Ph3P=CH2, DMSO
72%
1a
1b

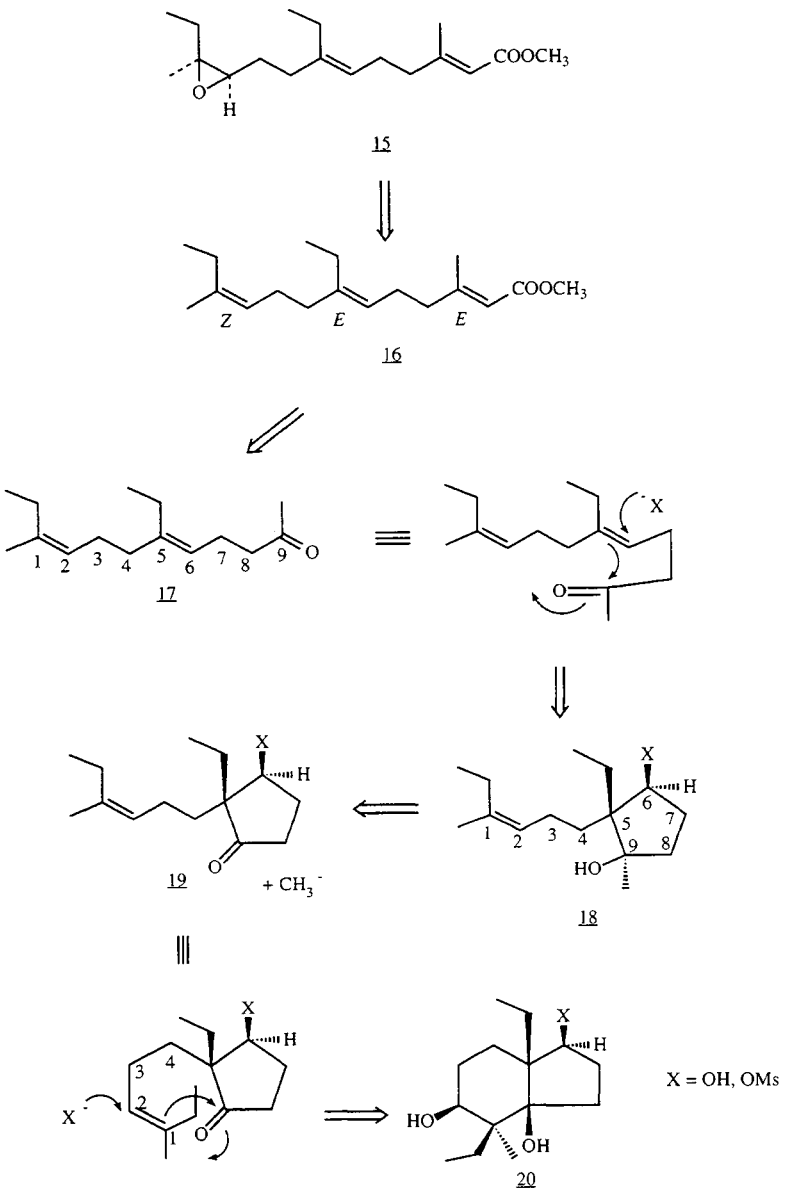
Scheme 13.3.3

13.3.2. The Wharton-Grob fragmentation and the cationic cyclisation of polyolefins. Synthesis of Cecropia *juvenile hormone and* d,l-*progesterone.*

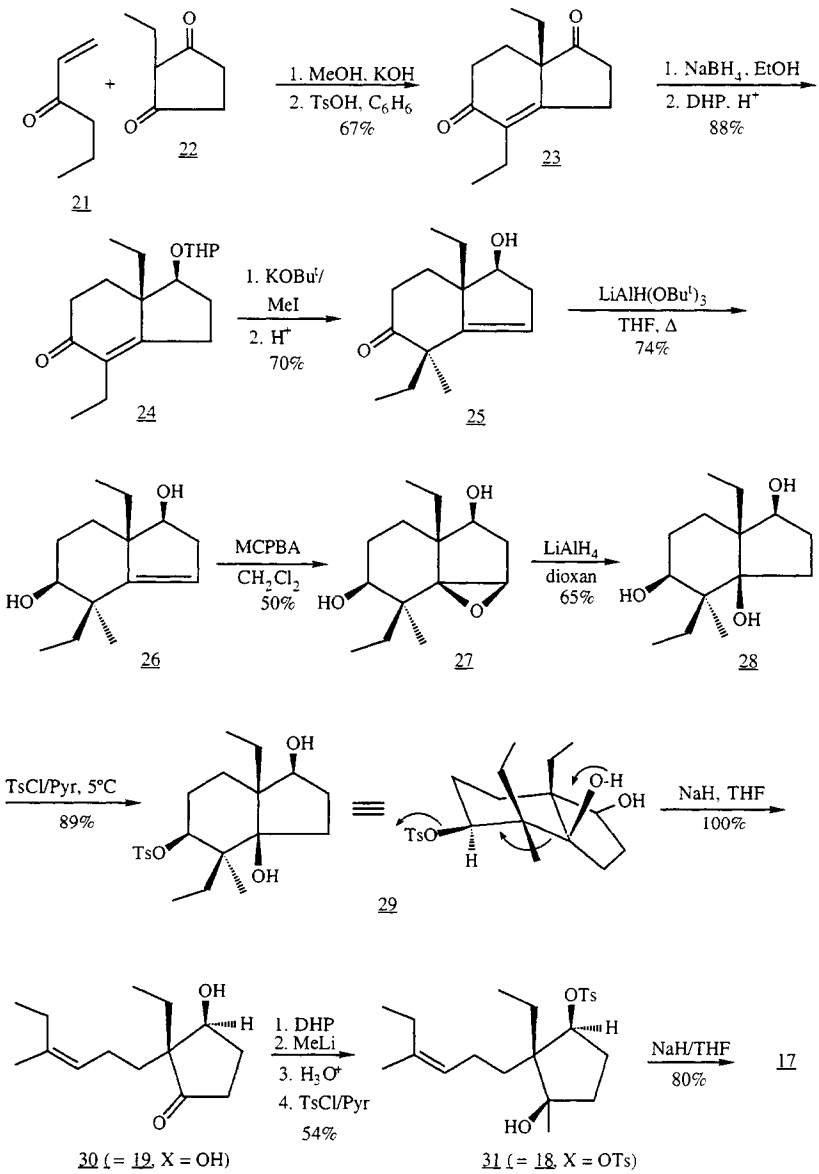
It is worthwhile emphasising that the Wharton-Grob fragmentation of 1,3-diols has been widely used in the synthesis of natural products and a review by J.A. Marshall was published in 1969 [5]. However, its application to stereoselective syntheses of linear polyunsaturated chains is not so evident. As an example, we will describe briefly the synthesis of *Cecropia* juvenile hormone (15) developed by the Syntex group [6]. In this synthesis the problem of controlling the geometry of the three double bonds (one as the corresponding epoxide) present in the molecule is reduced to the stereochemical control of a bicyclic fused system. The retrosynthetic analysis proceeds as outlined in Scheme 13.3.4 and starts by eliminating the epoxide to give the polyunsaturated ester 16 in which one double bond has a *(Z)*-configuration and the two remaining ones have the *(E)*-configuration. The disconnection of the conjugated double bond by a retro-Wittig reaction leads to the double unsaturated ketone 17. In the synthetic direction the reaction of the ketone 17 with a carbonyl-stabilised Wittig reagent or the equivalent carbanion from a phosphonate, should ensure the *(E)*-configuration.

In the retrosynthetic pathway followed by the Syntex group, since in the unsaturated ketone 17 the carbonyl group is two carbon atoms away from the *(E)*-double bond, it is "reconnected" to a cyclopentane-1,3-diol derivative (18). Nucleophilic dealkylation of the resulting tertiary alcohol gave a new unsaturated ketone 19 which has the carbonyl group three carbon atoms away from the *(Z)*-double bond and may be "reconnected" to the bicyclic derivative 20 bearing five chiral centres. In the actual synthesis the main problem was the stereoselective control of each one of these chiral centres which was achieved in a sequence of eleven steps, which are shown in Scheme 13.3.5. The synthesis starts with a Robinson annulation between propyl vinyl ketone (21) and 2-ethylcyclopentan-1,3-dione (22) to give the bicyclic dione 23, followed by chemoselective reduction of the isolated carbonyl group (*Cf.* the chemoselective control in the Wieland-Miescher ketone discussed in Heading *12.1.1*). The next steps leading to the key intermediate 28 (≡ 20, X = OH) involve the protection of the secondary alcohol as a THP derivative (24), followed by α-methylation of the carbonyl group with concomitant deconjugation (25), reduction of the carbonyl group with a bulky metal hydride to ensure attack from the less hindered side (26), stereoselective epoxidation of the double bond by intramolecular transfer of the oxygen to the β-face from the β-

hydroxyl-perbenzoic acid complex [7] and regioselective opening of the epoxide by $LiAlH_4$.



Scheme 13.3.4

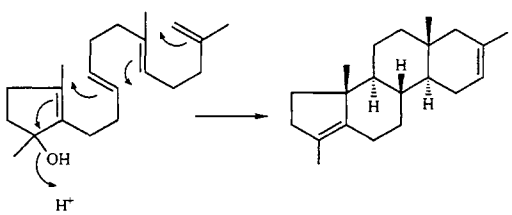


Scheme 13.3.5

The less hindered peripheric secondary hydroxyl group of the key intermediate 28 was chemoselectively tosylated (29), submitted to an internal Wharton-Grob fragmentation (30). After attack on the carbonyl group (31) with methyllithium and activation of the secondary alcohol as the corresponding tosylate, the resulting

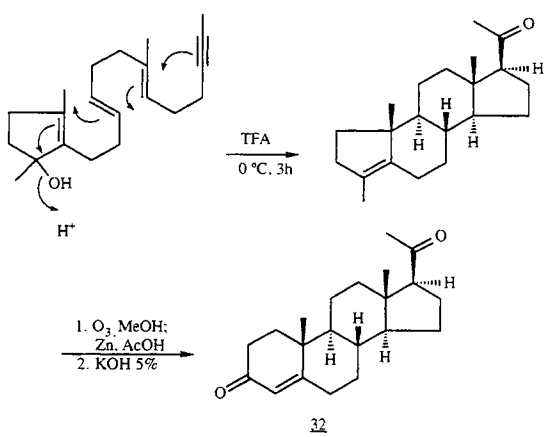
compound was submitted again to a Wharton-Grob fragmentation to afford finally the unsaturated ketone 17 with the two double bonds having the correct *(Z)*- and *(E)*-configuration. The two last steps of the synthesis are a Wittig-Horner reaction (or Wadsworth-Emmons reaction) which provides the third double bond in the correct configuration and the chemoselective epoxidation of the non-conjugated terminal double bond.

It is worth noting that in this synthesis of *Cecropia* juvenile hormone a strategy which is the reverse of the one developed by W.S. Johnson [8] for the synthesis of steroids and other fused polycyclic systems bearing cyclohexane rings is used. This method involves a non-enzymatic cyclisation of a polyunsaturated intermediate with the appropriate stereochemistry (*all-trans*) (Scheme 13.3.6). Such cyclisation occurs with a really amazing stereoselectivity and several new chiral centres with the correct stereochemistry are created in one single step:



Scheme 13.3.6

Substitution of an acetylene triple bond for the terminal double bond provides an easy entry to *d,l*-progesterone (32) [9] (Scheme 13.3.7):



32

Scheme 13.3.7

The idea that such cyclisations should be highly stereoselective derives from the Stork-Eschenmoser hypothesis, according to which the double bonds in polyalkenes of the squalene type are properly arranged to undergo cyclisation to fused polycyclic systems with the natural *trans-anti-trans* configuration.

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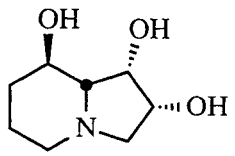
13.4. SWAINSONINE: *Sharpless synthesis*

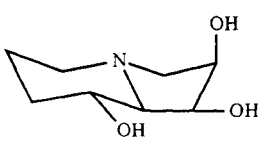
(-)-Swainsonine (1) is of great biochemical interest since it is a potent and specific inhibitor of both lysosomal α-mannosidase and mannosidase II, which are involved in the cellular degradation of polysaccharides and in the processing of asparagine-linked glycoproteins, respectively [1].

(-)-Swainsonine is a trihydroxylated bicyclic indolizidine alkaloid with four chiral centres, whose relative stereochemistry was determined by X-ray crystallographic analysis and the absolute configuration was deduced on the basis of biosynthetic and asymmetric induction studies, and then confirmed by an enantiospecific synthesis from D-mannose [2a].

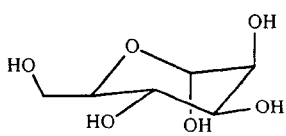


1

The similarity between swainsonine (1) and α-D-mannose (2) would explain not only its biological activity, but also the fact that six syntheses starting either from glucose or mannose derivatives have been described [2]. Another synthesis from glutamic acid has also been described [3]. Moreover, the fact that syntheses of polyhydroxylated natural products, including the whole series of the unnatural hexoses, by using Sharpless asymmetric epoxidation [4] have been succesfully accomplished, led Sharpless and his group to undertake the synthesis of (-)-swainsonine by the same methodology [5].



1

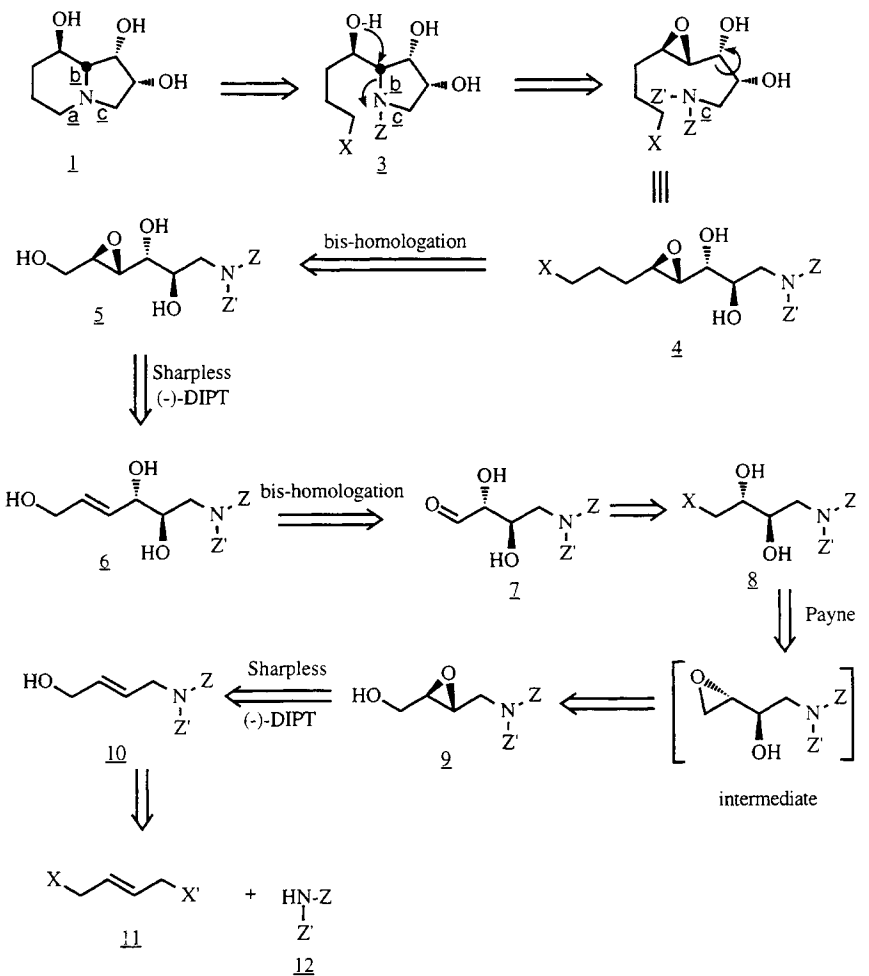


2

The general strategy for the synthesis of (-)-swainsonine [5] is to prepare an acyclic key intermediate with the required stereochemistry and proceed then to a double intramolecular cyclisation.

The retrosynthetic analysis proceeds according to Scheme 13.4.1 and starts with the application of the heuristic principle number 8 (HP-8); i.e., performing the systematic disconnection of the nucleophilic heteroatom attached to the carbon backbone. Of the three bonds connecting the nitrogen atom, bond a is the most

suited to be disconnected in the first place since is *exo* to another ring[43] and it is three carbon atoms away from a chiral centre (1 ⟹ 3); bond b can be then disconnected by a plausible mechanism involving the "intramolecular nucleophilic attack" of the hydroxyl group at the *ipso* carbon atom to nitrogen (3 ⟹ 4). The retrosynthesis involves then two retro-bis-homologations and two retro-Sharpless asymmetric epoxidations, the second one with a concomitant Payne ring-opening rearrangement. Finally, the remaining C-N bond is disconnected to afford the diallylic derivative 11 and the secondary amine 12.



Scheme 13.4.1

[43] Cf. Corey's rules for strategic bonds.

In order to succeed in the actual synthesis, Sharpless had to make rational use of some protecting groups for both the hydroxyl groups and the nitrogen function. The requirements for the nitrogen protecting groups -in order to make it compatible with the iterative Sharpless epoxidations- are that they must render the nitrogen resistant to oxidation and that neither the nitrogen nor the protecting groups themselves act as internal nucleophiles towards the epoxide function. Sharpless demonstrates in this synthesis that the *N*-benzyl-*p*-toluenesulfonamide group meets these requirements.

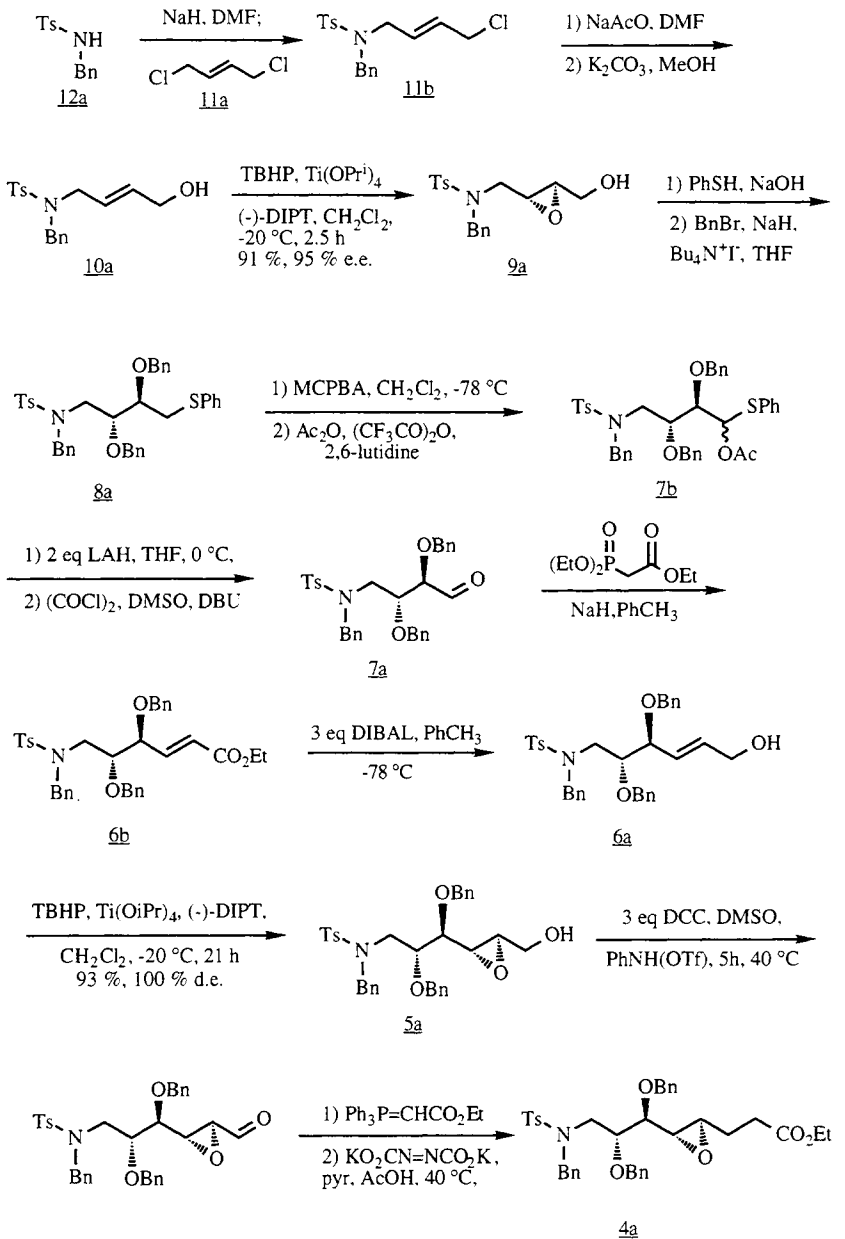
The synthesis is outlined in Scheme 13.4.2, in which the numbering of the synthetic intermediates parallels that of the retrosynthetic scheme.

Alkylation of *N*-benzyl-*p*-toluenesulfonamide (12a) with a threefold excess of *trans*-1,4-dichloro-2-butene (11a) gives the allylic chloride 11b, which is treated with sodium acetate in DMF followed by hydrolysis to afford the allylic alcohol 10a in an overall 68% yield.

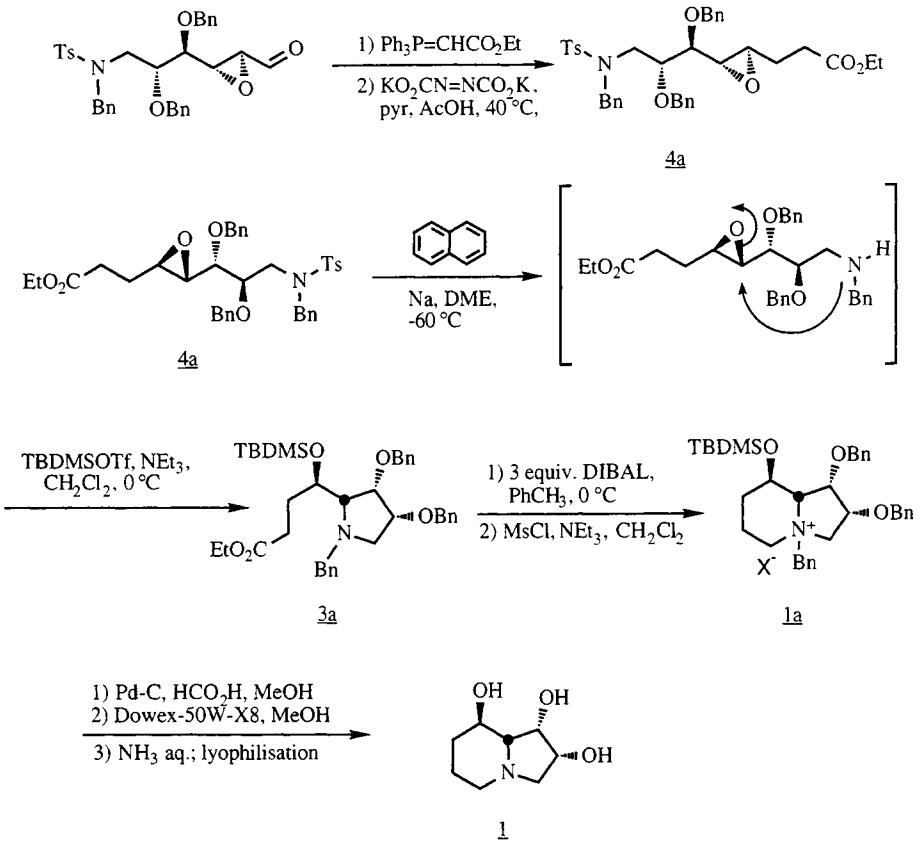
Asymmetric epoxidation of 10a under standard conditions yields the crystalline epoxy alcohol 9a in 95% ee (91% chemical yield). Treatment of 9a with thioanisol in 0.5N NaOH, in *tert*-butyl alcohol solution, gives -after protection of the hydroxyl groups as benzyl ethers- the sulfide 8a (60% overall yield) through an epoxide ring-opening process involving a Payne rearrangement. Since the sulfide could not be hydrolysed to the aldehyde 7a without epimerisation at the α-position, it was acetoxylated in 71% yield under the conditions shown in the synthetic sequence (8a ⟶ 7b) and then reduced with LAH to the corresponding alcohol, which was oxidised according to the method of Swern to afford the aldehyde 7a without epimerisation. Treatment of 7a with triethyl phosphonoacetate gives the desired ester 6b (*E*:*Z* = 32:1), which is reduced to the allylic alcohol 6a, and then epoxidised employing (-)-DIPT to give the epoxy alcohol 5a in a ratio ≥321:1 (in the presence of (+)-diethyl tartrate resulted in a ≤1:450 ratio). The bis-homologation required for the swainsonine backbone is performed by Moffat oxidation of 5a followed by direct addition of (ethoxycarbonylmethylene)triphenylphosphorane. Diimide reduction of the resulting α,β-unsaturated esters affords the epoxyester 4a in 74% yield from 5a.

The tosyl protecting group of 4a is removed with sodium naphthalide at -60 °C, and an intramolecular nucleophilic attack of the nitrogen lone pair to the epoxide takes place spontaneously to afford the pyrrolidine hydroxy ester as a labile reaction product, which is immediately protected as the corresponding silyl ether 3a in 68%

yield from 4a. Reduction of the ester function of 3a to the corresponding alcohol (79% yield) and activation as the corresponding mesylate, leads directly to a mixture of *cis*- and *trans*-fused bicyclic quarternary ammonium salts 1a.



Scheme 13.4.2



Scheme 13.4.2 (continued)

The ammonium salt 1a is debenzylated to a single amino diol in quantitative yield from 3a, which is then desilylated with Dowex 50W-X8 (H^+ form) and washing the resin with 10% NH_4OH followed by lyophilisation of the eluates gives (-) swainsonine 1 in 84% yield, identical by direct comparison with an authentic sample.

This synthesis of (-)-swainsonine involves 21 steps and proceeds with an overall yield of 6.6% from *trans*-1,4-dichloro-2-butene. It is not only the first reported noncarbohydrate route to this natural product, but it allows the stereoselective access to all 16 epimers and/or enantiomers of swainsonine as well.

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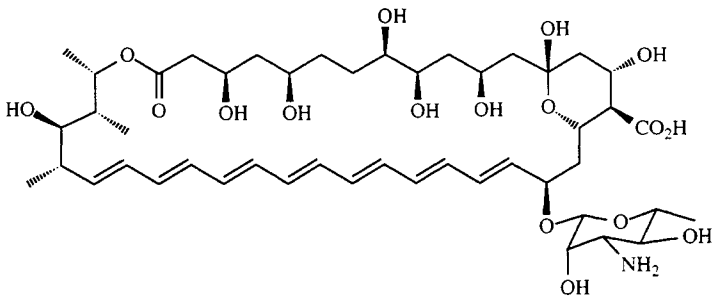
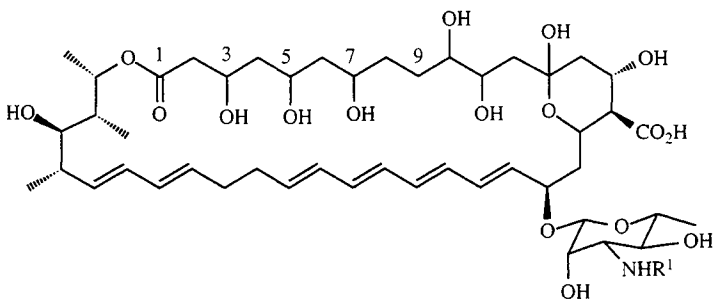
13.5. POLYENE MACROLIDE ANTIBIOTICS AMPHOTERICIN B AND NYSTATIN A_1.

In connection with the synthetic work directed towards the total synthesis of polyene macrolide antibiotics -such as amphotericin B (1)- Sharpless and Masamune [1] on one hand, and Nicolaou and Uenishi on the other [2], have developed alternative methods for the enantioselective synthesis of 1,3-diols and, in general, 1, 3, 5...(2n + 1) polyols. One of these methods is based on the Sharpless asymmetric epoxidation of allylic alcohols [3] and regioselective reductive ring opening of epoxides by metal hydrides, such as Red-Al and DIBAL. The second method uses available monosaccharides from the "chiral pool" [4], such as D-glucose.

We will describe here the first method as developed by Nicolaou [2] which has recently been applied to the synthesis and stereochemical assignment of the C(1)-C(10) fragment of nystatin A_1 (2) [5].



1: Amphotericin B



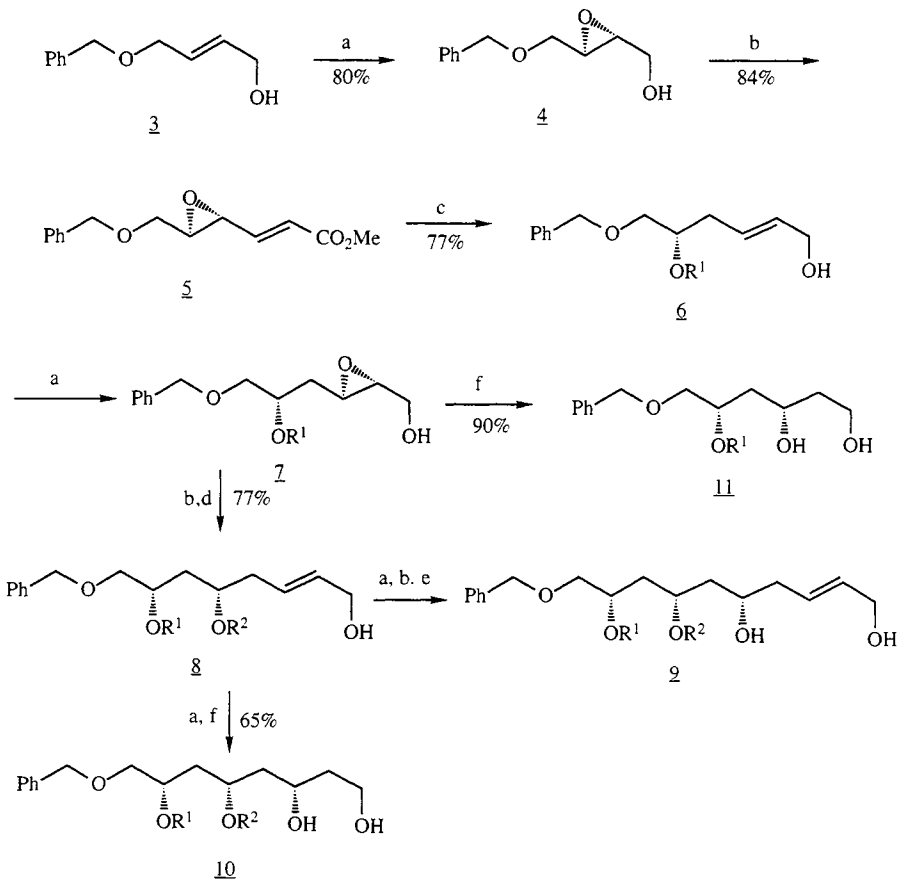
2: Nystatin A_1

13.5.1. Stereocontrolled synthesis of 1, 3, 5...(2n +1) polyols.

As outlined in Scheme 13.5.1, the asymmetric epoxidation of allylic alcohol 3 afforded the epoxide 4 with a stereoselectivity of 99:1, which was oxidised by the Swern method and then reacted with (methoxycarbonylmethylene)phosphorane to give a 84:16 mixture of (*E*):(*Z*)-γ,δ-epoxy-α,β-unsaturated esters 5, which were separated chromatographically. The regioselective reductive opening of the epoxide was cleanly effected with DIBAL, which also reduced the ester group. Temporary protection of the resulting primary hydroxyl group as a pivaloate ester, silylation of the secondary OH and deprotection of the primary alcohol led to the monoprotected intermediate 6. Compound 6 was then converted to the higher homologue 8 through a similar sequence of reactions, *via* epoxide 7 which was obtained with a stereoselectivity of *ca.* 91:9. The 1,3-diol derivative 8 was again submitted to the same sequence of reactions to give the 1,3,5-triol system 9 (stereoselectivity of epoxidation ca. 95:5) which in principle could be homologated to the higher member of the series 1, 3, 5...(2n + 1) polyols by an iterative process.

Using the reductive epoxide ring opening of the intermediate hydroxyepoxides with Red-Al the sequence leads then to polyols 10 and 11. On the other hand, since

the Sharpless asymmetric epoxidation provides either of the two enantiomers, the method is highly flexible and any desired stereochemical combination can in principle be achieved.



R^1 = $SiBu^tPh_2$, R2 = $SiBu^tMe_2$.

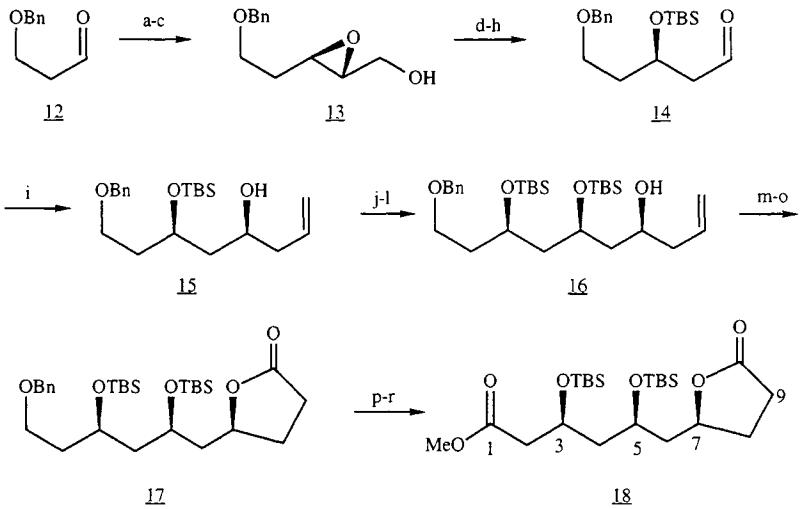
Reagents: a) 1.1 equiv. Bu^tOOH, 2.2 equiv. $Ti(OPr^i)_4$, 1.1. equiv. (-)-diethyl tartrate, CH_2Cl_2, -23 °C; b) 1.5 equiv. $(COCl)_2$, 2.0 eq. DMSO, 5.0 equiv. Et_3N, CH_2Cl_2, -78 °C to 25 °C; 1.1 equiv. $Ph_3P{=}CHCO_2Me$, PhH, 25 °C; c) 6.0 equiv. DIBAL, CH_2Cl_2, -78 °C; 1.1 equiv. Bu^tCOCl, 4.0 equiv. pyridine, CH_2Cl_2, 25 °C; 1.2 equiv. Bu^tPh_2SiCl, 4.0 equiv. imidazole, 25 °C; 2.5 equiv. DIBAL, CH_2Cl_2, -78 °C; d) as for c) except Bu^tPh_2SiCl is replaced by Bu^tMe_2SiCl; e) as for c) but first part of sequence only; f) 1.1 equiv. Red-Al, THF, 0-25 °C.

Scheme 13.5.1

13.5.2. Synthesis and stereochemical assignment of the C(1)-C(10) fragment of nystatin A_1.

Following an almost identical methodology, Nicolaou has synthesised the *(3S, 5S, 7S)*-lactone 18 corresponding to the C(1)-C(10) fragment of nystatin A_1 [5], which he had previously obtained by degradation from the natural antibiotic. However, the synthetic lactone (see below) exhibited opposite optical rotation to the one from natural nystatin A_1, which must therefore have the *(3R, 5R, 7R)* absolute configuration. The synthesis proceeded as depicted in Scheme 13.5.2.

The elaboration of 12 to the epoxy alcohol 13 was carried out using the Sharpless epoxidation procedure, in 77% overall yield and 91% e.e. Regioselective epoxide opening with Red-Al [6] led to the corresponding 1,3-diol in 95% yield, which was then elaborated to the aldehyde 14 as indicated in Scheme 13.4.2. Addition of allyl Brown reagent $Ipc_2BCH_2CH{=}CH_2$ (prepared from (-)-methoxydiisopinocampheylborane and $BrMgCH_2CH{=}CH_2$) [7], led to compound 15 in 92% yield and 83% d.e. Flash chromatography afforded the pure compound 15 from which the pure higher homologue 16 was prepared by: i) protection of the secondary hydroxyl group; ii) ozonolysis-Ph_3P; iii) reiteration of the Brown addition process and iv) chromatographic purification (88% overall yield). The conversion of compound 16 to the lactone 18 for direct comparison with the degradative material, required the following steps: i) temporary protection of the alcohol as ethoxyethyl ether; ii) hydroboration of the double bond with 9-BBN followed by basic hydrogen peroxide; iii) oxidation of the resulting alcohol with PCC with concomitant deprotection-cyclisation-oxidation to lactone 17 (44% overall yield); iv) hydrogenolysis of the benzyl ether and v) oxidation of the new alcohol to the lactone methyl ester 18 either through the aldehyde or directly (58% overall yield). The synthetic lactone showed an optical rotation of $[\alpha]_D^{21}$ + 27.9° (c 1.48, $CHCl_3$) opposite to the one of the lactone from natural nystatin A_1. The CD spectra of the two samples also showed opposite Cotton effects indicating their enantiomeric nature.



a) 1.0 equiv. $(EtO)_2P(O)CH_2COOEt$, $KOBu^t$, THF, -78 °C, 30 min, 91%; b) 2.5 equiv. DIBAL, PhMe, -78 -45 -0 °C, 2h, 95%; c) 0.12 equiv. L-(-)-diethyl tartrate, 0.10 equiv. $Ti(OPr^i)_4$, 2.0 equiv. Bu^tOOH, 20% wt 2A molecular sieve, 0.1M in CH_2Cl_2, -20 °C, 12h, 89%; d) 1.5 equiv. Red-Al, THF, -20 °C, 12 h, 95%; e) 1.1 equiv. Bu^tCOCl, pyridine, -20 °C, 10 min, 89%; f) 1.2 equiv. Bu^tMe_2SiCl, imidazole, DMAP, cat, DMF, 25 °C, 12 h, 98%; g) 2.5 equiv. DIBAL, THF-hexane, -78 °C, 1h, 96%; h) 1.1 equiv. $(COCl)_2$, 2.5 equiv. DMSO, 5.0 equiv. Et_3N, CH_2Cl_2, -78 - 0 °C, 1h, 98%; i) 1.1 equiv. $Ipc_2BCH_2CH{=}CH_2$, Et_2O, -78 -25 °C, 2h; 30% H_2O_2-3N-NaOH, 50 °C, 2h, 92%; j) same as f, 98%; k) O_3, CH_2Cl_2-MeOH (100:1), -78 °C; 2.0 equiv. Ph_3P, 25 °C, 2h, 94%; l) same as i), 95%; m) 1.2 equiv. $CH_2{=}CHOCH_2CH_3$, PPTS, cat., CH_2Cl_2, 25 °C, 30 min, 71%; n) 1.5 equiv. 9-BBN, THF, 0 - 25 °C, 3h, 92%; o) 5.0 equiv. PCC, 4A molecular sieve, 25 °C, 1h, 68%; p) H_2, $Pd(OH)_2$, cat., THF, 25 °C, 3h, 94%; q) 4.0 equiv. PDC, 4A molecular sieve, CH_2Cl_2, 25 °C, 1.5h, 78%; r) 6.0 equiv. PDC, 6.0 equiv. MeOH, DMF, 25 °C, 24h, 78%.

Scheme 13.5.2

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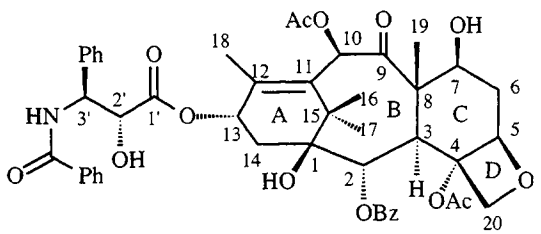
13.6. TAXOL



1

Taxol 1 is a naturally occurring substance isolated from the Pacific yew tree (*Taxus brevifolia*), which has been approved for clinical treatment of cancer patients. Taxol enhances polymerization of tubulin and the consequent formation of stable microtubules, inhibiting cellular mitosis.

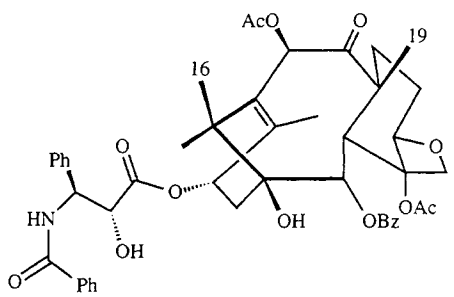
The semisynthesis of taxol [1], as well as the synthesis of taxoid model systems have been the focus of extensive research efforts in many laboratories, all over the world, which have greatly simplified the total synthesis of taxol itself. An excellent review by Nicolaou *et al.* has recently been published in *Angewandte Chemie* [2].

We will deal here only with the total syntheses described, independently, by Nicolaou [3] and Holton [4], and their associates, at the beginning of 1994.

13.6.1. Structural features of taxol.

The basic structure of taxol is that of a tetracyclic compound -A, B, C and D rings-, in which the central B ring is an eight-membered carbocycle. In principle, the formation of this medium sized ring appears somewhat problematic because of both entropic and enthalpic factors.

Some complicating features are: i) the geminal dimethyl group, which projects inside of the B ring and would increase the normally high transannular strain of 8-membered rings; ii) a bridge linking the A and B rings, and iii) a double bond at the bridgehead, which clearly violates Bredt's rule. However, Dreiding molecular models (see Fig. 13.6.1) show that an almost free strain conformation exists which minimises the interaction between the 16-CH_3 and the 19-CH_3 groups.



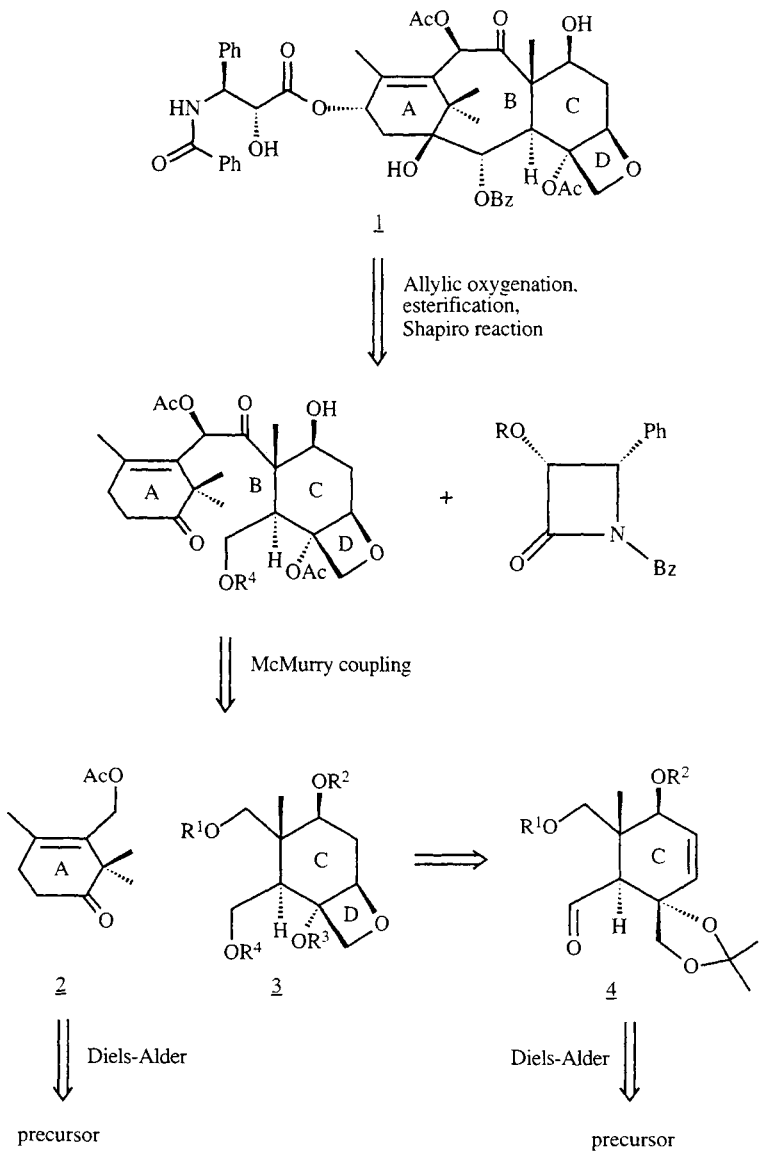
Conformation and configuration of rings			
A	B	C	D
Twist (skew) boat	boat-chair	chair	almost planar
A/B C_1-bridge	B/C trans	C/D cis	

Fig.13.6.1

MM calculations are in agreement with the boat-chair conformation of C_s symmetry being slightly more stable than the crown conformation [5].

13.6.2. Nicolaou's total synthesis of taxol

The strategy followed by Nicolaou and his group for the total synthesis of taxol was based on a retrosynthetic analysis already devised by the author in 1992 [6], which implies a convergent synthesis (Scheme 13.6.1).



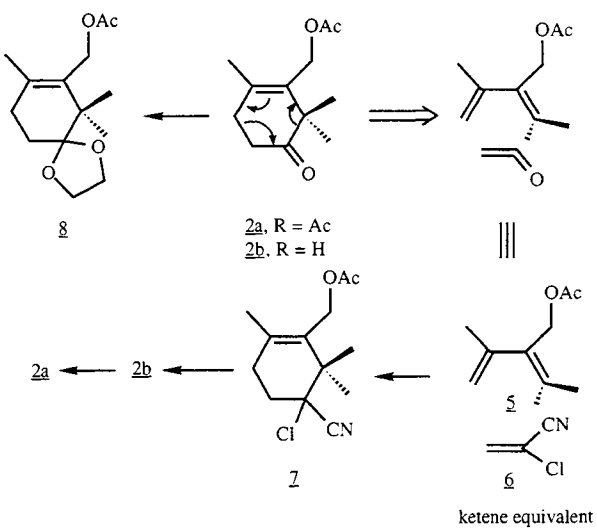
Scheme 13.6.1

It must be noted that the retrosynthetic analysis outlined in Scheme 13.6.1 is a rather atypical one in the sense that involves splitting of an 8-membered ring which is not a synthetically significant ring. However, some sort of "potential pseudosymmetry" present in taxol molecule justifies the disconnection of the 8-membered ring, leading to two quasi-equivalent synthons: the highly functionalised cyclohexenes 2 and 4, which are the A and C rings of taxol, respectively.

The intermediates 2 and 4 can then be traced back to simple precursors *via* retro-Diels-Alder condensations, which are very well known stereospecific pericyclic reactions.

A total synthesis following this route would be highly convergent bearing all the advantages that this type of synthesis offers. One could expect, therefore, that a short and efficient, as well as stereocontrolled, synthesis of taxol could be worked up starting from simple precursors.

A) Synthesis of A ring system: Retrosynthetic analysis of cyclohexanone 2a leads to diene 5 and 2-chloroacrylonitrile 6 as a ketene equivalent (Scheme 13.6.2) as the starting materials.

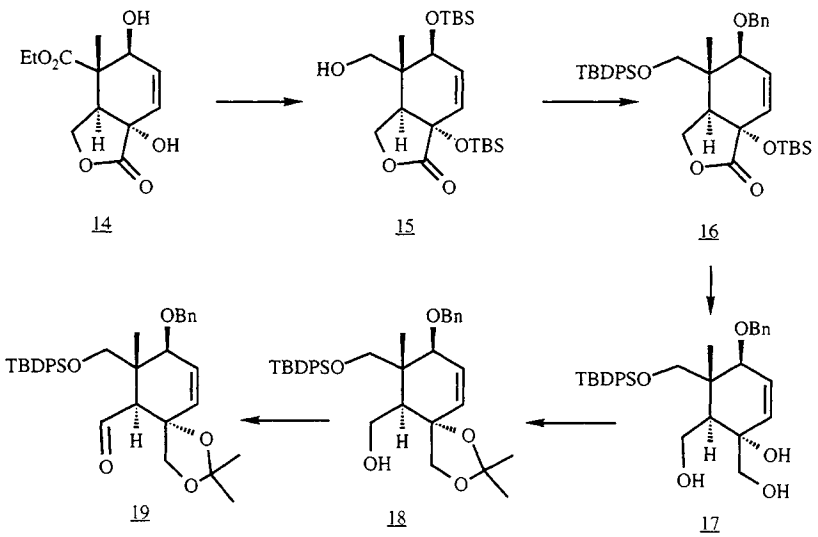


Scheme 13.6.2

In the synthetic way, heating reagents 5 and 6 at 135 °C for 96 h in a sealed tube afforded adduct 7 in 85% yield, which was hydrolysed under basic conditions by acetate to give the corresponding hydroxy ketone 2b (90% yield based in 70%

conversion). After reacetylation under standard conditions (2b ⟶ 2a) in 98% yield, the ketone was converted to acetal 8 in 92% yield and then to the tosylhydrazone 9 (see Scheme 13.6.4).

B) Synthesis of C ring: Scheme 13.6.3 shows the synthesis of aldehyde 19, which contains the required C ring of taxol, from the previously reported intermediate 14.[44]



Scheme 13.6.3

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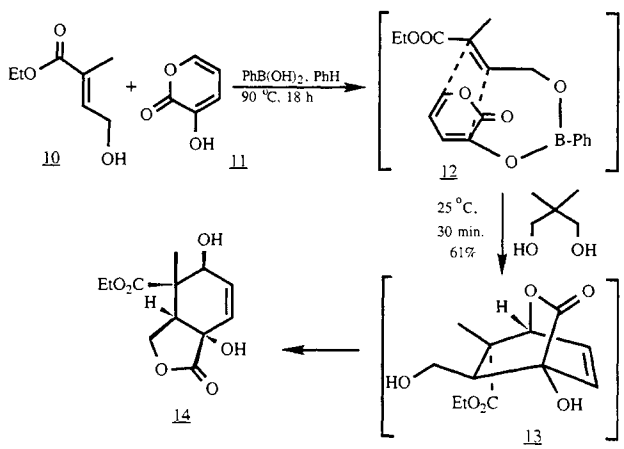
[44] The intermediate 14 was prepared by an "intramolecular Narasaka type Diels-Alder reaction" of dienophile 10 and 3-hydroxy-2-pyrone (11) in the presence of phenylboronic acid [7]:



Protection of the allylic secondary and tertiary hydroxyl groups in 14 with Bu^tMe_2SiOTf, in the presence of 2,6-lutidine and a trace of 4-DMAP in CH_2Cl_2, followed by selective reduction of the ester group with $LiAlH_4$ at 0 °C, afforded primary alcohol 15 in 94% yield. Acid-catalysed deprotection of the primary and secondary alcohols proceeded in a highly selective manner to give the corresponding diol (90% yield), which was then selectively protected with Bu^tPh_2SiCl (in the presence of imidazole, in DMF) at the primary functional group and with a benzyl group at the secondary one to afford compound 16 (80% overall yield).

Reductive γ-lactone ring opening, with concomitant desilylation at the tertiary position by $LiAlH_4$, gave triol 17 in 80% yield. Finally, acetonide formation followed by oxidation with tetra-n-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide oxidation, led to the target aldehyde 19 in 80% overall yield.

C) Coupling of intermediates 9 *and* 19 *(*A *and* C *rings)*: Scheme 13.6.4 summarises the coupling of intermediates 9 and 19, which afforded, after elaboration of the resulting product, the tricyclic system 24. The coupling took place according to a Shapiro reaction [8] (a variation of the classical Bamford-Stevens Reaction [9]), using n-BuLi in THF at -78 °C, to give a single diastereomer of hydroxy compound 20 in 82% yield.

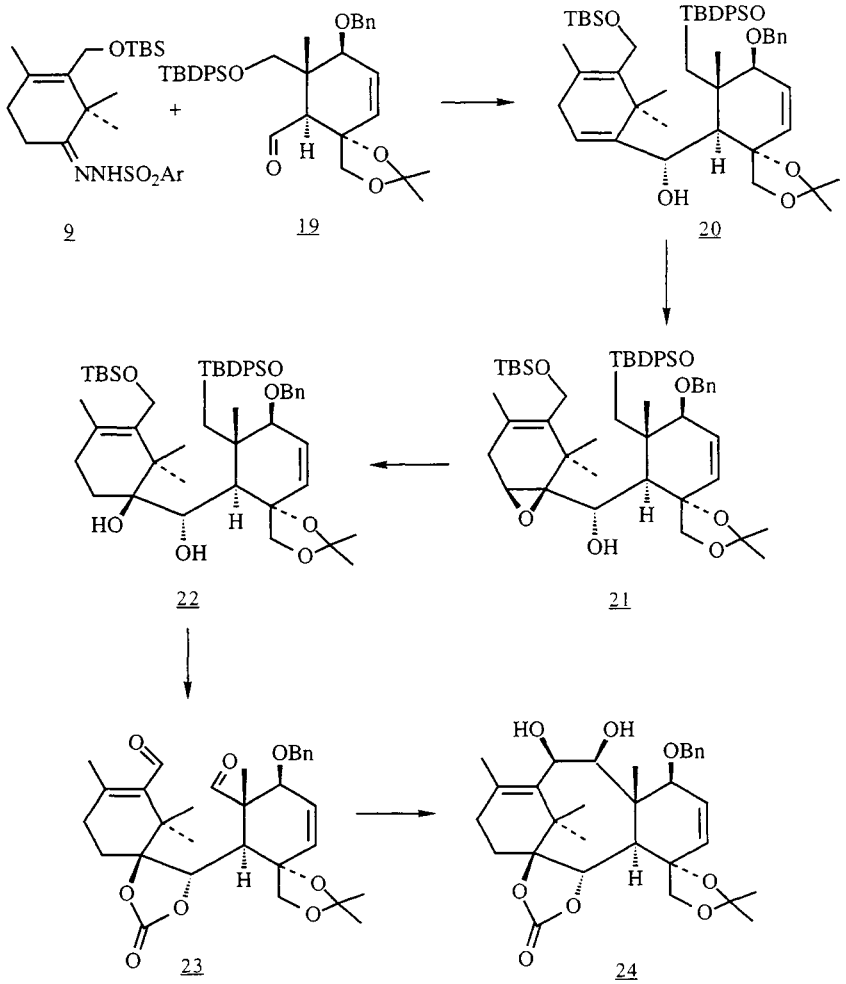
Direct epoxidation of compound 20 with Bu^tOOH in the presence of $VO(acac)_2$ [10], proceeded chemoselectively to give the epoxide 21 which was regioselectively opened with $LiAlH_4$ to afford the 1,2-diol 22 (76%). X-ray diffraction analysis of this compound confirmed the assigned stereochemistry for intermediates 20-22.

D) Synthesis of ABC ring system: In order to prepare the molecule for closure of the 8-membered B ring, diol 22 was converted to its cyclic carbonate by treatment with phosgene in the presence of KH.

After desilylation with tetra-n-butylammonium fluoride and oxidation with tetra-n-propylammonium perruthenate the dialdehyde 23 was obtained in 32% overall yield.

The cyclic carbonate in compound 23 plays the role of a rigid auxiliary ring which facilitate the ring closure of the preorganised dialdehyde 23 by a McMurry type cyclisation [11] to afford the taxoid ABC ring system 24 in 23% yield, the

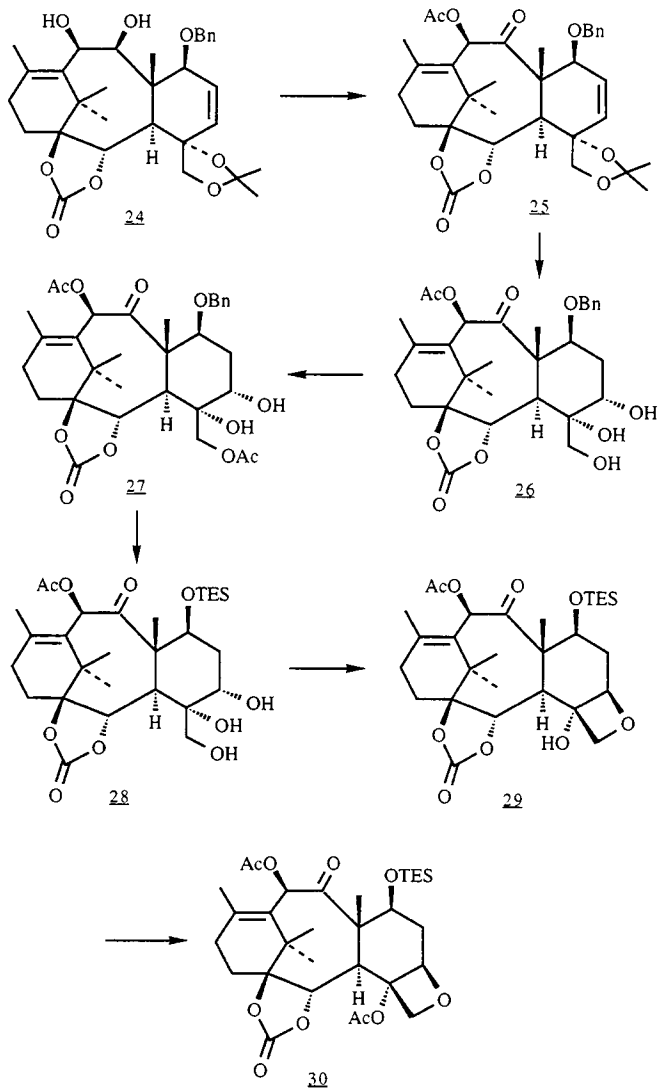
stereochemistry of the newly formed centres being assigned by X-ray diffraction analysis.



Scheme 13.6.4

The next important steps to the key intermediate 30 are outlined in Scheme 13.6.5. Monoacetylation of 24 followed by oxidation with tetra-n-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide, afforded regioselectively in 88% overall yield, ketoacetate 25.[45]

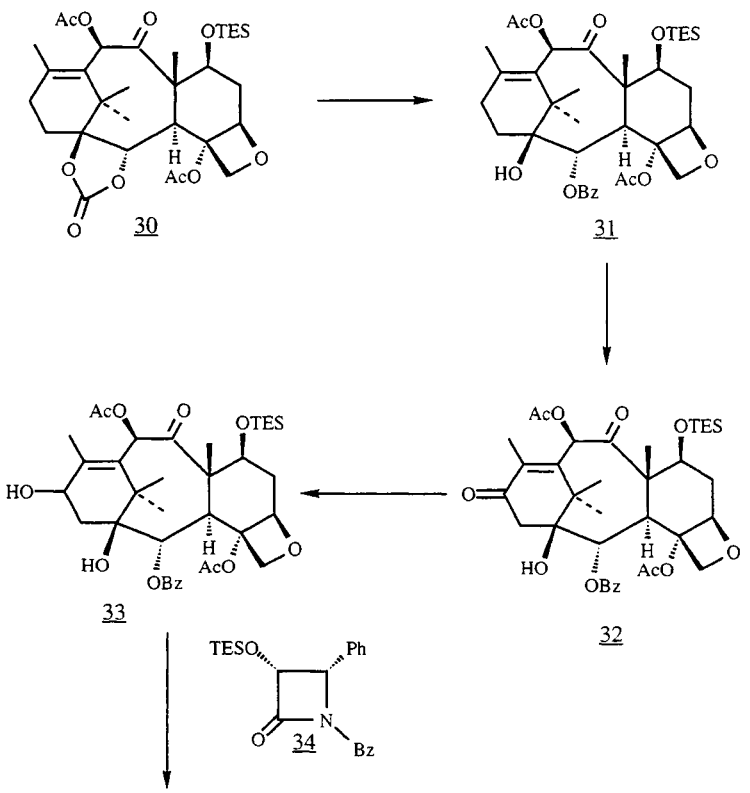
[45] The stereochemistry of the acetate group at C(10) was confirmed by X-ray diffraction analysis of the corresponding benzoate.



Scheme 13.6.5

Hydroboration of compound 25 and working up of the mixture obtained after hydrogen peroxide treatment, led to a 3:1 mixture of two regioisomeric alcohols (55%). Acid-catalysed removal of the acetonide group and chromatographic separation furnished the triol 26 as the major product (33% yield from 25). Chemoselective acetylation of the primary hydroxyl group gave 27 in 95% yield, which was converted to compound 28 by substitution of the benzyl group by a

triethylsilyl group (TES) and monodeacetylation under basic conditions.[46] The oxetane ring was finally formed by sequential monosilylation with TMSCl (primary OH), triflate formation (secondary OH) and mild acid treatment to give 29. Acetylation of the remaining tertiary OH afforded the key intermediate 30 in 38% overall yield [12]. Racemic 30 resulting from this synthetic sequence was identical in all respects with an authentic sample generated from natural taxol. Synthetic optically active 30 was obtained by the same route using enantiomerically pure diol 24 by resolution with 1(*S*)-(-)-camphanic chloride.



TAXOL 1 (87%; 90% conversion)

Scheme 13.6.6

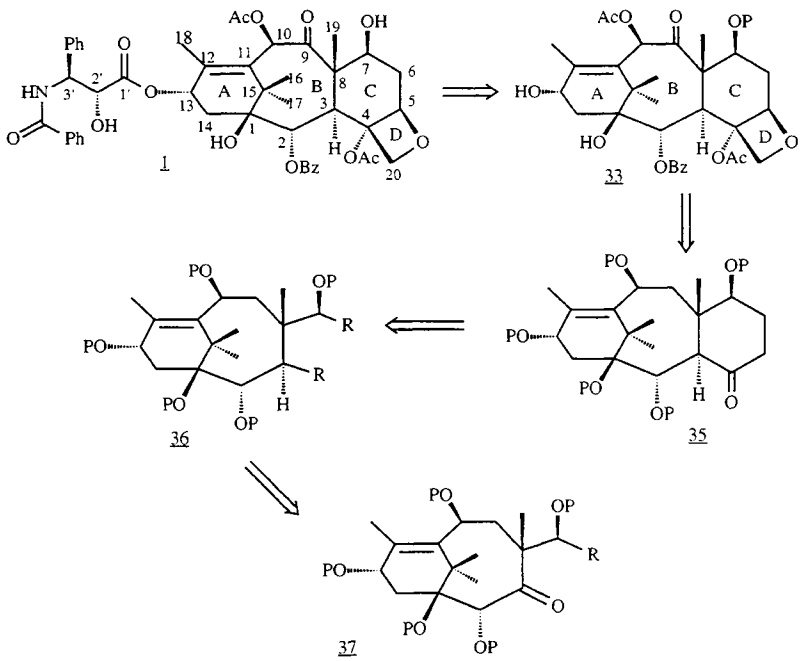
[46] The reasons for exchanging the protecting groups arose in later steps of the synthesis.

E) Total synthesis of taxol: The last steps of the synthesis from 30 involve (Scheme 13.6.6) [13]: 1) regioselective opening of the carbonate ring by excess PhLi at -78 °C, to afford the desired hydroxybenzoate 31 (80%); 2) allylic oxidation by PCC-NaOAc in benzene, to introduce the carbonyl group at C(13) with $NaBH_4$-MeOH (75%); 3) stereoselective reduction of the carbonyl group to the corresponding hydroxyl group at C(13) (83%); 4) sodium alcoholate formation by treatment with $NaN(SiMe_3)_2$ and then Ojima's β-lactam 34 [14] to introduce the side chain, followed by alcohol deprotection with HF-pyridine (87% yield, based on 90% conversion).

Synthetic taxol was found to be identical in all respects with natural taxol, including spectroscopic characteristics (IR, NMR, MS, optical rotation) and biological activity (microtubule stabilisation and cytotoxicity against Molt-4 leukaemia cells).

13.6.3. Holton's total synthesis of taxol

The total synthesis of taxol (1) by Holton and his associates [4] is based in the retrosynthetic analysis outlined in Scheme 13.6.7.

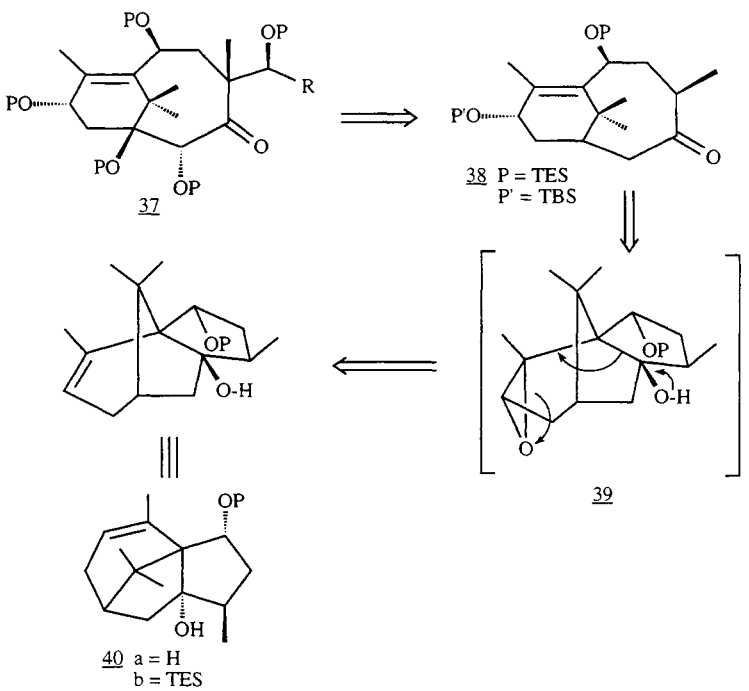


Scheme 13.6.7

In contrast to Nicolaou's synthetic plan, the retrosynthetic analysis of Holton's approach preserves the non-synthetically significant B ring and proceeds through disconnection of bonds which are involved in the D and C rings, to arrive finally to the bicyclo[5.3.1]undecane derivative 37, as the starting material.

Previous work by Holton [15] on the synthesis of taxane ring systems, indicated that the preparation of the bicyclo[5.3.1]undecane skeleton lies basically on the work of Büchi on patchouli alcohol [16], which led him to the development of the so-called "epoxy alcohol fragmentation" [15a].

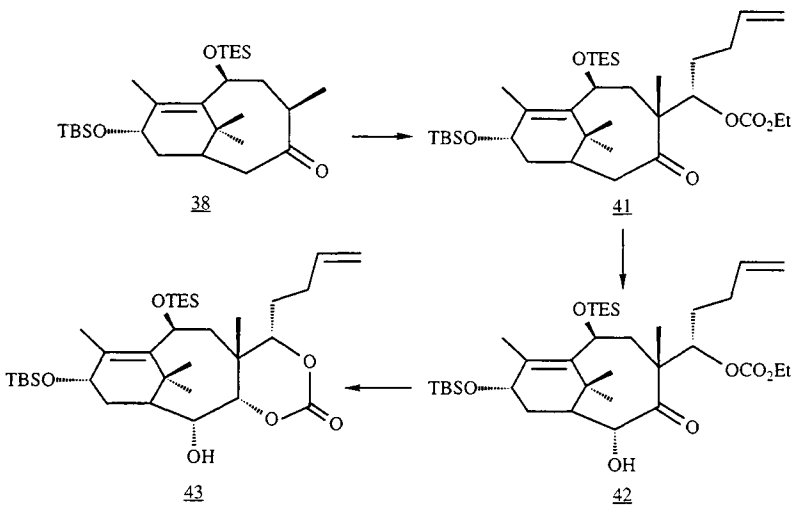
Scheme 13.6.8 shows how compound 38, which has the basic bicyclo[5.3.1]undecane ring system of taxol, can be prepared by this procedure from a taxusin intermediate readily available from camphor in either enantiomeric form [15b]. Compare the structure of 40 with α-patchoulene 5, in Scheme 1.1 (pag. 10).



Scheme 13.6.8

In order to proceed according the outlined synthetic plan, a C(10)-α silyloxy substituent was used in the ketone 38 as a conformational control element which

ensures the deprotonation at C(8)[47] and the subsequent aldol condensation (Scheme 13.6.9). Therefore, silylation (TESCl, pyridine) of 40a gave 40b, which then underwent epoxy alcohol fragmentation (see 39) and protection at C(13) to give 38 in 93% overall yield.



Scheme 13.6.9

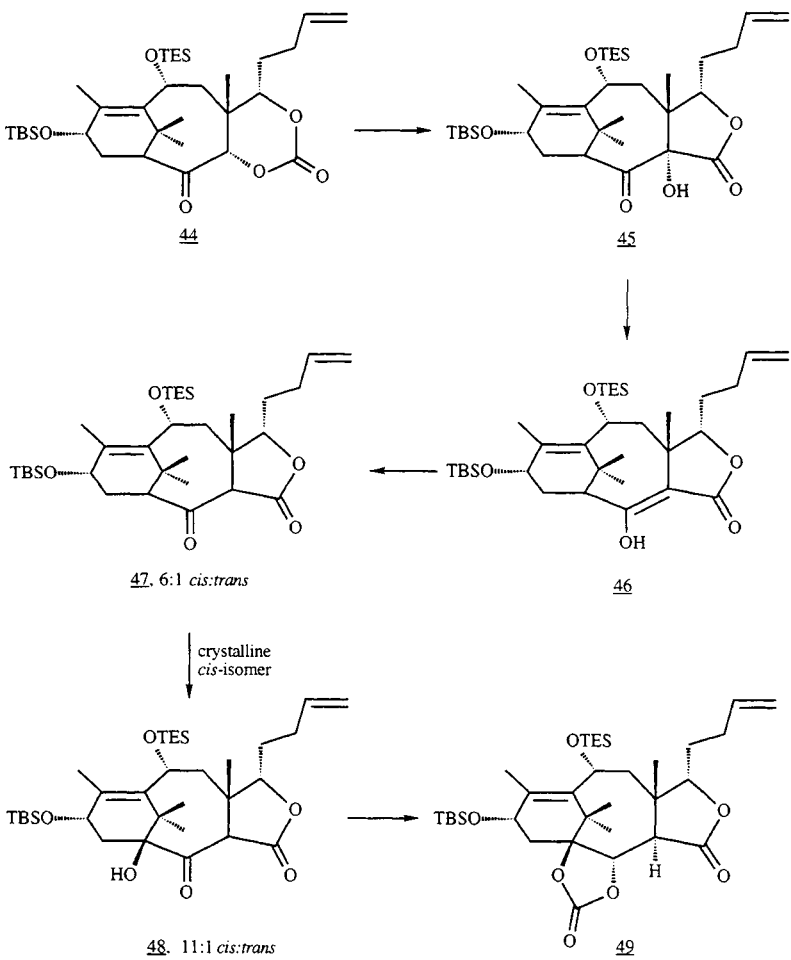
The following steps in this synthesis are shown in Scheme 13.6.9. Magnesium enolate of ketone 38 ($HNPr^i_2$, THF, MeMgBr, 23 °C, 3h, then 38, 1.5 h) was condensed with 4-pentenal and the crude reaction product directly protected with Cl_2CO in pyridine/CH_2Cl_2/EtOH, to give the ethyl carbonate 41 in 75% yield. Hydroxylation at C(2) (41, LDA,THF, 1.0 molar equiv. of (+)-camphorsulfonyl oxaziridine) [17] afforded the hydroxy ketone 42, in 85% yield. Reduction of the carbonyl group with Red-Al, in toluene at -78 °C, gave a triol which, without isolation, was transformed to carbonate 43 in 97% yield (Cl_2CO, in pyridine/CH_2Cl_2, at -78 to 25 °C).

At this stage of the synthesis, it was necessary to resort to a second conformational control element (shifting the B ring from a chair-chair to a boat-chair conformation), which ensures the generation of the C(1)-C(2) enolate of a C(2) ketone and allows the epimerisation of the substituent at C(3)α (which will return the B ring to the chair-chair conformation).

---

[47] For complete conformational studies of this intermediate see the original paper, ref. 15a.

Thus, 43 was submitted to Swern oxidation to give the C(2) ketone 44, in 95% yield (Scheme 13.6.10), which was treated with LTMP at -25 °C to afford hydroxy lactone 45, through a process similar to Chan rearrangement [18]. Removal of the C(3)α hydroxyl group by samarium diiodide reduction led to the stable enol 46, which, upon treatment with silica gel, afforded a 6:1 mixture of *cis*- and *trans*-fused lactones 47. The *cis*-fused lactone 47 could be separated by crystallisation and the *trans*-isomer was recycled through the enolate and quenching with acetic acid, the overall yield of 47-*cis* being higher than 90%. Treatment of 47-*cis* with 4 molar equiv. of LTMP at -10 °C followed by addition of (±)-camphorsulfonyl oxaziridine to the enolate at -40 °C gave 88% yield of 48-*cis*, along with 8% of 48-*trans*.



Scheme 13.6.10

As Holton and his associates emphasise, it is quite remarkable that *deprotonation of* 47*-cis with LTMP apparently occurs first, and perhaps only, at C(1)*, even though the C(3) proton should be expected to be much more acidic. Reduction of 48*-cis* with Red-Al (THF, at -78 °C, 1.5 h), followed by basic workup gave C(2)α-hydroxy *trans*-fused lactone (88%), which was treated with phosgene (10 equiv., pyridine, CH_2Cl_2, -23 °C, 0.5 h) to give quantitatively the carbonate 49.

As outlined along the Schemes 13.6.8 to 13.6.10, 40a can be converted to lactone carbonate 49 in 12 steps in 40% overall yield.

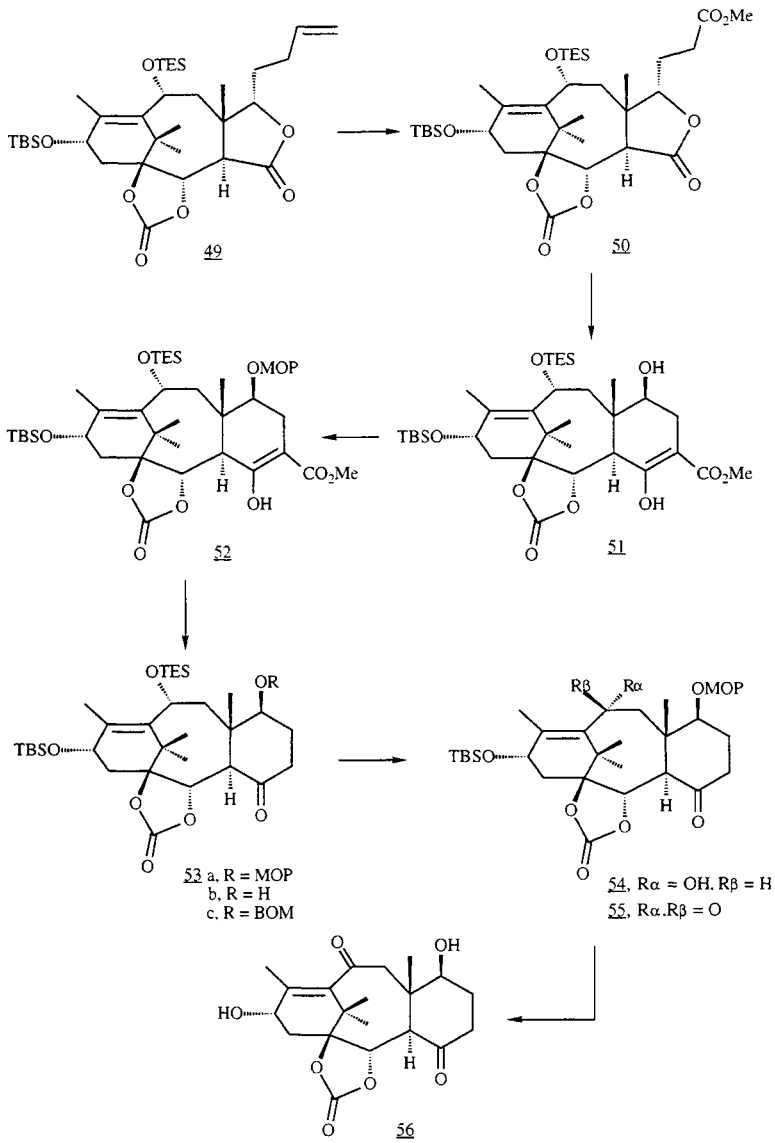
Conversion of 49 to taxol requires: i) completion of C ring; ii) introduction of D ring and iii) oxidation at C(9) along with adjustment of the C(9), C(10) regio- and stereochemistry (Scheme 13.6.11).

Oxidative cleavage of the terminal double bond of 49 by ozonolysis to the aldehyde followed by permanganate oxidation to the acid and esterification with diazomethane produced the methyl ester 50. Dieckmann cyclisation of 50, following the procedure developed in Holton's laboratory (LDA, THF, -78 °C, 0.5 h, then HOAc, THF), gave the enol ester 51 in 93% yield (90% conversion). Decarbomethoxylation of 51 was carried out by temporarily protection of the secondary alcohol (*p*-TsOH, 2-methoxypropene, 100%), and heating the resulting compound 52 with PhSK in DMF, at 86 °C (3 h) to provide 53a or, after an acidic workup, the hydroxy ketone 53b, 92% yield.

Unambigous structural confirmation was obtained by converting 53a to diol carbonate 56, which was independently synthesised from baccatin III. Selective deprotection of 53a with TBAF gave alcohol 54, which was oxidised with tetra-n-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide (CH_2Cl_2, molecular sieves, 25 °C, 1.5 h) to ketone 55 in 86% overall yield from 53a. Deprotection (HF, pyridine, CH_3CN, 96%) of 55 gave diol carbonate 56, identical to the compound prepared from baccatin III.

With the structure of 53a securely stablished, the synthesis of taxol proceeded as outlined in Scheme 13.6.12.

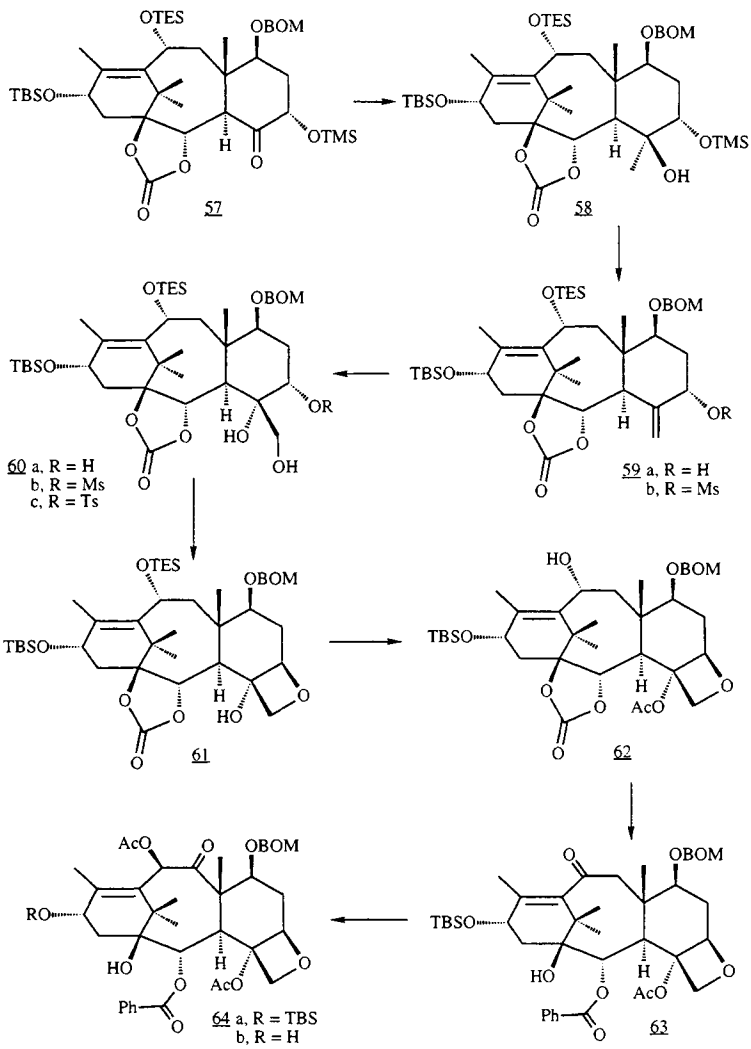
In order to built up the oxetane D ring, a bulky protecting group at C(7) which would survive the remainder of the synthesis and assure the β configuration of the substituents was necessary. Thus, 53b reacted with BOM chloride (EtN^iPr_2, CH_2Cl_2, Bu_4NI, reflux, 32 h) to give 53c in 92% yield.



Scheme 13.6.11

Next, the TMS enol ether of 53c underwent oxidation with MCPBA to trimethylsilyloxy ketone 57 in 86% yield (86% conversion). Addition of methylmagnesium bromide in methylene chloride proceeded in almost quantitative yield (95%) to give tertiary alcohol 58. Dehydration with Burgess' reagent [19] and acidic workup provided the allylic alcohol 59a in 63% yield, which was converted

to oxetane 61 through either mesylate 60b or tosylate 60c, via osmylation of 59b, and temporary protection of the C(20) hydroxyl group. Cyclisation to oxetanol 61 (DBU, pyridine, DMAP, 24 h, 25 °C) took place in 80-85% yield [20]. Acetylation of oxetanol 61 and removal of the C(10) TES protecting group gave 62 in 70-75% yield. Addition of phenyllithium to 62 afforded the C(2) benzoate, which was treated with tetra-n-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide (CH_2Cl_2, molecular sieves, 25 °C, 1.5 h) to give ketone 63 in 85% yield.



Scheme 13.6.12

A THF solution of the enolate of ketone 63 (4 equiv. $KOBu^t$, THF, -78-0 °C, 0.5 h) was added to a suspension of benzeneseleninic anhydride (8 equiv., THF, 0 °C, 40 min), and the product was directly treated with further $KOBu^t$ and acetylated providing 7-BOM-13-TBS baccatin III (64a) quantitatively.

The last steps of the synthesis involved: i) removal of the TBS group with TASF [21], to give 7-BOM baccatin III (64b); ii) reaction of the corresponding lithium alkoxide with β-lactam 34 from Scheme 13.6.6; iii) desilylation of the resulting product and iv) removal of the C(7) BOM group by hydrogenolysis (H_2, Pd/C, EtOH, reflux, 1h) to give taxol in 93% yield from 64b. The synthesis produces (-)-taxol from (-)-borneol and *ent*-(+)-taxol from (-)-patchino. The overall yield from 40a is *ca.* 4-5%.

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PART B. COMPUTER-ASSISTED ORGANIC SYNTHESIS

14. COMPUTERS, COMPUTATION, COMPUTERISATION AND ARTIFICIAL INTELLIGENCE. THE "EXPLORATION TREE"

Digital "computers" were originally devised as powerful "calculating machines" to perform complicated numerical calculations (or *computations*) in the same way that the analog "slide rule" had been used until then to carry out simpler calculations. Accordingly, computers found their first applications mainly in theoretical quantum chemistry, as well as in statistical analysis, chemical engineering calculations (design of reactors and heat-exchangers), X-ray crystallographic analysis, etc. Later on, computers also became useful tools for ordering,[48] storage and retrieval operations of large sets of data (information) and this initiated the rise of "Information Science". In 1964 *Chemical Abstracts* introduced the use of digital computers in order to handle the huge amount of chemical data with which they must continuously deal. Nowadays, there exist powerful informatic systems that allow the access to the chemical reactions published in the literature (ORAC [1], REACCS [2], SYNLYB [3], CASREACT [4], etc.)

Very soon, however, it was realised that "computers" could also perform some operations other than the simple *computation* and *ordering* of different kinds of data. Computers can in fact be considered as a "means of expression", i.e. as a device similar to "paper-and-pencil", which can be used for writing (either prose or poetry, science or arts, words or mathematical formulae), drawing, memorising, designing and playing. "Computerisation", in contrast with "computation", is being used wherever computers are used for such purposes. A further step, which was however felt at a rather early stage, is the simulation of some human faculties related to intelligence, as decision-making processes and deductive thought, which led to studies into a direction presently known as "artificial intelligence" (A.I).

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[48] In French and Spanish computers are known, respectively, as "ordinateurs" and "ordenadores", from Latin *ordo, ordinem.*

The question of how to explore in an optimal form a great number of possible actions (decisions) directed to the achievement of a given objective is a theme frequently posed in A.I [5]. In general, every adopted decision opens several new possibilities, in such a manner, that in planning a succession of possible actions a dendritic or tree-like branched structure results: it is the so-called "exploration tree". Considering the game of chess, for instance, from a given situation ("starting state") a series of intermediate states must be explored which will lead to a series of final states (or results) (Diagram 14.1, left side).

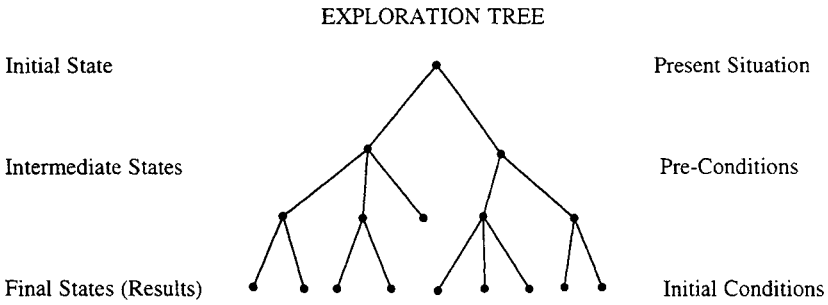

Diagram 14.1

In order to achieve the mate, a quantitative evaluation of every possible intermediate state is also necessary. This is done by assigning different values for the menace to and/or the capture of the different pieces. However, the most important aspect to be emphasised here is that the exploration of all possible intermediate states from the first move down to the last move (checkmate) would represent an arduous and practically impossible task even for a big computer. S. Turner [6], who has also referred to chess in the context of organic synthesis, has emphasised the fact that at the end of the first move the total number of possible options is already 400. Then the number of possible moves grows exponentially, so that the amount of information to be held and processed is beyond the capability of any computer. Yet, as stated by Turner, very small computers play chess reasonably well. In fact, any chess program incorporates some *heuristic principles* or *strategies* which allow the "exploration tree" to be pruned and to make the problem more manageable and workable for a computer. These heuristic strategies are familiar to any fairly good chess player and refer, for instance, to occupying the centre of the board because there the piece can attack more squares than at the edge

or to moving those pieces, such as knights and bishops, which are more powerful than pawns, or the necessary cooperation of different pieces to attack some point of weakness in the oponent's defence, etc.

Let us consider now the problem of how a given "situation" (which may be in principle a social, political, psychological or simply a material "situation") has been attained (Diagram 14.1, right side). A series of possible "pre-conditions" (or "pre-situations") resulting from some "initial conditions" (or "initial situations") must be explored and the result is again an "exploration tree" (but now extending from *the-present-to-the-past*, rather than from *the-present-to-the-future* as in the game of chess). If the given "situation" is the molecular structure of a natural product, for instance, it is clear then that the "exploration tree" is in fact what we have called before (*Heading 3.1*) the "synthesis tree" (Diagram 14.2). Therefore, the design of syntheses is just a particular case of the more general problem with which "artificial intelligence" is continuously faced. And, as in the game of chess, it is possible to write programs for digital computers in which some *heuristic principles* governing the retrosynthetic analysis, as well as the evaluation of all the possible "decisions" may be incorporated. The first programs for computer-assisted organic synthesis (or, more properly, computer-assisted synthetic analysis) appeared in the late sixties.

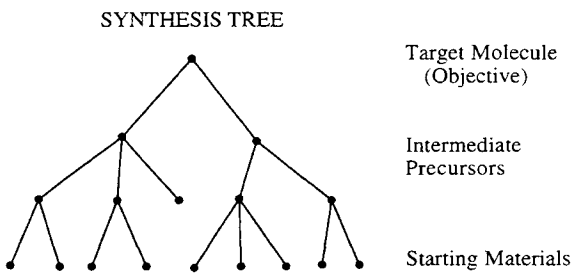

Diagram 14.2

14.1. Software available for computer-assisted organic synthesis

In 1969 Corey and Wipke [7] reported the program OCSS (Organic Chemical Simulation of Synthesis) which was the precursor of one of the most powerful programs known at present which has been named LHASA (the acronym of Logic and Heuristics Applied to Synthetic Analysis) [5b] [8]. Since then, different

programs for designing organic synthesis have been reported in the chemical literature [2] [9] which, according to I. Ugi [10], may be classified into two main groups: i) logic-oriented programs (such as EROS [10], IGOR [11], "Synthon Model" [12], SYNGEN [13] [14] and TOSCA [15]), and ii) information-oriented programs (such as LHASA [8b], SECS [16], SYNCHEM [17], MARSEIL/SOS [18], etc.). In practice however, as has already been stated, some "heuristic principles" must usually be implemented in order to "prune" the synthesis tree and make the programs really useful. Besides this, they may also be classified as interactive or non-interactive programs, depending upon whether the operator may or may not interact with them and thus have the opportunity of modifying or redirecting the course of the retrosynthetic analysis.

However, all the programs have a similar "structure" (except perhaps some of the logic-oriented programs, such as EROS and IGOR. See Appendix B-1), and must carry out a series of different "jobs" (or "tasks") which are performed by a definite part of the program, which we will call "modules". In the first place, one needs to introduce the target molecule, a task which is performed by the "graphic module". Although the user draws the molecule in the language familiar to the organic chemist -i.e., according to the principles of the "Classical Structural Theory"- the information is stored in the form of tables and matrices, which are "understandable" for the computer. All the significant structural features are then perceived by the "perception module". From this information, the "automatic processing module" of the program generates in the retrosynthetic direction a limited set of "intermediate precursors" which can be transformed into the target molecule in one step. Since these intermediate precursors will not usually be commercially available compounds, they will be treated as new "target molecules" and a "synthesis tree" will be elaborated. An *ordinal* number is automatically assigned to each one of the structures: to the target molecule as well as to the corresponding intermediate precursors. The numbers constitute the "nodes" of the synthesis tree which can be activated by the cursor on the screen. Some programs -such as SYNGEN [13] [14], for instance- can generate automatically (non-interactive program) a whole synthesis tree, from the "target" to easily available "starting materials". The program finds whether or not the generated intermediates are good starting materials by comparing them with a list of "good starting materials" which are stored in a database. Once the "starting materials" match each other, the program automatically stops. Finally, the program offers either the complete "synthesis tree",

which may be explored in all directions (horizontally or by "families", and vertically or by "lineages"), or the complete synthetic sequences from a given starting material chosen in the "synthesis tree". This process may be represented by the following "flow diagram" or *ordinogram.*[49] (Diagram 14.3).

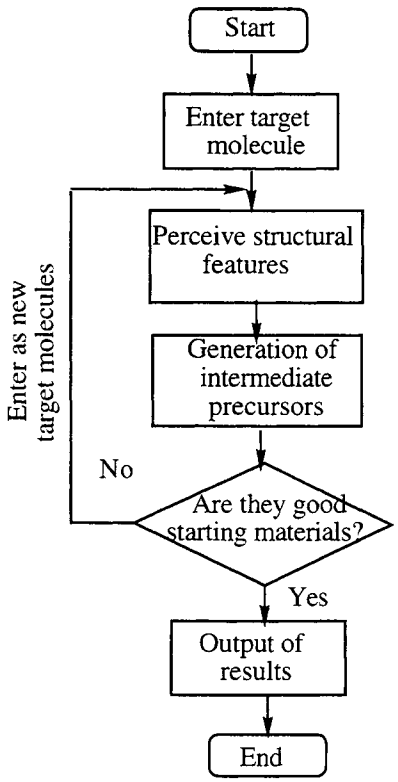

Diagram 14.3

Since there exist several recent accounts and reviews about the different programs (see references cited, specially [2]), in the next few pages we give a detailed description of our miniprograms CHAOS (Computerisation and Heuristics Applied to Organic Synthesis) and CHAOSBASE, copies of which are included in this book.

[49] See footnote 48.

14.2. CHAOS and CHAOSBASE, a heuristic aid for designing organic synthesis

14.2.1. CHAOS

The program CHAOS has been mainly developed as a didactic tool; i.e., as a heuristic aid for designing organic syntheses in such a manner that the student may use it, at his own pace, at different levels following the heuristic principles and methodologies developed in the present book. Two versions of CHAOS, one for IBM PCs (or "fully compatible" PCs) with Windows® 3.1 or later, and another one for Macintosh computers are available. A summary of some of the main improvements of the present versions follows:

1) Improved graphic interface.

2) Introduction of *sequences of disconnections* (see below).

3) Introduction of an *algorithm of unique numbering* [19] [20]. This algorithm avoids the presentation of repeated precursors to the user, and allows to find identical precursors in a synthesis tree.

4) Possibility of using *disconnections defined by the user* through the program CHAOSBASE.

5) Naming of the corresponding reaction in the synthetic direction, when the program performs a disconnection.

The "Instruction manuals" for the programs CHAOS and CHAOSBASE are included in Appendix B-2,[50] which is complemented by a list of the basic disconnections given in Appendix B-3.

14.2.2. Modules of the CHAOS program

Graphic module: The target molecule is introduced by drawing its structure on the screen with the aid of the "mouse" and the "facilities" incorporated in the module, such as ring templates, atoms other than carbon, atomic groups, etc. which are described in the manual. All the structural information is stored automatically in the program as "connectivity matrices" and "tables" (one for each atom) in which the nature of the atom and other characteristics are indicated.

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[50] A rather provisional and "crude" version 1.0 of CHAOS was already presented at the 7th IUPAC Conference on Organic Synthesis, held at Nancy (France) in July 4-7, 1988, and some copies of it were privately distributed. The more refined version 2.0 was included in the first edition of this book. The present versions 3.0 for Macintosh and 1.0 for PC with Windows® have been re-programmed *de novo* and include many improvements. To those who are familiar in writing computer programs the following words (stated in a quite different context) by one of the characters of Bertolt Brecht will make sense: "I'm hard at work preparing my next error".

Perception module: From this information the program *perceives* the pertinent structural features such as functional groups, bifunctional relationships, rings and synthetically significant rings, and on requirement the program can also perceive the core bonds, bridgeheads and strategic bonds (if any).

Automatic processing module: This module tries to apply to the target molecule a series of "transforms" or "disconnections" defined in the program (these transforms are listed in Appendix B-3). A "transform", for the CHAOS program, consists of the following information:

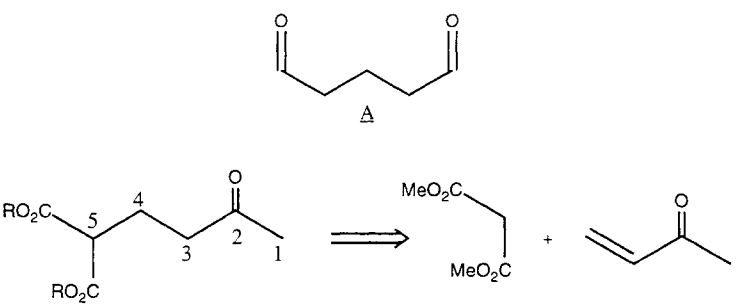
1) A "substructure" or "retron", that is to say, a group of atoms with a given connectivity and characteristics.

2) A "disconnection table" that is a series of instructions which indicate to the program how to treat the corresponding "substructure".

The program recognises the "retrons" or "substructures" within the target molecule, applies the corresponding "disconnection table" and then generates retrosynthetically the intermediate precursors. For instance, if the program recognises "substructure" A in the example below, the "disconnection table" will indicate:

-Break a bond between atoms 4 and 5
-Make a new bond between atoms 3 and 4

which corresponds to a "retro-Michael disconnection":



From now on, the terms "transform" or "disconnection" and "retron" or "substructure" will be used indistinctly.

Actually, the "substructures" and the "disconnection tables" are somewhat more complicated than what we have described here, but a detailed description is outside the scope of this book.

Although the philosophy of CHAOS is the classical one and very similar to that of other programs which work with a "database" (LHASA, SECS, MARSEIL, etc.), the difference lies in the fact that the "substructures" and the corresponding "disconnection tables" are not in a separate "database", but are an integral part of the program itself. This allows fast access to the necessary information. However, the major novelty of CHAOS is, perhaps, the way in which the "substructures" have been organised for access to them.

14.2.3. The "heuristic principles" as a guide to "disconnections"

Throughout the book we have been dealing with different "heuristic principles" (HPs). Some of these have been implemented into the program in order to guide it in the retrosynthetic analysis and in the concomitant generation of the intermediate precursors. However, because computers, in contrast to human minds, are far from being "intuitive", we have had to organise and classify these "heuristic principles" within the program in some arbitrary order.

The heuristic principles which have been implemented into the program are based in the fact that:

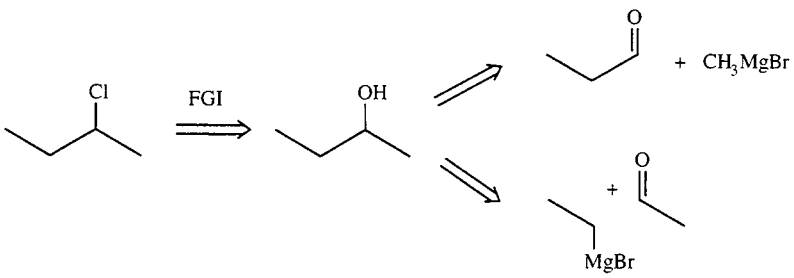
1) Some disconnections must have -in the retrosynthetic direction- high priority. For instance, the elimination (or modification) of protecting groups (especially hydrolytic cleavages) or particularly unstable functional groups.

2) Some disconnections, as for example, retro-annulations or cycloreversions, greatly simplify the molecular skeleton.

3) "Bifunctional relationships" allow most of the C-C disconnections.

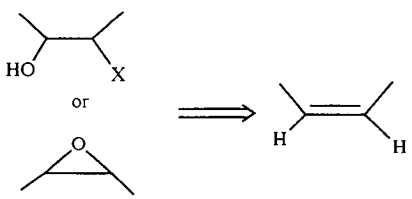
4) In the retrosynthetic direction, consonant relationships must be disconnected, in principle, *before* the dissonant ones (this means that in the actual synthesis the more difficult reactions leading to dissonant relationships must be attacked in the first place. It is always less painful to deal with failures in the first stages of a synthesis).

5) If the above considerations do not apply to some particular molecule, typical "monofunctional disconnections" or FGI should then be attempted, as for instance:



Keeping all these considerations in mind, the "disconnections" which the CHAOS program may perform have been classified into six different groups of decreasing priority:

1) PRELIMINARY, which eliminate (or modify) protecting groups or unstable goups. The hydrolytic cleavage of an acetal or an imino group, for instance, leaves the free carbonyl group which is much more versatile for proceeding to a variety of well known disconnections. This algorithm also modifies some 1,2-D systems and dissonant 3-membered rings:



2) MONOFUNCTIONAL, which allow disconnections or FGI of "isolated" functional groups (that is to say, a functional group which does not belong to a bifunctional relationship, from 1,2-D up to 1,6-D).

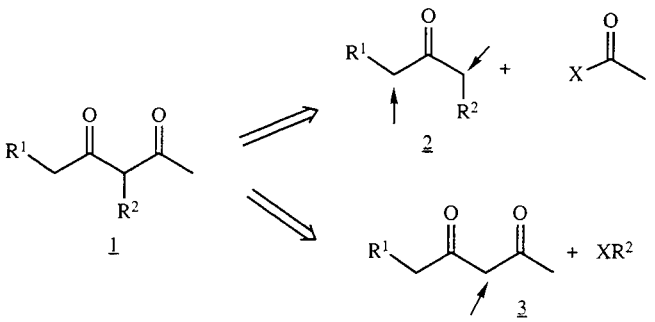
3) CONSONANT, which disconnect bifunctional consonant relationships (1,3-C and 1,5-C).

4) RINGS, which perform either retro-annulations or cycloreversions which greatly simplify the molecular complexity.

5) DISSONANT, which disconnect bifunctional dissonant relationships (1,2-D, 1,4-D and 1,6-D).

6) FINALS, which perform disconnections only if none of the above algorithms could be applied. This usually happens if only one functional group not included in group 2 is present: for instance, hydration of an isolated double bond. However, the consonant 1,3-dicarbonyl systems are also included in this group

because many of them are easily available starting materials, as for instance the malonic ester or the acetoacetic ester or simple derivatives of them. Let us consider a very simple example: the retrosynthetic analysis of compound 1.

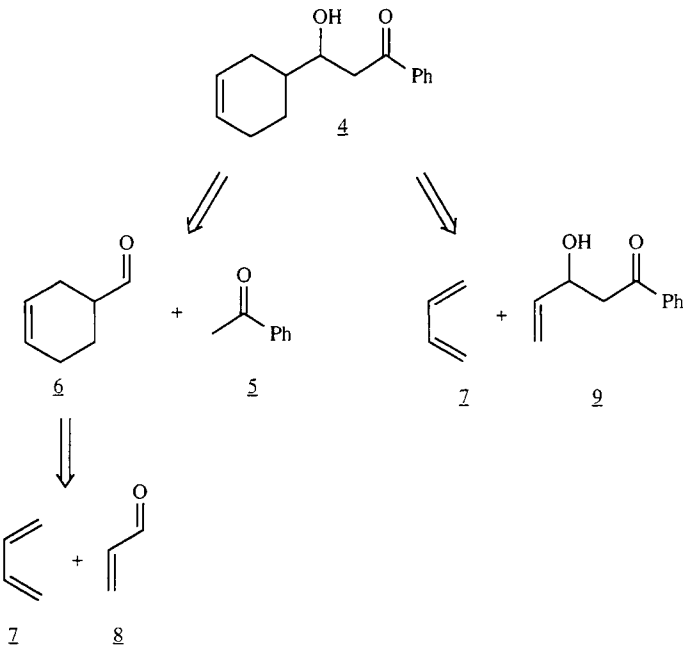


As shown, the disconnection of the consonant 1,3-dicarbonyl system present in 1 would lead to the precursor 2, the acylation of which would present problems of regioselectivity. However, disconnection of the alkyl group R^2 at the α-position of the carbonyl groups leads to precursor 3, the alkylation of which would not present any problem of regioselectivity.

As stated before, these six different groups operate according to a decreasing priority order. This means that the program attempts in the first place disconnections of group 1. If it succeeds, the program stops and shows the resulting fragments. If it fails, the program goes then to group 2 and so on. Therefore, in the first case the program does not explore the next group but it performs all the disconnections of group 1 and shows only those which have been successfully applied.

Although the way in which the groups are classified is subjective and arbitrary, it works reasonably well for a great number of molecules of moderate complexity. However, we realised very soon that some "flexibility" was also necessary in order to give more versatility to the program and improve its scope and efficiency. Accordingly, we introduced an option which allows the chemist to interact with the program and "control" the disconnections by changing the pre-defined (or default) order. This may have two different consequences: on one hand, it may just change the order of the disconnections (or reactions in the synthetic direction) without introducing new ones; and, on the other, it may generate precursors which otherwise would not be generated. Let us consider structure 4: if the pre-defined (or default) order is applied the resulting fragments will be acetophenone 5 and

cyclohexene 6, which can then be disconnected by a "retro-Diels-Alder" to give butadiene 7 and acrylic aldehyde 8. However, if we change the order and give priority to the group "RINGS" over the "CONSONANT" one, a "retro-Diels-Alder" to give butadiene 7 and the dienophile 9 will be performed.



We believe that this possibility of "guiding" the program is highly didactic since it encourages the student to discover and explore new synthetic routes and to compare the results of "his" strategy with the pre-defined order. That is to say, according to the *heuristic method* [21] "the pupil is trained to find out things for himself".

Appendix B-3 gives the complete lists of the disconnections which belong to each group. A few "heterocyclic" disconnections have been also implemented which must be activated from a different menu (see the "Instruction Manual" for CHAOS in Appendix B-2).

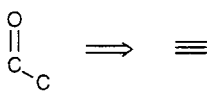
14.2.4. Some comments on the concept of "transform" in the CHAOS program

As we have said, Appendix B-3 shows all the "transforms" incorporated to CHAOS. The "retrons" are represented at the left side, and the result of their disconnection (the "synthons") appears at the right side. However, the user will

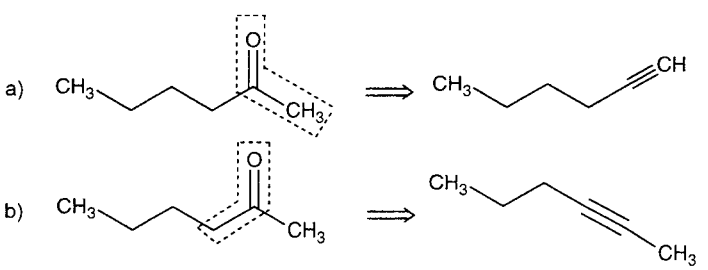
observe that on some occasions, a molecule with a specific retron is not disconnected, even though this retron appears in the Tables and should have been recognised by CHAOS.

Why this? Because the *substructures* or *retrons* are actually more complex than a simple "group of atoms connected in a specific way", since they also contain certain information mainly thought to *restrict* the application of the *transform*. This information has been included because the mere existence of a retron does not guarantee that its disconection could be satisfactory from the chemical point of view.

To understand what we have just said, let us consider the following example: a ketone can be obtained by hydration of a triple bond. If the triple bond is a terminal one, the ketone that will form does not pose any doubt; however, if the triple bond is in the middle of a carbon chain there is a question of regioselectivity, since the ketone can be formed in two different positions. The transform corresponding to this reaction can be represented with the following scheme:



The following figure shows two molecules that present the substructure corresponding to this disconnection. Nevertheless, the second disconnection (b) is not satisfactory, since it gives a triple bond whose hydration is ambiguous.



Therefore, the transforms must include some information to define with greater precision *in which conditions* can they be applied.

In the CHAOS program, the transforms also include some "optional" additional information (it has not been included for all of them; only when it has been considered convenient). This type of information can be classified in two groups:

1) Information that, if it exists, can be associated *to each one of the atoms of the substructure or retron.* It can consist of:

a) Obligation to belong to a bifunctional relationship.

b) Obligation to be at the end of the carbon chain.

c) Obligation to be an sp^3 carbon atom.

d) Obligation to be an sp^3 carbon atom and *to have at least a hydrogen atom* (that is to say, it can not be a quaternary carbon atom).

e) Obligation to belong to a benzene ring.

f) Obligation to belong to a ring.

g) Obligation to belong to a specific functional group.

In summary, the information given here is obligation for the affected atom of having or not having the indicated characteristics. For instance, all the disconnections of group 2, "MONOFUNCTIONAL", have expressed in some of their atoms the "obligation of not belonging to a bifunctional relationship".

2) Information intrinsic to the transform *that prevents its application* in the specific cases listed below:

a) If the transform implies *the disconnection of a core bond.*

b) If the result of the disconnection implies an intramolecular reaction.

c) If it implies a reconnection to a ring smaller than 8 members, or a secondary ring.

d) If it implies the formation of a double bond in a "bridgehead atom".

e) If it implies the formation of triple bonds in rings smaller than 8 members.

The detailed discussion of the reasons that promted us to include each one of these informations or restrictions is beyond the scope of this chapter, although some of them are obvious. All these characteristics can be defined by the user for new disconnections, through the program CHAOSBASE (the way to do this is explained in the instruction manual for CHAOSBASE, Appendix B-2).

Appendix B-3 shows which transforms present some of the above-mentioned characteristics.

14.2.5. A different approach to artificial intelligence: sequences of disconnections

Obviously, many of the steps of an organic synthesis are performed not as goals for themselves but because they constitute previous steps to reach an specific target molecule. For instance, a suitable functionalization is often needed in a part of a molecule in order to carry on a certain reaction. Again an analogy with chess can be established: if we analize a chess match, *foreseeing some movements in advance*, we can find *an specific sequence of particularly advantageous movements,* that lead you to a superb position, that can even give you the match.

In organic synthesis design, like in chess, it can also be interesting to outline some medium- or long-term intermediate "target molecules". We can perharps perform disconnections to obtain certain intermediates, whose structure is appropriate in order to apply transforms of special interest. If this *transform* represents a reaction that affords the basic skeleton of the target molecule, probably we have attained an excellent retrosynthetic scheme.

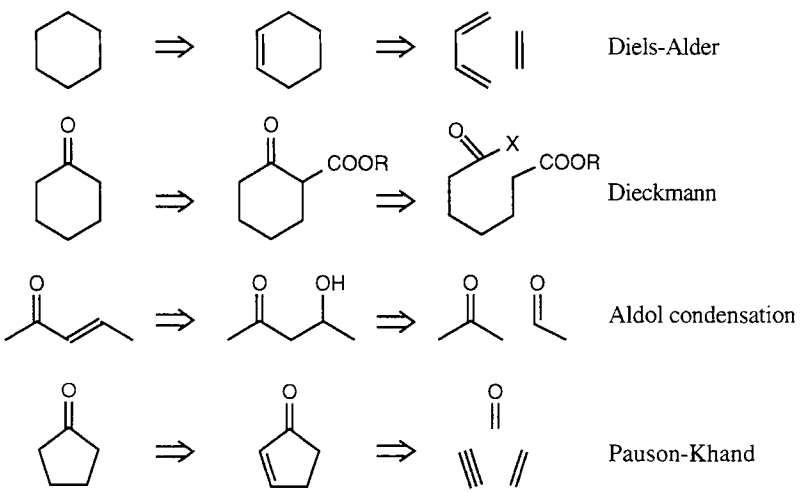
When planning an organic synthesis in this way, we cannot apply an individual *transform* only because the corresponding *retron* is present in the target molecule. It is necessary to carry on an accurate analysis with a *perspective (outlook) of several retrosynthetic steps,* in order to see if a particularly adequate sequence of transforms exists.

Corey refers to this type of retrosynthetic analysis as "long-range strategies" [8a] [22]. In fact, the LHASA program incorporates several "long-range strategies", each one with the final goal of applying a transform that is considered of special interest. The analysis of a target molecule according to these strategies is called by Corey "multi-step look-ahead" [22]. For instance, if using LHASA, the "long-range strategy" based on the Diels-Alder reaction is chosen, the program tries to apply different transforms to the target molecule directed to find the apropriate *retron* for the "retro Diels-Alder" disconnection. If the program affords it, the sequence of transforms performed is shown to the user.

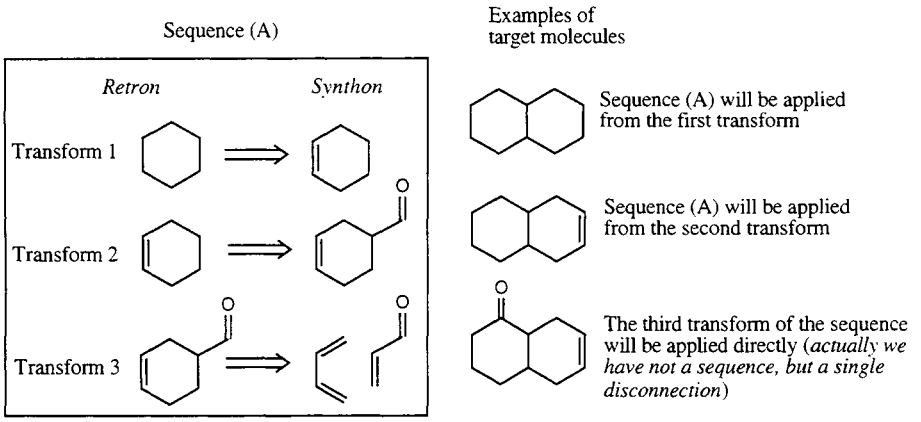
When designing the CHAOS program, we realised that the classification of the disconnections in groups of "decreasing priority" was not enough in order to obtain retrosynthesis of great interest. Such retrosynthesis could only be obtained if a "multi-step look-ahead" analysis was performed. For this reason we decided to create "sequences of disconnections". We define a *sequence of disconnections as the set of retrosynthetic steps that have to be performed in order to apply an specific*

transform. So, in CHAOS, *the sequences of disconnections are formed by individual transforms that have been connected to each other in a sequence.*

The sequences of disconnections operate in the following manner: suppose that CHAOS applies successfully a transform that *forms part of a sequence*, and then, *instead of showing to the user the precursor generated* (as it occurs with the "normal" transforms), *this is automatically subjected to the following transform in the sequence*. When the last transform is reached, the whole sequence, with all the intermediates, is showed. If for any reason, the sequence has not been applied until the end, nothing is showed to the user. Some of the sequences that the program is able to realize at present are represented in the following figure:



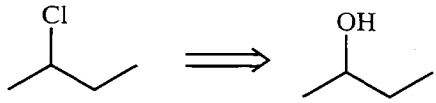
An important detail to be kept on mind is that the sequences not only act from the first transform that forms part of them, but they can also be applied from any of the intermediate transforms, provided that the required retron is present in the target molecule. The following figure shows with an example what we have just said (the disconnection sequence A is hypothetical and at present is not defined in CHAOS):



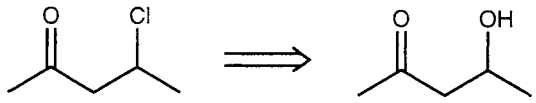
The sequences of disconnections in the CHAOS program do not afford the sophistication of the "long-range strategies" of the LHASA program, but give very satisfactory results. Furthermore, the user can define new sequences using the program CHAOSBASE (see below *Heading 14.3*). The tables in Appendix B-3 indicate which disconnections implemented in CHAOS are connected in a sequence.

14.2.6. Some general remarks on disconnection groups

Some disconnections are found, apparently, in more than one group. For instance, whereas in "MONOFUNCTIONAL" the following disconnection (in fact, a FGI) is included,



in the "CONSONANT" group this other one is found:



and one could ask if the first one would not suffice. The answer is that the first one only operates on isolated halogen atoms and will not affect the β-chloroketone. But, why restrict the halogen-hydroxyl FGI to isolated halogen atoms? Simply, because is reasonable to think that not all halogen atoms come from an alcohol. The β–

chloroketone may be synthesised by addition of hydrogen chloride to the corresponding α,β-unsaturated ketone or an α-chloroketone may be obtained by direct chlorination. Accordingly, the halogen-hydroxyl FGI works well in all cases in which the halogen atom is "isolated", but in other cases it will depend on the functional group relationships existing in the molecule. In the β-chloroketone it happens by chance that the FGI is of interest because it allows a retro-aldol disconnection. But an α–chloroketone is treated in the program simply by elimination of the halogen atom.

In fact, any student with a minimum knowledge of organic chemistry will realise that many of functional groups included in "MONOFUNCTIONAL" would be treated in a different way if there were some other groups near by. For example, in "MONOFUNCTIONAL", an isolated cyanide group is converted into an halogen. But, if a carbonyl group is three carbon atoms away from the cyanide, this group is disconnected in "CONSONANT" according to a retro-Michael.

Some disconnections implemented in the "FINALS" group are also found in other groups. Nevertheless, they are used here in a very unrestricted context. The reason for introducing them again is based on the fact that disconnections in the other groups are more restrictive (for instance, the ones in "MONOFUNCIONAL" act only on isolated functional groups). It is possible that, through the "pre-defined order", the target molecule had not been disconnected by means of the preceding groups of disconnections. Then, the program applies the "FINALS" group of disconnections at the end, which act ignoring the context within the molecule in which they occur. In other words, *since it has not been possible to do something better, a typical monofunctional disconnection is carried out whatever the result may be.* If the resulting disconnection is simply "nonsense" the user may always reject it ("Ignore", see Appendix B-2).

It is not necessary to emphasise here that the inadequate use of the "control" (see instruction manual, Appendix B-2) for changing the order of disconnections may "spoil" the logic of a retrosynthetic analysis. Thus, giving the highest priority to "FINALS", for example, may destroy all the existing bifunctional relationships which would offer the best solutions.

The "FINALS" group also incorporates some special disconnections which cannot be included in the other groups. For example, hydration of "isolated" double bonds, deconjugation of α,β-unsaturated ketones (Stork method), Wharton-Grob-

type reconnections, oxy-Cope rearrangements, etc., so that the group is in fact a miscellany.

14.2.7. About some special algorithms implemented in CHAOS

CHAOS besides performing disconnections, also gives some structural information which is useful from a didactic point of view. For instance, CHAOS not only finds all the rings present in a molecule and the set of synthetically significant rings, but in the case of bridged systems, also finds the core bonds, the bridgeheads and the "strategic bonds" as defined by Corey [23] (see Corey's rules in *Heading 7.2.1*). However, the program does not use all this information in performing the disconnection, but only shows them when it is required to do so. The last Corey rule referring to chiral centres is not taken into account since the present version of CHAOS does not recognise, as stated below, the stereochemical features of a molecule.

CHAOS, of course, also finds and shows (if required) all the bifunctional relationships which are classified as "consonant" and "dissonant" .

14.2.8. Limitations of CHAOS

Finally, we must deal honestly with the limitations and deficiencies of our CHAOS program.

Two main limitations of CHAOS are: i) it does not recognise stereochemical features and ii) it does not deal with typical aromatic electrophilic substitution (only Friedel-Craft-type disconnections are performed).

Probably, you will find some other limitations we have missed and notice some simple improvements which could be easily implemented. Let the authors know. They will appreciate all kinds of constructive criticism.[51]

Remember, however that CHAOS does not intend to be a database of "synthetic methods" presently available to organic chemists. CHAOS is aimed at finding the intermediate precursors of the "synthesis tree" by means of selected basic disconnections (either "consonant" or "dissonant"). In the author's view, it is of minor importance, for instance, how a "carbene" -resulting from a -(2 + 1) cycloelimination- is generated, or whether a double bond is the direct result of a Wittig reaction or the dehydration of an alcohol formed in a Grignard reaction. In

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[51] Suggerences can be sent by electronic mail to: XICART@FARMACIA. FAR.UB.ES

both cases the retrosynthetic analysis leads ultimately to a carbonyl compound and an organic halide. Rather than an "encyclopaedia", CHAOS is a heuristic aid for designing organic syntheses for beginners. However, in the present version the CHAOSBASE program has been incorporated by which the user can introduce new disconnections and work with his/her own chemistry.

14.2.9. CHAOSBASE. A program for introducing new disconnections to CHAOS

The CHAOSBASE program, like CHAOS, is offered in two versions: one for IBM PCs (or fully compatible PCs) with Windows®, and another for Macintosh computers. CHAOSBASE allows to *create transforms* that can be subsequently used by CHAOS. Thus, the user can dispose of disconnections considered necessary, and that CHAOS does not perform.

In some computer programs for the Design of Organic Synthesis, the incorporation of new *transforms* is not a trivial process. For instance, in the LHASA program a language called CHMTRN (Chemistry Translator) [8a] has been specially created, which is formed by a limited vocabulary of "pseudoenglish" words. The incorporation of a new transform requires writing the transform in CHMTRN language and then translating this information to the appropriate format in order to be read by LHASA. The complexity of the process and the necessity of knowing the CHMTRN language, imply that the *transforms* are written by specialists and distributed together with the LHASA program. The CHMTRN language is very rich and allows to describe the transforms with great detail. For example, LHASA can *evaluate* the possibilities of success in the laboratory of the chemical reaction resulting of applying an specific *transform* [8a] [24] and identify and protect the interfering functional groups [8a] [25]. To do this, different factors are taken into account: substrate functionalization, reaction conditions, etc.

CHAOSBASE does not offer so many possibilities, but gives the chance to create new transforms in an easy and quick way. The information created through CHAOSBASE is stored up in files that can be always modified and enlarged by the user.

The process for creating new *transforms* through CHAOSBASE takes place in retrosynthetic direction and includes the following steps:

1) Creation of the *retron or substructure*. The user "draws" the *retron* on the computer screen with the mouse. Different menus allow the introduction of the necessary heteroatoms and atomic groups.

2) Creation of the *synthon* from the retron. The user *carries out on the retron structure the corresponding changes to elaborate the synthon.* For example, if we want to convert, in retrosynthetic direction, an alcohol into a carbonyl (the equivalent to a *reduction reaction*), an alcohol group has to exist in the retron, and the user must indicate "the formation (retrosynthetic) of a carbon-oxygen bond".

When a transform created through CHAOSBASE is applied by CHAOS, the same transformations realised by the user on the synthon, will be carried out automatically by the program on the target molecule.

Therefore, when elaborating a retrosynthesis, two types of transforms can be used: the ones incorporated to CHAOS, which can not be modified (*internal transforms*, Appendix B-3), and the ones created through CHAOSBASE and stored in files (*external transforms*). This scheme is very versatile, since it allows to define different *files of transforms* each one specialised in a concrete topic of organic chemistry reactivity. The user can specify in each moment which *files of transforms* have to be used.

Both types of transforms (internal and external) are identical for CHAOS. The only difference is the speed with which the program uses them, which is much higher with the internal transforms. The reasons for this are: first, that *these transforms are part of the program* and the access to them is very fast; and second, that they have been written in such an *optimized* way that its application takes place as quickly as possible (to explain what this optimization consists of, is beyond the scope of this chapter).

CHAOSBASE not only allows to create transforms but also permits to connect several transforms to create sequences of disconnections, similar to the ones present in CHAOS, formed by as many as ten individual transforms connected between them.

The instruction manual for CHAOSBASE is in Appendix B-2.

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Appendix B-1

UGI'S THEORY OF CHEMICAL CONSTITUTION: EROS AND IGOR

In fact, the programs developed by Ugi and his colleagues [1] are not intended only as a tool to generate new synthetic routes of a given target molecule, but they constitute a more general mathematical approach to the logical structure of chemistry. The molecules are represented by matrices and the chemical reactions as recombinations of such matrices. Instead of resorting to a "library" of known reactions, the program attacks the problem of designing a chemical synthesis as a game, using combinatorial analysis. Although many of the "chemical reactions" generated by these programs may not represent "bench chemistry", by exploring all the conceivable recombinations the program may find new reactions and be a source of inspiration and creative research for the user. However, the generation of synthetic sequences by an exhaustive combinatorial analysis leads to a number of possibilities that grows exponentially and produces a lot of "garbage", so that some selection rules are necessary in order to "prune" the synthesis tree.

In Chapter 1 we have stated that the classical structural theory is the only way to "visualise" the synthesis of a more or less complex organic compound. However, all or most of the information given by a structural formula can also be expressed by a matrix (see also Appendix A-1). There are different kinds of matrices: for example, the adjacency matrix J, which originates in graph theory and indicates only which atoms are bonded, or the connectivity matrix C, whose off-diagonal entries are the formal covalent bond orders. For instance, the corresponding matrices of hydrogen cyanide are:

J (HCN) =

	H	C	N
H	0	1	0
C	1	0	1
N	0	1	0

C (HCN) =

	H	C	N
H	H	1	0
C	1	C	3
N	0	3	N

In the constitutional model of Ugi, rather than molecules, "ensemble of molecules" (EM) are used in which the molecules can be either chemically different or identical. Like molecules, an EM has an empirical formula, which is the sum of the empirical formulae of the constituent molecules and describes the collection A of atoms within the EM under consideration. All the EM's which can be formed from A have the same empirical formula <A>. Therefore, an EM(A) consists of one or more molecules which can be obtained from A using each atom which belongs to A only once. Moreover, a FIEM(A) or a family of isomeric EM, is the collection of all EM(A) and it is determined by the empirical formula <A>. On the other hand, a chemical reaction, or a sequence of chemical reactions, is the conversion of an EM into an isomeric EM, and therefore a FIEM contains all EMs which are chemically interconvertible, as far as stoichiometry is concerned. In summary, a FIEM(A) contains, at least in principle, the whole chemistry of the collection A of atoms and since any collection of atoms may be chosen here, Ugi concludes that a theory of FIEM is, in fact, a theory of all chemistry.

To describe the EMs, Ugi uses the so-called BE-matrices (from Bond and Electron), the diagonal entries of which are the number of free valence electrones and the off-diagonal are the formal covalent bond orders. The sum of all the elements of a row (or a column, since all BE-matrices are symmetrical, i.e., they have the same number of rows than columns) give the total number of electrons surrounding the atom associated to this row. In fact, the n atoms of an EM can be enumerated in n! different ways, which would lead to n! distinguishable but equivalent BE matrices. However, by appropiate rules one of these numberings can be considered canonical.

The BE-matrices of hydrogen cyanide and hydrogen isocyanide (notice that since the neutral "carbenic" resonance structure has not the octets fully completed, the dipolar resonance structure is taken instead) are:

Hydrogen cyanide $\overset{1\ 2\ 3}{H\text{-}C\equiv N:}$ Hydrogen isocyanide $\overset{+\ -}{H\text{-}N\equiv C:}$ $\overset{1\ 3\ 2}{}$

$$BE(HCN) = \begin{vmatrix} H^1 & C^2 & N^3 \\ 0 & 1 & 0 \\ 1 & 0 & 3 \\ 0 & 3 & 2 \end{vmatrix} \qquad BE(HNC) = \begin{vmatrix} H^1 & C^2 & N^3 \\ 0 & 0 & 1 \\ 1 & 2 & 3 \\ 0 & 3 & 0 \end{vmatrix}$$

According to the theory of constitutional chemistry, a chemical reaction is interpreted as a redistribution of the valence electrons; i.e., as the transformation of an EM into an isomeric EM (in which both the atomic cores and the valence electrons are preserved). The difference between the final E (End) and the initial B (Begining) BE-matrices is called the R-matrix (Reaction matrix):

$$E - B = R$$

Accordingly, the addition of an R-matrix to a BE-matrix may be interpreted as the action of an operator R_{op} on B:

$$R_{op}(B) = B + R = E$$

Let us consider the rearrangement of hydrogen cyanide to hydrogen isocyanide:

$$\underset{(B)}{H\text{-}C\equiv N:} \longrightarrow \underset{(E)}{H\text{-}\overset{+}{N}\equiv\overset{-}{C}:}$$

$$BE(R) = \begin{vmatrix} 0 & -1 & 1 \\ -1 & 2 & 0 \\ 1 & 0 & -2 \end{vmatrix}$$

The positive elements in the R-matrix are the new formed bonds and the negative numbers the bonds broken. The diagonal entries are the number of electrons gained or lost in the "chemical reaction".

The more important property of an R-matrix is that the sum of all its elements is zero, which is associate with the principle of the conservation of the total number of electrons involved in the reaction. On the other hand, the fact that the BE-matrices cannot have negative elements (i.e., the elements are equal or greater than zero) implies that the negative elements of the R-matrix must be in absolute value equal or smaller than the corresponding B-matrix.

According to Ugi's more precise mathematical terminology, we will have:

$$B + R = E$$

Conservation principle: $\sum_{i,j} R_{i,j} = \sum_{i,j} E_{i,j} - B_{i,j} = 0$

Maximum value of $R_{i,j}$: $\forall_{i,j}$, $E_{i,j}$ and $B_{i,j} \geq 0$; if $R_{i,j} < 0$, then $|R_{i,j}| \leq 0$

Besides these mathematical restrictions, some chemical restrictions are also incorporated, such as the number of valences and free electrons that are possible for each chemical element. The "principle of minimum chemical distance" (PMCD) was implemented also into the program EROS [1b] in order to guide the program in choosing the right synthetic sequences. This principle is equivalent (and allows a quantitative evaluation) to the classical principles of the minimum topological changes or the minimum structural changes, and the minimum change of the electronic (and/or nuclear) distribution, all of which are also implicit in the Woodward-Hoffmann rules. The term "chemical distance" is defined as the number of valence electrons which must be shifted in order to interconvert isomeric EM under a given atom onto atom mapping. It is known that most of the chemical reactions proceed through a pathway of minimum chemical distance; i.e., along a pathway involving the minimum redistribution of valence electrons. Ugi has used the PMCD for substructure matching, as well as the evaluation of syntheses.

From a synthetic point of view the elaboration of the sequences of a "synthesis tree" involves the search of all R-matrices which fulfil all the stated mathematical and chemical restrictions, so that

B + R = E or, in the retrosynthetic direction, E + R = E - R = B,
where R = -|R-matrix|, i.e. the corresponding elements are given by

$$r_{i,j} = -r_{i,j}$$

Let us consider the decomposition of formaldehyde cyanohydrin (2-hydroxyacetonitrile) into formaldehyde and hydrogen cyanide which is equivalent to the retrosynthetic analysis. The corresponding BE-matrices and the R-matrix are:

		O	C	H	H	H	C	N
1	O	4	1	0	0	1	0	0
2	C	1	0	1	1	0	1	0
3	H	0	1	0	0	0	0	0
4	H	0	1	0	0	0	0	0
5	H	1	0	0	0	0	0	0
6	C	0	1	0	0	0	0	3
7	N	0	0	0	0	0	3	2

BE(B)

	O	C	H	H	H	C	N
O	0	1	0	0	-1	0	0
C	1	0	0	0	0	-1	0
H	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0
H	-1	0	0	0	0	1	0
C	0	-1	0	0	1	0	0
N	0	0	0	0	0	0	0

BE(R)

	O	C	H	H	H	C	N
O	4	2	0	0	0	0	0
C	2	0	1	1	0	0	0
H	0	1	0	0	0	0	0
H	0	1	0	0	0	0	0
H	0	0	0	0	0	1	0
C	0	1	0	0	1	0	3
N	0	0	0	0	0	3	2

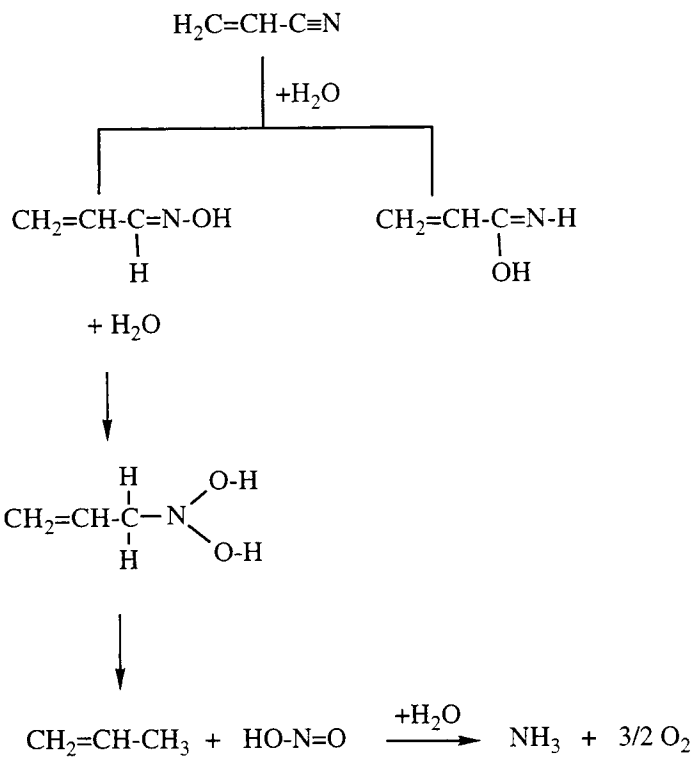
BE(E)

As an exercise, the reader may verify all the stated properties of these matrices.

Let us consider the synthesis of acrylonitrile from propene, ammonia and oxygen. The overall reaction is:

$$H_3C{-}CH{=}CH_2 + NH_3 + 3/2\ O_2 \longrightarrow H_2C{=}CH{-}C{\equiv}N + 3\ H_2O$$

The combinatorial generation performed by the program EROS give the following synthesis tree:



Dupont process

which ends with the addition of nitrous acid to propene, a process known as Dupont process, an industrial alternative route to abovementioned reaction. A subsequent analysis shows that nitrous acid may be obtained by oxidation of ammonia. Another proposed route is the dehydration of acryloamide. The most important lesson we may learn from this example is that the proposed routes by EROS are far from the synthetic procedures that the synthetic organic chemist usually considers as "normal" or "common" and that would probably be the solutions offered by an information-oriented program.

The program IGOR (Interactive Generation of Organic Reactions) is in fact an improved and interactive version of EROS which was reported more recently. According to Ugi [2], the unique efectiveness of this new program is based not only on the logical mathematical theory already reported, but in an analysis of the complete combinatorial set of conceivable solutions to a problem by means of a converging interactive hierarchic classification procedure of the chemical reactions.

In this approach chemical reactions are first classified according to the minimal number of valence electrons that must be redistributed in order to convert the reacting molecules into the products of the given reaction. This is accomplished by determining the minimal chemical distance between the reactants and products.

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Appendix B-2

INSTRUCTIONS FOR THE USE OF THE CHAOS AND CHAOSBASE PROGRAMS

1.INTRODUCTION

CHAOS is a program for the computer-assisted design of organic synthesis. CHAOSBASE is an auxiliary program, which makes it possible to create *retrosynthetic reactions data bases* that can then be used by the CHAOS program.

1.1. Disk Contents and Hardware requirements

Both programs exist in two versions:

1. Version for Macintosh® computers. To execute the programs in this version, you need a Macintosh computer with a 6.0.7. or later operating system and a hard disk with at least one Megabyte free.

2. Version for Windows®. To execute the programs in this version, a compatible PC installed with the Windows 3.1., or later, graphic system and a hard disk with at least one Megabyte free is required.

Since both versions of the programs are practically identical in their handling, the information in this manual is valid for both the Macintosh and Windows versions. Where there is a difference between the two, it is clearly indicated in the text. The illustrations in the manual belong to the Macintosh system. The Windows ones, however, look similar.

1.2. Use of the Macintosh® computer and the Windows® system

This manual assumes that the user is familiar with a Macintosh or Windows-type graphic operating system, with a mouse, windows, pop-up menus, etc. If this is not so, the user should first familiarise him/herself with the graphic system installed in his/her computer.

1.3. Installation of the programs

1.3.1. Installation of the Macintosh version

On the disk labelled MACINTOSH VERSION there are two icons, one of which represents the CHAOS program and the other the CHAOSBASE program. This is what these icons look like:

To install both programs in your computer, follow these instructions:

a) Create a *folder* with the command "New folder" from the *File* menu. Give the name ORGANIC SYNTHESIS to this folder.

b) Introduce the MACINTOSH VERSION disk into your computer. Double click on the icon of the disk. A window with the icons of the two programs will then come up.

c) Drag the two icons inside the ORGANIC SYNTHESIS folder and the programs will be copied onto your computer's hard disk.

1.3.2. Installation of the Windows version

On the disk labelled WINDOWS VERSION you will find the programs INSTALL.EXE, CHAOS.EXE and CHAOSBAS.EXE. You must have Windows already in your computer. Once you have started up the computer and inserted the WINDOWS VERSION disk, from the symbol "DOS Prompt" type WIN A:INSTALL and press "Enter":

*C:\WIN A:INSTALL (Enter)

Follow the instructions on the screen. When the program has been loaded, a new group of programs called "Organic Synthesis" with the icons of the CHAOS and CHAOSBASE programs will come up in the Windows "Program Manager". With a double click on these icons, you will be able to execute these two programs.

1.4. Learning the programs

A simple double click on their icons starts up both programs. Although they are fairly easy to use, we recommend that users go through the exercises suggested in this manual before starting to use them. Some functions (*unique numbering, activation disconnections* etc.) need detailed explanation and cannot be used efficiently without some practice beforehand. Also, in order to better understand program performance, it is important to read the sections relating to the "order of priority" of disconnections (see below *Headings 2.2.7 and 2.2.8*). In addition, we suggest you read the manual *while practising with the program, since some sections cannot be understood unless what is read in the manual is checked against what comes up on screen.*

1.5. How this manual is organised

The first part of the manual explains the running of the CHAOS program; and the second, the CHAOSBASE program. We believe the best way to read the manual is in the order in which it is printed.

2. RUNNING THE CHAOS PROGRAM

To begin with, it is important to remember that the disconnections incorporated into the CHAOS program are grouped in order of *decreasing priority*. The program uses these groups in the following way:

a) It analyses whether the application of *each one of the disconnections* to the target molecule is feasible or not, starting with the highest priority group. When a disconnection of a specific group is found to be applicable to this molecule, the program shows this to the user. Then the program tries to apply the remaining disconnections *in this group.*

b) Normally the program stops its attempts to apply disconnections *at the end of a group in which at least one applicable disconnection has been found.*

c) The user can make the program *not stop at the end of a group in which there are applicable disconnections*, but rather *continue exploring the lower-priority groups.* See *Heading 2.2.8.*

d) The user can also *change at will the established priority order of the groups.* See *Heading 2.2.7.*

e) An *order of priority has also been fixed between chemical reactions data*

bases, similar to the one for the groups of decreasing priority. So a), b) and c) above are equally valid for data bases (see *Heading 2.2.15*).

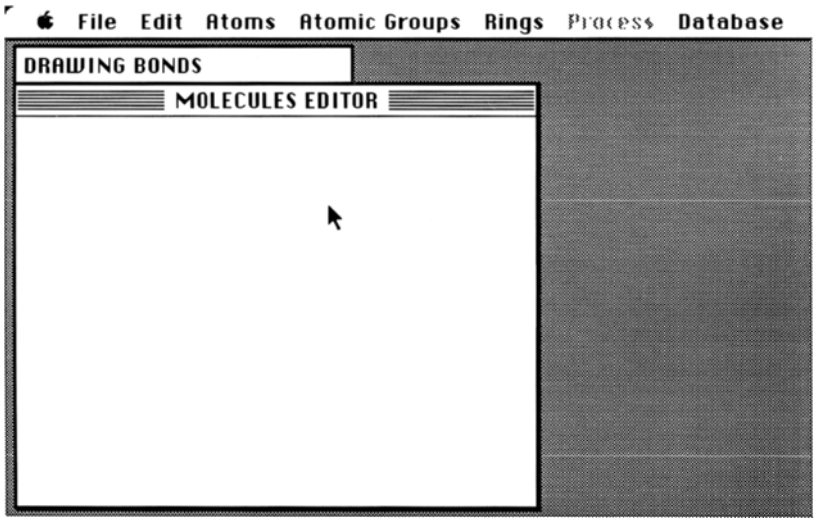
THE ABOVE POINTS SUMMARISE THE RUNNING OF THE PROGRAM AND ARE OF VITAL IMPORTANCE IN UNDERSTANDING ITS BEHAVIOUR.

The program has two *environments* which are used for different goals. The first one (which comes up on screen when you start the program) is called *Molecules editor*. The *Molecules editor* is used to draw the target molecule you want to process, i.e. the one you wish to propose that the computer disconnects. The second environment is the *Processing screen*. You will enter this when a molecule has been drawn and saved on the disk. From the *Processing screen* you will be able to ask the program to disconnect the molecule and you will also be able to ask for information on structural changes such as the number of rings, bifunctional relationships etc.

2.1. The Molecules editor

2.1.1. Starting up the program

When the CHAOS program is started up, the screen will look like the following figure:



This is the *Molecules editor* screen, which is used to draw the *target molecule* and introduce it into the computer. The drawing is made in the *window* shown in the figure (*editing window*). All the available drawing options are found in the *menu bar*. The option activated at any one moment is shown on the *status line*, a rectangle in the upper left part of the screen beside the *editing window*. When the program is started up, *Drawing bonds* can be read on this line: this tells you that drawing the bonds of the molecule is the operation now available.

2.1.2. Drawing a carbon-atom chain. Double and triple bonds. Clearing the screen

a) Start up the program. Make sure that *Drawing bonds* can be read on the *status line*.

b) Take the mouse to the *editing window*, press the button where you want to locate a carbon atom and then drag it (i.e. move the mouse without releasing the button). A line which follows the mouse's movements will then come up on screen.

c) Release the button in the place where you want to locate a second carbon atom bonded to the first one. A line representing a bond between two carbon atoms will have been drawn.

d) In order to continue drawing, press the button near one of these carbon atoms and repeat the process (drag and release in the appropriate place). "Near" a carbon atom means that the mouse must be sufficiently close to an atom so that, on the mouse button being pressed, the program detects the nearness of this atom. *If you press sufficiently close to a pre-existing atom*, the program will assume you want to draw a bond starting from this atom; whereas, if you press the mouse when too far away, the program will assume you want to locate a new atom where you have pressed the button. The following table illustrates the various possibilities for drawing a bond.

Press where no atom exists	⇨	Release where no atom exists	⇨	Creation of 2 C atoms with a bond between them
Press near a preexisting atom	⇨	Release where no atom exists	⇨	Creation of one more C-atom with a bond to another preexisting atom
Press where no atom exists	⇨	Release near a preexisting atom	⇨	Creation of one more C-atom with a bond to another preexisting atom
Press near a preexisting atom	⇨	Release near a preexisting atom	⇨	No a new atom created but a new bond created between 2 atoms

Note: Only carbon atoms can be drawn with this technique. When you want to draw a molecule with heteroatoms, you must first draw a carbon atom where you want to place a heteroatom and then "convert" the carbon atom into the heteroatom. How to do this will be explained later.

Practise drawing carbon-atom chains with the mouse until you are familiar with the technique.

e) Place the mouse near one of the carbon atoms you have drawn.

f) Press the button and, without releasing it, move the mouse to another atom bonded to the first. Release the button. You will see how a double bond between the two atoms appears. If you wish to draw a triple bond, simply repeat the process.

g) Go to the *Edit* menu and then to the option "Clear screen". You will see that the molecule drawn disappears and the program is ready to start a new drawing. Use this option with care, as *there is no way of recovering a cleared drawing.*

2.1.3. How to view all the carbon atoms in a molecule. Moving a molecule round the screen and modifying its size. Moving an individual atom

a) If you have a molecule on the screen, clear it with the "Clear screen" option (*Edit* menu). Now draw any carbon chain.

b) You will notice that the terminal CH_3 groups come up on screen automatically, whereas the other carbon atoms do not. Now go to the "Draw C-atoms" option (*Edit* menu). The carbon atoms with the appropriate number of H-atoms will automatically appear. If you then open the *Edit* menu again, you will

see that the "Draw C atoms" option is now *ticked.*

c) Go again to the "Draw C atoms" option. The drawing of the molecule will revert to how it was, with just its terminal atoms. This option does not contribute structural information on the molecule; it simply modifies the display. Note also that the *status line* does not change, either.

d) Click the "Move molecule" option (*Edit* menu). You will see that the *status line* now reads "Moving molecule".

e) Next move the mouse *anywhere* in the *editing window* and press the button without releasing it. You will see that the molecule is now surrounded by a rectangle with dotted lines.

f) Drag the mouse. The rectangle follows the mouse's movements. Take the rectangle where you wish and release the button: the drawing of the molecule is automatically relocated to this position. Normally it is better to draw the molecule so that it is centred over the *editing window.*

g) Click the "Resize" option (*Edit* menu). The *status line* will read "Resizing molecule".

h) Move the mouse to another part of the *editing window* and press the button, without releasing it. You will see that the molecule is again surrounded by a dotted rectangle.

i) Move the mouse vertically (keeping the button pressed down). You will see that the rectangle varies in size, becoming larger or smaller, depending on the movements you make. Adjust the rectangle to the size you want and release the button. The molecule will adopt the size of the rectangle.

j) Click the "Move atom" option (*Edit* menu). The *status line* will now read "Moving atom".

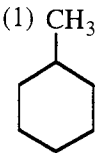
k) Move the mouse near any atom and press the button, without releasing it. Now drag the mouse: you will see that the atom follows the mouse's movements for as long as you keep the button pressed down.

l) Move the mouse to the position you want and release the button. The atom will now remain fixed in its new position.

2.1.4. Using the Atoms menu

This menu lets you introduce heteroatoms in the molecule. In order to use it:

a) Clear any molecule you may have on screen. Draw the following molecule:



b) Select "Oxygen" from the *Atoms* menu. The *status line* will read: "Adding oxygen atom."

c) Take the mouse near atom 1 and click it. This atom is now automatically converted to oxygen.

Note: A heteroatom can only be introduced by converting a pre-existing atom. Therefore, a C atom always has to be drawn first and then converted.

d) Now choose the "Draw bonds" option (*Edit* menu). The *status line* will read "Drawing bonds".

e) Draw a bond between the oxygen atom and the adjacent carbon atom. You will see that *the alcohol has been converted into a carbonyl group.* In fact, you could have drawn the double bond before introducing the oxygen atom and have then converted the carbon to an oxygen atom.

f) Now go to the *Atoms* menu and select "Carbon". The *status line* will now read "Adding carbon atom".

g) Click the mouse on the oxygen atom, which converts it to a carbon atom again. This option has been introduced so as to be able to correct drawing errors. In fact any atom on the *Atoms* menu can be converted into any other on the menu *as long as the valence of the atom in question is not violated.* You will also have noticed that the program automatically assigns to an atom the number of hydrogens needed to satisfy its valence.

Note: Hydrogen appears on the Atoms menu. Do not use it. It has only been introduced into the menu for use in later versions of the program which will deal with stereochemistry. The program ignores it when it tries to disconnect a molecule.

2.1.5. Using the Atomic groups menu

a) If you have a molecule on screen, clear it with "Clear screen" (*Edit* menu).

Draw again methylcyclohexane.

b) Select the atomic group which you want from among those which appear on the *Atomic groups* menu. The *status line* will now read "Adding *** group" (*** being the name of the atomic group selected).

c) Move the mouse to near atom 1 and click it. This atom is then automatically converted to the group you selected. As above, *there must be a pre-existent atom* in the place where you wish to introduce an *atomic group*. You can also interconvert the different groups among themselves as long as the valence of each one is not violated.

2.1.6. How to use the Rings menu

Rings of between 3 and 8 members may be drawn directly as follows:

a) Clear the screen. Select the 6-membered ring from the *Rings* menu. The *status line* will read: "Drawing 6-membered ring".

b) Move the mouse anywhere on the screen and press without releasing the button. Then drag the mouse. You will see that a ring appears on the screen and follows the mouse's movements. Note too that, where you first pressed the button, one of the vertices of the ring remains fixed (we will call this the "fixed vertex" of the ring), while the rest of the molecule turns round this vertex, becoming bigger or smaller and even changing position, whenever you move the mouse. Controlling the mouse to draw a ring correctly needs a certain amount of practice. The user will *maintain control* over the size and position of the ring as long as the button remains pressed down.

c) Release the button. The ring will remain in a fixed position. Observe that the *status line* still reads: "Drawing 6-membered ring".

d) Choose any ring from the *Rings* menu. Move the mouse to the *editing window* and press the button near an atom. You will see how the program uses this atom as the fixed vertex of the ring. Move the mouse near another atom. The vertex which accompanied the mouse will now fuse with the second atom. This vertex can be fused with any pre-existing atom. When the button is released, a system of fused rings will have been created.

Note: While a ring is being drawn, only the fixed vertex and the vertex accompanying the mouse in its movements can be fused with pre-existing atoms. If you try to fuse any other of the ring's atoms, an error message will appear.

2.1.7. Erasing an atom or a bond

a) Draw any molecule. Select the option "Delete atom" from the *Edit* menu. The *status line* will read "Erasing atom".

b) Click on any atom. This atom will automatically disappear.

c) Select the option "Delete bond" from the *Edit* menu. The *status line* will read "Erasing bond".

d) Move the mouse to one of the ends of a bond.

e) Press the button and, without releasing it, drag the mouse to the other end of the bond. A line following the mouse's movements will appear.

f) When you have reached the other end of the bond, release the button and the bond will disappear. This option allows a bond between two atoms to be erased, but *the atoms remain in existence.*

Note: If you erase a bond between two atoms joined by a triple bond, this becomes a double bond. Similarly, a double bond will become a single bond.

2.1.8. How to save a molecule on disk and transfer it to the "Processing screen"

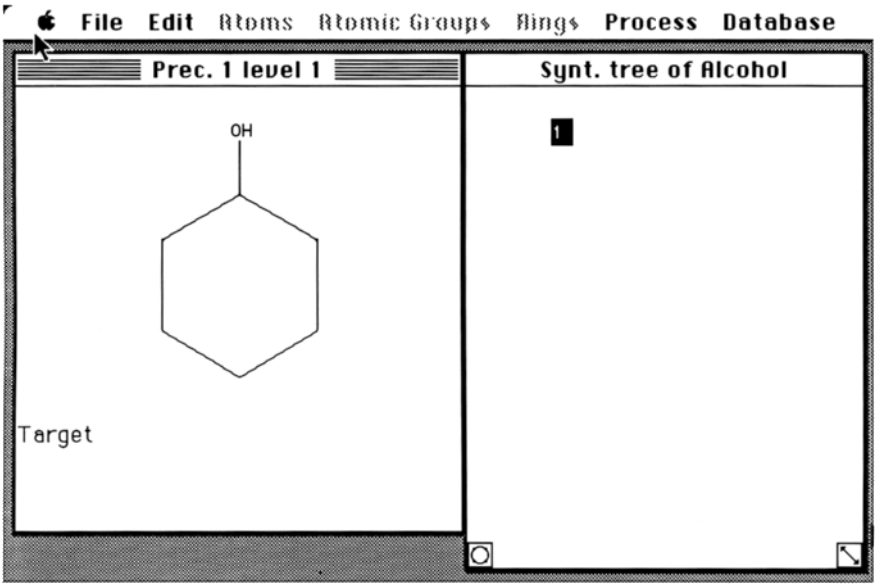
To process a molecule (that is to say, to get the program to disconnect), the molecule has to be previously saved on the hard or floppy disk. To do this:

a) Draw a molecule.

b) Go to the option "Save molecule and process" (*File* menu). A "dialog box," which allows you to save the molecule, will come up. Where it reads "Untitled," you can write the name you want for the synthesis of the molecule you have drawn. Click *Save* and the program:

1. Will create on the hard or floppy disk the files required for the synthesis.
2. Will automatically move to the *Processing screen.*

Click *Save*. Your screen should then look as follows:



You are now in the *Processing screen*, whose running is explained in *Heading 2.2* of the manual.

Note. When you click *Save*, what the program does depends on the version you are using:

In the Macintosh version a new folder is created in the hard or floppy disk, with the name given to the synthesis. Inside the folder, there are two files linked to the synthesis.

In the Windows version, two files are created directly in the working directory, with the same name as that given to the synthesis, but with .ATS and .TRE extensions.

When you want to erase completely a synthesis created by the CHAOS program, you must erase these two files which form a part of it.

Do not try to work with a synthesis which lacks one of these 2 files, as it will not function (this can only happen if you have accidentally erased one file and yet have kept the other on your disk).

2.1.9. How to "open" a pre-existing synthesis

The syntheses which you have composed using the CHAOS program remain

on your disk and can be recovered at any time with the option "Open molecule and process" (*File* menu). If this is the first time you are reading the manual and you have still not practised using the program, we suggest you move forward to *Heading 2.2* and return to this section when you have various syntheses on your disk.

The option "Open molecule and process" can be used at any time, whether we are in the *Molecules editor* or the *Processing screen.*

When you want to open a synthesis created previously:

a) Go to the option "Open molecule and process" (*File* menu).

b) A "dialog box" will come up. This allows you to explore the different directories and files on the disk.

c) 1. For Macintosh users. Locate the folder whose name coincides with that of the synthesis you wish to open. *Open* this folder. You should be able to view a file which has againg the same name as the synthesis. *Open* this file. The program will automatically transfer you to the *Processing screen*, displaying the synthesis at the point you left it the last time you worked on it.

2) For Windows users: Locate directly the file with the same name as the synthesis you wish to open (the file will have the extension ".ATS") and *open* this file.

Note: If you are working with one synthesis on the Processing screen and you decide to open another, the first one will close automatically. It is not possible to work simultaneously with several syntheses. However the first one can be recovered at any time with the option "Open molecule and process".

2.2. The Processing screen

With the *Processing screen* you can:

1) Ask the program to *disconnect the target molecule automatically*, using the disconnections set into the program.

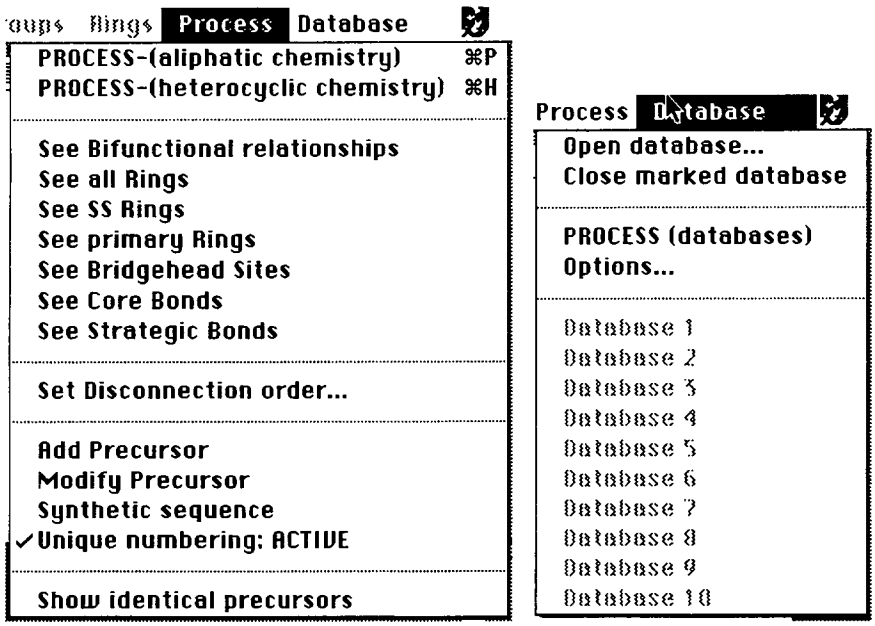
2) Disconnect the molecule yourself (manually).

3) Obtain structural information on the molecule.

4) Open one or several *reactions data bases* which have been previously created by the CHAOSBASE program.

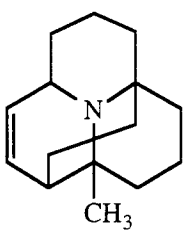
5) Ask the CHAOS program to disconnect the *target molecule* using the disconnections existing in the data bases open at that moment.

The options for the Processing screen are contained in the "Process" and "Database" menus. The following figure shows these options, which will be discussed further in the following sections:

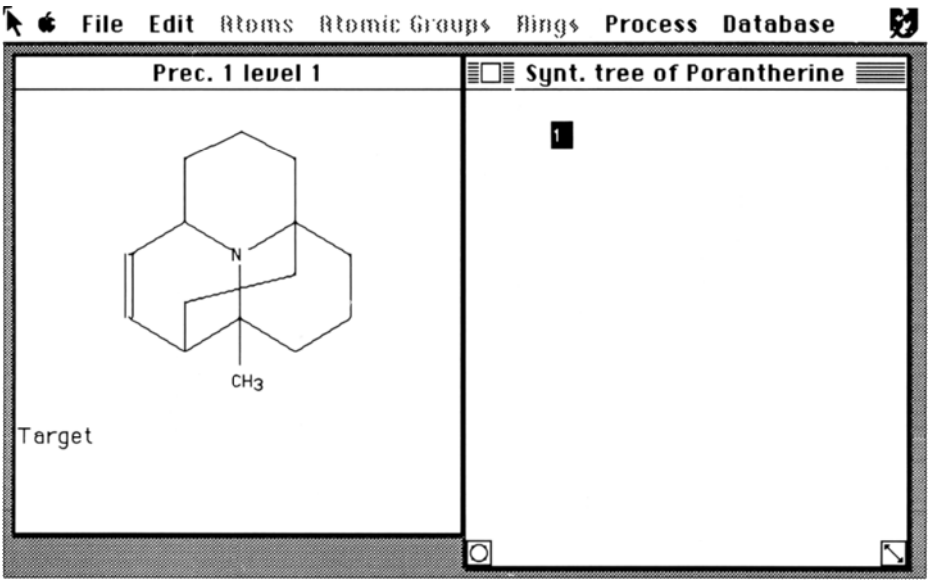


2.2.1. Automatic processing ("PROCESS-(aliphatic chemistry)")

a) Enter the CHAOS program and using the Molecules editor, draw and save the following molecule, giving it the name "Porantherine":



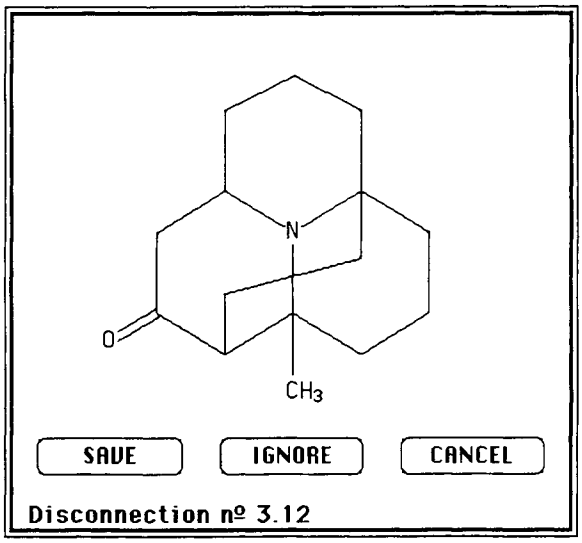
b) Once you have saved the molecule you will find that the screen looks like this:



You will see a smaller image of the *target molecule* in a window in the upper left part of the screen. We will call this the *active molecule*. In the upper part of this window you will see the molecule's *title bar*, which shows the level it occupies in the synthesis tree and its *number*. In the lower part you will see *target*, since this molecule is in fact our target molecule. As our synthesis tree is, for the moment, formed by only one molecule (i.e. the *target molecule* we have just introduced), the *title bar* reads "Prec.1 level 1".

Observe too that, on its right, there is a window with a "1" in a box. The synthesis tree will appear in this window as we generate it. In the upper part of this window you can read "Synt. tree of Porantherine".

c) Go with the mouse to the option "PROCESS-(aliphatic chemistry)", belonging to the *Process* menu. This will cause the program to try to *disconnect the molecule introduced, using the disconnections set into the CHAOS program.* These disconnections are in the tables in Appendix B-3 and are called *internal disconnections* because they form part of the program itself. After a brief wait, you will find a disconnection applicable to porantherine, which will be shown in a *dialog box* like the following one:



As you can see, the program has *added a ketone group* to the initial target molecule. This means that, in a *synthetic sense*, the target molecule can be obtained by reduction of this ketone and dehydration of the corresponding alcohol. Although there has been no breaking of bonds, we will say that the program has *disconnected the target molecule*. In the lower part of the dialog box, "Disconnection nº 3.12" can be read. This shows that the disconnection produced *belongs to the third group of disconnections ("Consonants"), concretely to Disconnection nº 12 in this group* (see the disconnection tables in Appendix B-3). You will see that the buttons labelled *Save*, *Ignore* and *Cancel* are displayed on the lower part of the screen.

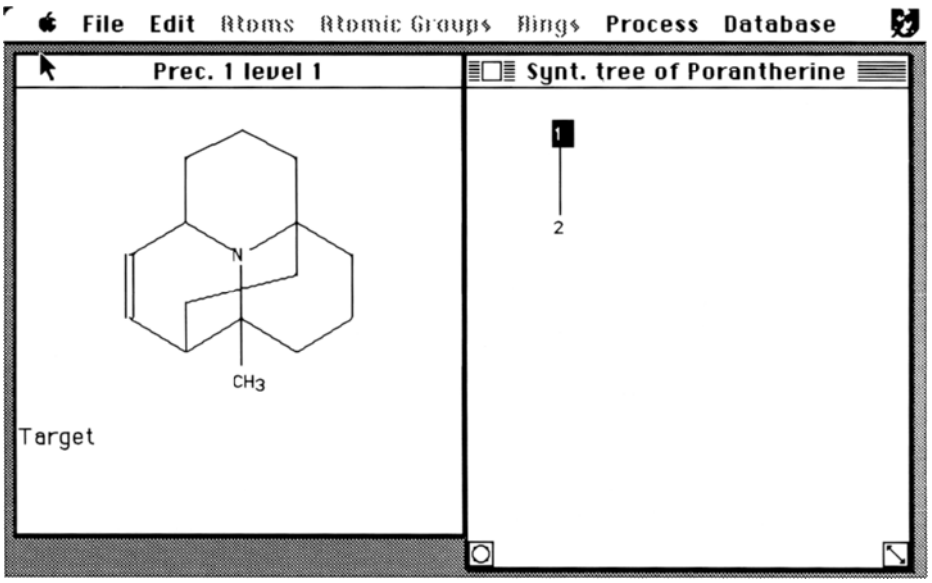
1. By clicking *Save*, you are telling the program to save this precursor and, in addition, to try to disconnect the target molecule in other ways (there may be other valid disconnections for the initial target molecule).

2. By clicking *Ignore*, you are telling the program you do not want to save this precursor (possibly because you yourself have decided it is not the most suitable from a chemical point of view), but that you do want the programme to try and disconnect the molecule in some other ways.

3. Clicking *Cancel* tells the program that you do not want to save the molecule and that it should not keep trying to disconnect the target molecule.

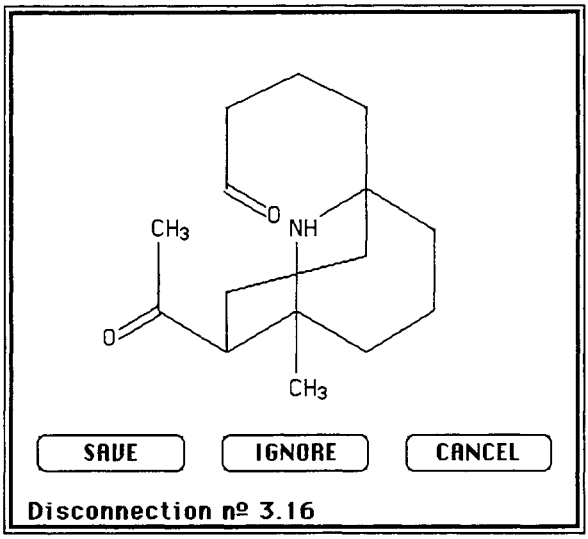
d) Click *Save*. After a short wait, the program will stop trying to disconnect the target molecule, as it will find no more disconnections applicable to this

particular molecule *within the third group of disconnections*. The screen will now look like this:



Note that a small synthesis tree with the numbers "1" and "2" has appeared. We will call each of the components of the tree a *node*. Click on node 2. In the *active molecule* window the ketone which the program has previously suggested appears. "Prec.2 level 2" can now be read in the *active molecule* window, while the name of the disconnection appears in the lower part. By clicking on any node in the tree you will be able to see the precursor represented in this node.

e) Convert Molecule n^{o} 2 into the *active molecule*. The program will understand that this molecule is at this moment the *target molecule*. Next, go again to the option "PROCESS-(aliphatic chemistry)" (*Process* menu). The program now disconnects this molecule by suggesting the precursors needed to perform a Mannich reaction (disconnection 3.16). Click *Save*. You can now see that the program offers another Mannich-type disconnection. This is because *the substructure corresponding to this disconnection has been found twice in the target molecule* Click *Save* again. No more applicable disconnections are found and the program halts.



Observe how the synthesis tree has grown. As we have seen, the most common way of using the CHAOS program is:

1. Convert the molecule you wish to process into the *active molecule.*

2. Go to the menu "PROCESS-(aliphatic chemistry)" so that the program can process this molecule.

Note also that the program is not able to generate an entire synthesis tree by itself. On each occasion it is the user who has to signal the precursor to be disconnected.

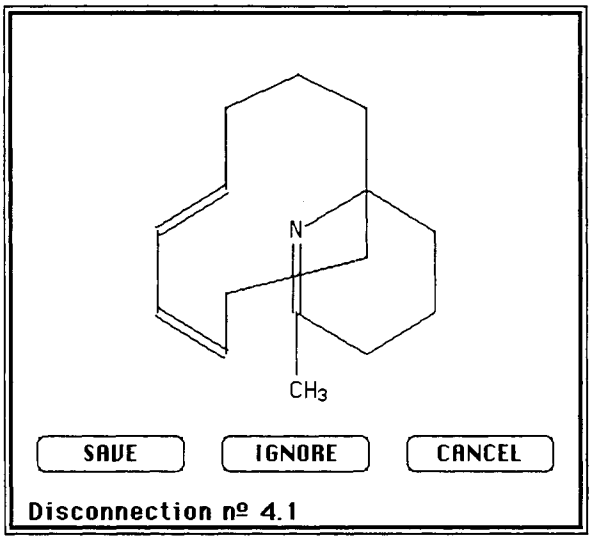
f) Convert molecule nº 1 into the *active molecule* and process it again. The program will generate the same precursor it had already generated and saved. This shows you can *re-process* a molecule. Normally this does not make much sense, but could be useful if you had not saved one of the precursors and wanted to recover it (to do this just click *Save* when the precursor comes up). Click *Ignore*, since you have already saved this precursor. If you click *Save*, this precursor will be *repeated* on the tree.

2.2.2. Automatic processing leaving out disconnections

a) Continuing with the example from the previous section, convert molecule nº 1 into the *active molecule* and process it (option "PROCESS-(Aliphatic chemistry)").

b) The program will suggest disconnection 3.12. Click *Ignore.*

c) Continuing in its efforts to disconnect the molecule, the program will now propose the following precursor:

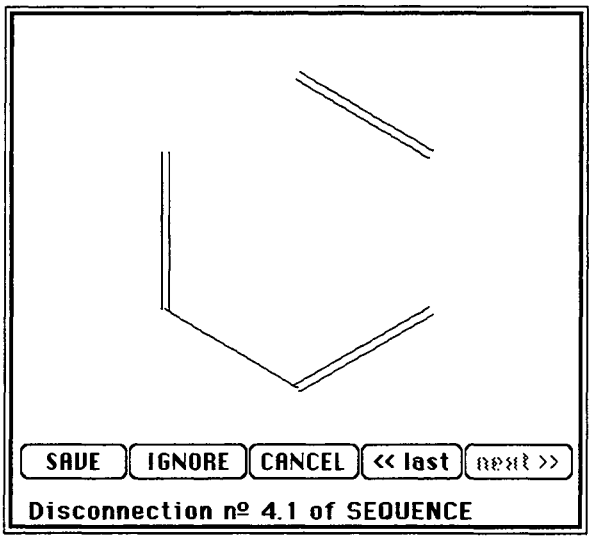


This is a Diels-Alder type disconnection. In the lower part of the dialog box you can read "Disconnection nº 4.1", i.e. *the first disconnection belonging to Group 4*. The following has occurred: you *ignored* the only disconnection with Group 3 that the program was capable of offering. Consequently, the program had no alternative but go to the disconnections in the following group (Group 4) trying to find a precursor. As can be seen, if you click *Ignore* for all the disconnections in a group, the program will automatically move forward to the disconnections in the following group. However, if you have saved any of the disconnections in a group, the following groups of disconnections will be considered lower-priority and so not be explored. Click *Cancel.*

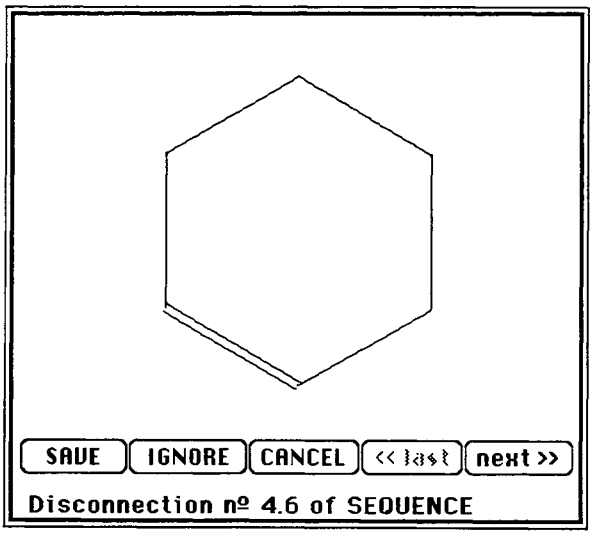
2.2.3. Automatic processing. Disconnections belonging to a sequence. Automatic separation of fragments

a) Draw *cyclohexane* with the Molecules editor. Save it under the same name.

b) Go now from the Processing screen to the option "PROCESS-(aliphatic chemistry)" (*Process* menu). The following dialog box will appear on screen:



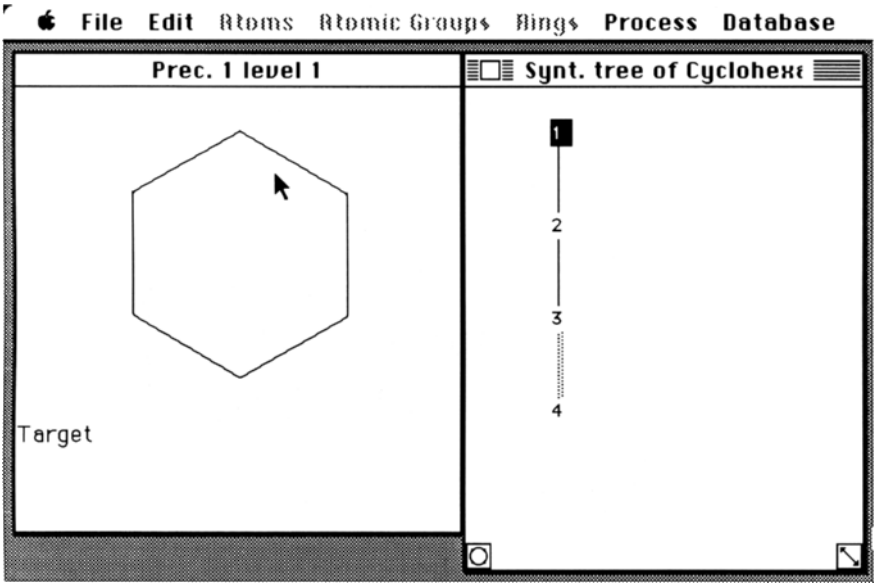
c) Click "Last" and the following figure will appear:



The following has occurred: the program has found a *disconnection belonging to a sequence* applicable to the target molecule. This disconnection is 4.6 and is *linked* to 4.1. Therefore both disconnections have been applied in tandem (i.e. *the fragments from the 4.6 disconnection have been in turn disconnected in line with 4.1*). The intermediate precursors of the sequence can be

seen using the buttons *Last* and *Next*.

d) Click *Save* and the resulting synthesis tree will look something like this:



Nodes 2 and 3 correspond to the two precursors generated during the sequence. A *dotted line* comes out of precursor 3.

e) Click on node 4. You will see that this contains the fragment of butadiene which was already present in node 3. The following has occurred: if *several fragments are generated* on disconnecting a molecule, the program assigns a node of the tree to the entire group of fragments (node 3 in our example) and also generates a separate node for each one of them, *provided they have at least 4 atoms*. To show that a node comes from a "separation into fragments," the program places dotted lines on the synthesis tree. A separate node was not assigned to the ethylene fragment because it has only 2 atoms.

2.2.4. Exploring the synthesis tree

a) With the synthesis tree generated in the previous example still on screen, move the mouse to the window where the synthesis tree appears and press the button, without releasing it, *anywhere there is no node*. Then drag the mouse and you will see how the tree moves round the screen. Release the button anywhere and the tree will remain set in that position. *Moving the tree* is useful for reaching

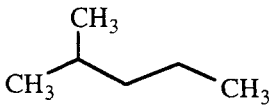
possibly hidden parts of the tree, since a synthesis tree often has so many "branches" that it does not completely fit in the window.

b) If you are using the Macintosh version, click the *circle* which appears in the box in the left lower part of the window. If you are using Windows, click the + sign in the upper left part. You will see that the synthesis tree *now fills the whole of the window*. This option is especially useful when a synthesis tree is very big and we want a quick overview of its shape and dimensions. If you again click on the circle (Macintosh) or + sign (Windows), the tree will again occupy its normal standard position and dimensions.

c) Different nodes on a synthesis tree may often represent in fact the same precursors or, to put it another way, *different syntheses can have common intermediates or use the same starting materials*. If you want to detect which nodes on the synthesis tree are identical to any other node, simply double click on it. All the precursors which are identical to each other as well as identical to the one we have double-clicked, will at once appear highlighted in *black* on the tree. If the intermediate we have double-clicked is the only one on the tree, the message "*no identical molecules to this one were found*" will appear.

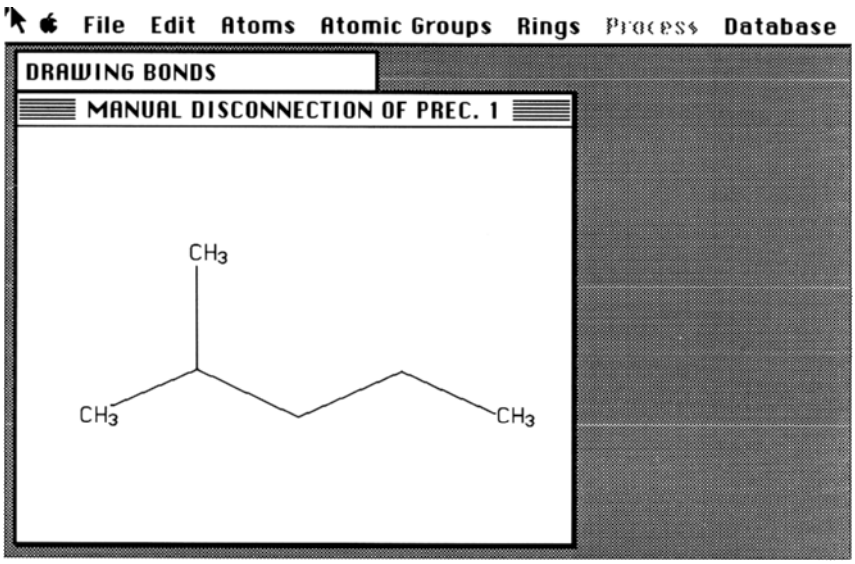
2.2.5. Manual processing of a molecule

a) Draw, with the Molecules editor, the molecule in the following figure, saving it under whatever name you want:



b) From the Processing screen go to the option "PROCESS-(aliphatic chemistry)" (*Process* menu). You will see that the program advises it cannot disconnect this molecule and asks the user to introduce some functional group.

c) If you want, you can disconnect the target molecule *manually*. To do this, go to the option "Add Precursor" (*Process* menu). You will see that the program *transfers you to the Molecules editor and brings up on screen the molecule which was previously in the "active window" of the Processing screen*. The upper part of the *editing window (title bar)* will now read "manual disconnection of prec. nº 1". On the *status line* the drawing operation which was *active* the last time the Molecules editor was used is shown (see figure):



d) Create a double bond between any two carbon atoms.

e) Go to the option "Save molecule and process" (*File* menu). You will see that the program *transfers you again to the Processing screen, but now a "branch" which did not exist before starts from molecule nº 1. This corresponds to the precursor you have added manually and is found in node nº 2.*

f) Click on node 2, so that molecule 2 becomes *active*.

g) Go to the option "PROCESS-(aliphatic chemistry)" (*Process* menu). This time the program is able to suggest precursors. In reality you have done a *trick* by adding *manually* a precursor, which can then be processed. *At any moment it is possible to disconnect manually (manual processing) any precursor on the tree.*

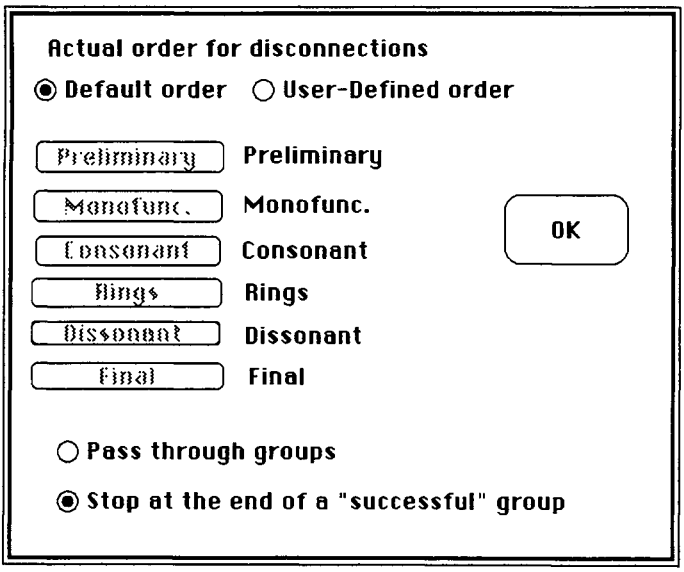
2.2.6. Heterocyclic disconnections

The program includes a few characteristic disconnections from the field of heterocyclic chemistry, which can be activated via the option "PROCESS-(heterocyclic chemistry)". These have only been included as examples. The Tables corresponding to these connections can be found in Appendix B-3. If the user really wants to use the CHAOS program in the field of heterocyclic chemistry, we suggest he/she should construct a *heterocyclic reactions data base* using the CHAOSBASE program.

2.2.7. Changing the order of disconnections

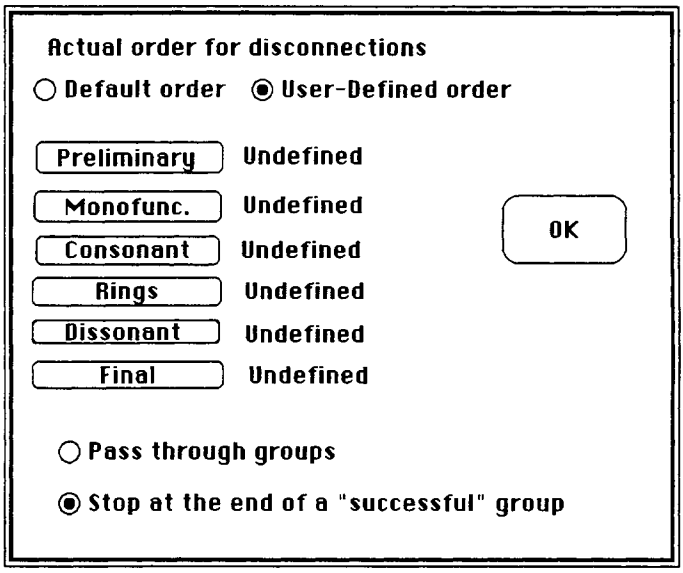
The disconnections included in the CHAOS program are arranged in *groups activated in order of decreasing priority*. The program contains a fixed order of priority for the groups. However, the user can change this priority as follows:

a) Go to the option "Set Disconnection order" (*Process* menu). The following dialog box appears on screen:

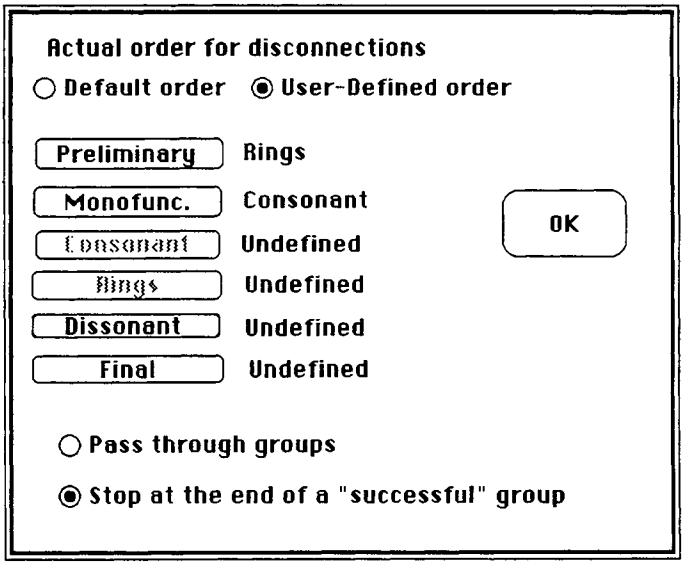


Observe that the command "Default order" is marked, which means that the program is working on a *normal* order of priority, i.e. the one set into the program. Consequently disconnections will be activated in the order in which they appear in the previous figure.

b) Click on the command "User-defined order". You will find that the buttons on the left are activated, the dialog box now looking like this one in the following figure:



c) Click the different buttons, *in the order in which you want to activate the different groups*. If, for example, you first activate "Rings" and then "Consonants," the screen will look like this:



d) Click "OK" to *tell the program you are only activating "rings" and "consonants" and in this order*. You do not need to activate all the groups. If you

then *process* a molecule (option "PROCESS-(aliphatic chemistry)"), the program will use these two groups in the order you decided.

e) Go again to the option "Set Disconnection order" (*Process* menu). You will see the order of disconnections just as you had left it. Click *default order*. This reestablishes *"normal" order*. If you want, by clicking *User-defined order* again, you can decide another different order of priority. We suggest you practise freely with the program, using different *disconnection orders* for different molecules and observing the results. Bear in mind the following points:

- *If not all the groups are activated*, the program may say that it cannot disconnect the molecule. If this occurs, either activate the *predetermined order* or propose your own order in which all the groups are present. The program may now be able to offer precursors. If not, it means that there is no disconnection in the program that can be successfully applied to this particular molecule.

- We suggest the following experiment: "activate" each time just one group and try to disconnect any molecule with this single group activated. Do this with each of the 6 existing groups and you will be able to see the disconnections which arise from each group in turn.

2.2.8. Permission to explore all the disconnection groups

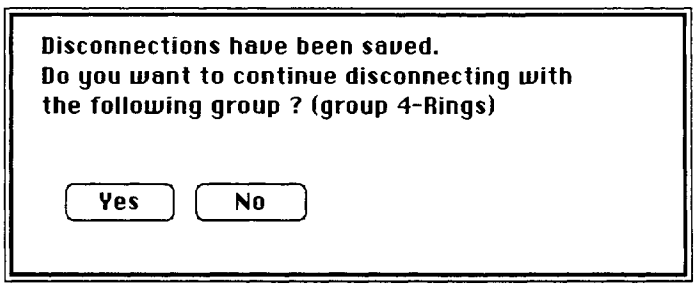
Look at the last figure. In the lower part of the window there are two controls with the names "Pass through groups" and "Stop at the end of a successful group". To understand their functioning:

a) Go to the option "Set disconnection order" (*Process* menu).

b) Activate the option "Pass through groups". Make sure the *default order* for disconnections is activated. Click OK.

c) *Open* the synthesis created earlier for porantherine. Convert precursor nº 1 of porantherine into the active molecule. Process this molecule (option "PROCESS-(aliphatic chemistry)" in the *Process* menu). When the program disconnects it (disconnection 3.12), click *Save*.

d) The following dialog box will then appear:



Clicking "Yes" tells the program to continue trying to disconnect porantherine.

Clicking "No" halts the disconnection process.

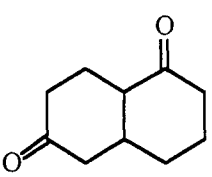
e) Click Yes. You will find that the program continues to suggest precursors for porantherine. *Save them.*

f) Each time the program reaches the end of a group, the dialog box in the last figure will return. Allow the program to reach the last group of disconnections.

In summary, when "Stop at the end of a successful group" is activated, *the program stops the process of disconnecting a molecule if it has managed to make at least one disconnection by the time it reaches the end of a group and if the user has decided to save the relevant precursor.* This is what happened with the examples discussed in earlier sections. However, if "Pass through groups" is activated, *the program will be able to apply all the disconnections in the program, ignoring the priority between groups, but "asking for permission" each time it has to pass from one group to another.*

2.2.9. Perception of bifunctional relationships

a) Use the Molecules editor to draw the following molecule. *Save it* under any name you want.

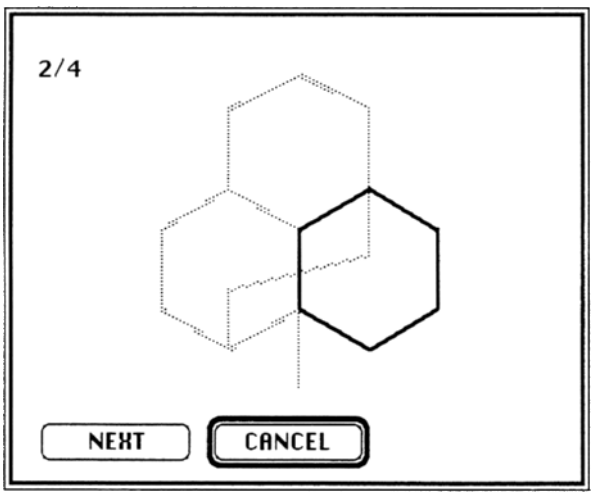


b) Once in the Processing screen, go to the option "See bifunctional relationships" in the *Process* menu. A dialog box will come up, in which the program shows one of the "bifunctional relationships" present in the molecule and

indicates whether it is "consonant" or "dissonant". In the lower part of this screen are buttons with the names "Next" and "Cancel". Click "Next" and you will see the other bifunctional relationships come up on screen, one after the other. You can click "Cancel" at any moment to leave out the bifunctional relationships which have still not come up. You can see the bifunctional relationships of any molecule, just by converting it into the *active molecule* and then moving to the option "See bifunctional relationships".

2.2.10. Perceiving rings

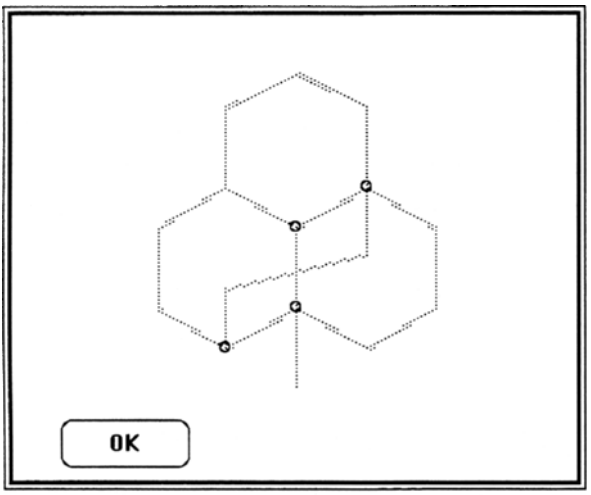
The program is able to give information on the *total number of rings* found in the *active molecule*, how many of them are *synthetically significant* and which are *primary* ones. Use, respectively, the options "See all rings," "See SS rings" and "See primary rings," all in the *Process* menu. After activating these options, a dialog box tells you how many rings there are in the *active molecule*, followed by another box like the one in the following figure, where the rings are pictured one by one.



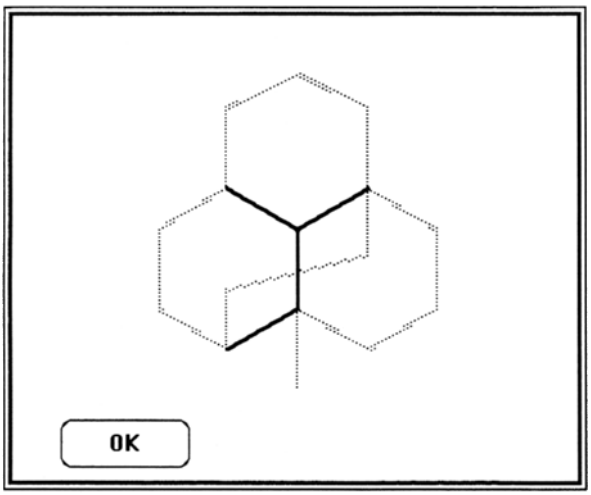
Click "Next" to see the following ring (the rings appear in the same order in which the program has detected them. This order cannot be predicted). At any moment you can click "Cancel" to leave out the rings which have still not come up. In the upper left part of this dialog box you can check how many rings out of the total number have been seen.

2.2.11. Perception of other structural features

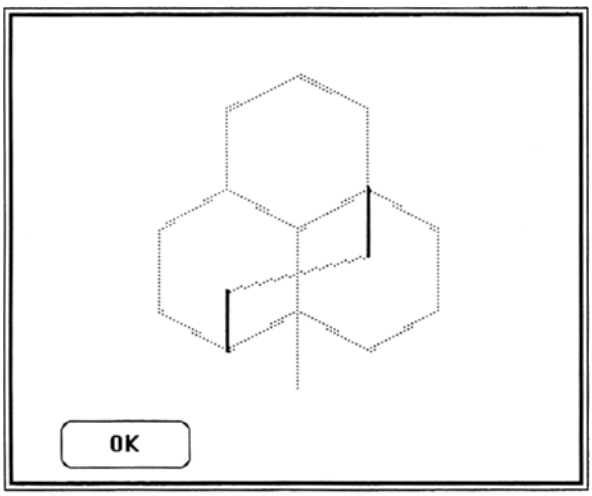
The program also allows you to see the *bridgeheads* (for polycyclic bridge systems), *core bonds* and *strategic bonds* of the *active molecule*. You must enter the appropriate menus: "See bridgehead sites," "See core bonds," and "See strategic bonds" (*Process* menu). Examples of the application of these options to the porantherine molecule are shown:



Bridgeheads.



Core bonds.



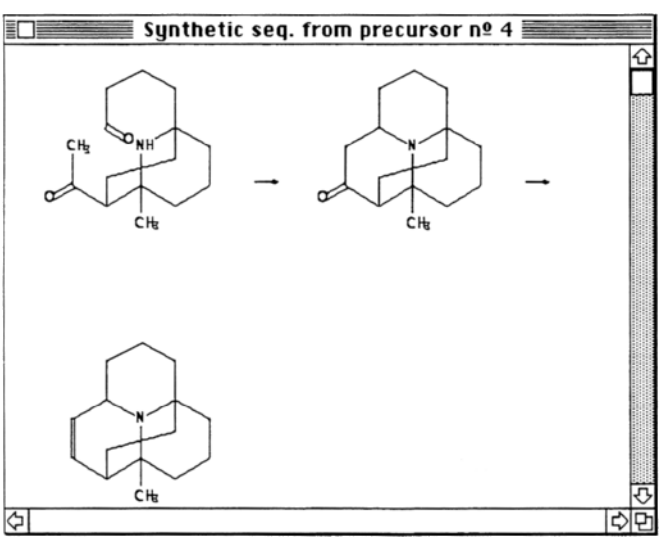
Strategic bonds.

2.2.12. Viewing an entire synthetic pathway

The option "Synthetic sequence" (*Process* menu) brings up a window where you can see what a synthesis proposed by the program looks like, starting from any precursor on the tree. To use it:

a) Convert the precursor of the tree, *from which you wish to view the synthetic pathway*, into the active molecule.

b) Go to the option "Synthetic sequence" (*Process* menu). A window comes up on screen which, taking porantherine as our example, would look like this:



You will see a molecule sequence starting at the active molecule and following the synthesis tree in an "upwards" direction until it reaches molecule nº 1. In other words, the screen shows *how to arrive, in a synthetic sense, at molecule nº 1 beginning with the molecule you have marked as "active".*

If you want to see the synthetic sequence starting from another precursor, you must follow these steps:

c) Close the window of the "synthetic sequence" by clicking on its *close box.*

d) Convert the precursor wanted into the *active molecule.*

e) Activate again the option "Synthetic sequence".

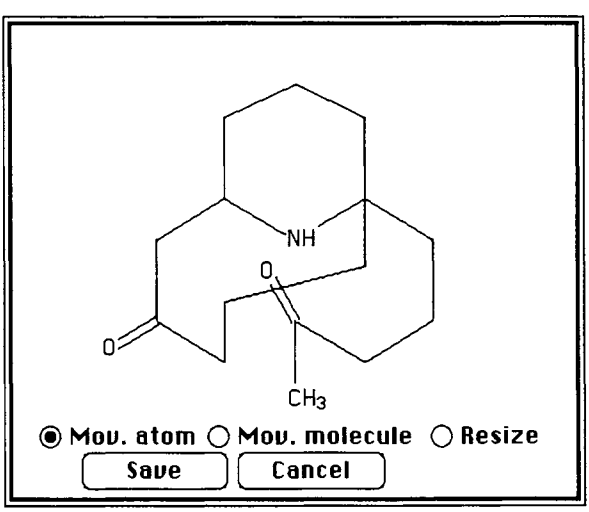
2.2.13. Modifying the drawing of any precursor

The option "Modify precursor" (*Process* menu) permits you *to modify the position of the atoms in any precursor on the synthesis tree.* It has been introduced because, when the program disconnects a molecule, partially overlapping atoms may appear, or the precursor generated may come up in an impossible conformation.

To use the option "Modify precursor":

a) Convert the molecule whose appearance you wish to modify into the *active molecule.*

b) Go to the option "Modify precursor" (*Process* menu). A dialog box like the one in the following figure will appear:



As you can see, the command "Mov. atom" is activated.

c) Move the mouse to any atom, press the button and, without releasing it, drag this atom to the position you want. Then release the button and the atom will be set in its new position.

d) You can also move the entire molecule and modify its size, using the controls "Mov. molecule" and "Resize," respectively. These functions are used identically to the analogous options in the Molecules editor.

e) Either click *Save* on the modified molecule and return to the Processing screen or *Cancel* to discard the changes.

2.2.14. Disactivating the option "Unique numbering"

You will observe that an option reading "Unique numbering: ACTIVE" appears at the end of the *Process* menu. This option has a *mark* on its left. To understand its function, do the following:

a) *Select* this option.

b) Bring up the *Process* menu again. It will now read: "Unique numbering: INACTIVE."

Each time you go to this option, it changes status: i.e. if it is active, it changes to inactive and viceversa.

c) Make sure the option is *inactive*. Use the Molecules editor to draw *cyclohexane. Save it* under this name.

d) Now go from the Processing screen to the option "PROCESS-(aliphatic chemistry)" (*Process* menu). You will see that *the program repeatedly proposes (twelve times in fact) the same disconnection.* Click *Ignore* each time.

e) *Activate* the option "Unique numbering".

f) Go again to the option "PROCESS-(aliphatic chemistry)". This time the program will display only one disconnection.

Briefly we can say that, because of the nature of the *search for retrons* algorithm, the program finds the retron needed for disconnection with the Diels-Alder reaction *twelve times*, due to the symmetry of the cyclohexane molecule. With the option "Unique numbering" activated, the program *is able to check whether the precursor about to be shown has already been shown. If it has, its display is suppressed.*

The user can activate or disactivate this option at will, since its use, although it does avoid the display of repeated information, can make the computer work too

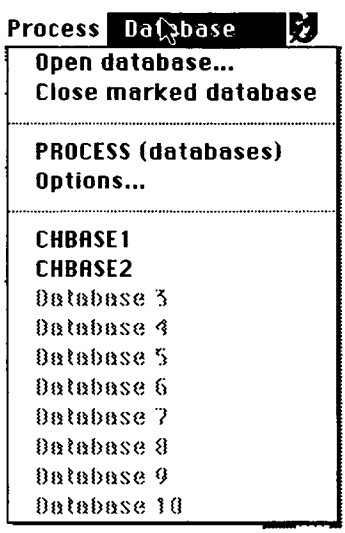
slowly for some molecules. This will depend on the particular molecule, the disconnection and the speed of the computer.

2.2.15. Working with data bases

Before reading this section, you should read *Heading 3* of the manual, which deals with *creating reactions data bases* with the CHAOSBASE program. In addition, you will have to have created the *data base* shown there ("CHBASE1") in order to follow the exercise in this section.

For the CHAOS program to function with a previously created *data base*, you must first *open it*. The option "Open database" (*Database* menu) brings up a dialog box with which you can locate and open the data base you want.

The CHAOS program permits a maximum of 10 data bases to be open simultaneously. The data bases' names will come up on the same *Database* menu, as the user opens them. If you have two data bases open, called "CHBASE1" and "CHBASE2," the menu will look like this:



You can *close* a data base at any moment. To do this:

a) Select the data base you wish to close from the *Database* menu, which will then be *marked.*

b) With a data base marked, go to the option "Close marked database" (*Database* menu). The data base in question will be *closed* and will no longer

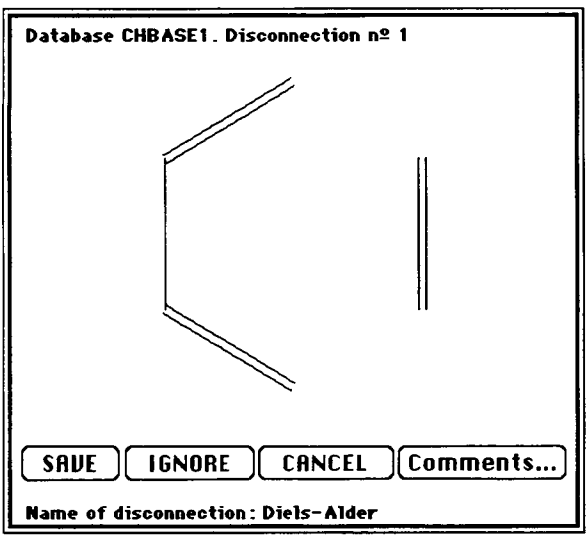
appear on the *Database* menu.

So that the program can disconnect a molecule using the *data bases* open at that moment, you will have to go to the option "PROCESS-(Databases)" (*Databases* menu).

c) Open the "CHBASE1" database, created in the exercises in *Heading 3* of this manual.

d) Use the Molecules editor to introduce the cyclohexene molecule into the CHAOS program.

e) From the Processing screen, go to the option "PROCESS-(Databases)" (*Databases* menu). You will find a dialog box looking like the following figure. This dialog box varies slightly between the Macintosh and Windows versions.



As can be seen, the name of the data base used to make the disconnection is shown, as is the name of the disconnection and its position within the data base.

The buttons *Save*, *Ignore* and *Cancel* are used in the same way as when the program is working with the disconnections already set in (option "AUTOMATIC PROCESS - (aliphatic chemistry)").

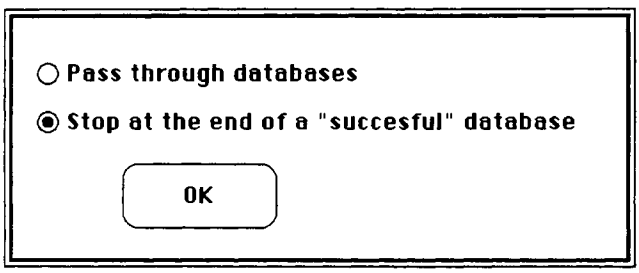
There is an additional button *Comments*, which lets you see *comments on the disconnection which you introduced via the CHAOSBASE program in the moment of creating it.* These comments will usually be bibliographic references, reaction conditions, etc.

f) Click *Save* to save the precursors proposed.

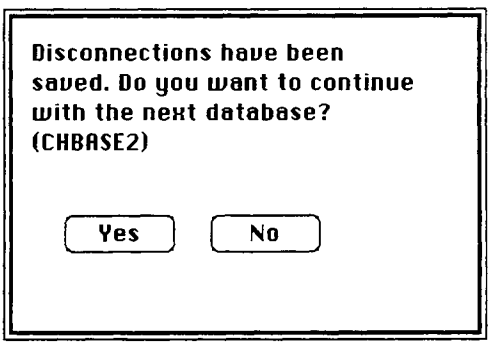
Sequences of disconnections can be built by the CHAOSBASE program, analogous to those included in the CHAOS program. If CHAOS finds a sequence included in a data base, applicable to the target molecule, a dialog box will come up, which is very similar to the one in the last figure but also contains the buttons *Last* and *Next*. These buttons allow you to see the various intermediate precursors generated in the sequence.

It is important to bear in mind that the data bases opened behave exactly as if they were "groups of predetermined disconnections," i.e. the data bases take an order of priority according to the order in which they were opened. Therefore, when the program has successfully made one or more disconnections with a particular data base, then it does not explore the lower-priority data bases.

However, the program can be made to ignore this order of priority. To do this, use "Options" (*Database* menu), which brings up the following dialog box:



Click on "Pass through databases" and the program (after successfully applying at least one of the disconnections of a data base) will display a dialog which looks like as follows:.



Click "Yes" and the program will move to the next data base opened. Click "No" and it will halt. In short, the option "Pass through databases" is equivalent to the option "Pass through groups".

2.3. Other available options

2.3.1. Copying figures on the Clipboard

What is described in this section is only applicable to the Macintosh version.

The CHAOS program can *export* pictures to other programs. To do this:

a) Draw any molecule using the Molecules editor.

b) Select the option "Select" (*Edit* menu), which will then be ticked on the menu.

c) Go with the mouse to the *editing window*. The cursor will adopt the shape of a square with dotted lines on two of its sides, which shows that the program is in *select mode*.

d) Situate the cursor in the *editing window*, so that the molecule is *under it and to its right*. Press the button and drag the mouse. A rectangle which follows the mouse's movements will appear. Place the molecule inside the rectangle and release the button. The molecule will be surrounded by a rectangle of dotted lines.

e) Go to the option "Copy" (*Edit* menu) and you will *save on the clipboard the whole area surrounded by the rectangle*. The drawing in this area can be introduced into any program capable of displaying *pictures*, such as a drawing program or the majority of word processors.

f) Go again to the option "Select," which will disactivate this option.

The option "Select" can be used to copy on the "clipboard" *any figure* appearing in the windows of the CHAOS program. For example, you can copy *synthetic pathways obtained with the option "Synthetic sequence" (Process menu)*, synthesis trees, etc.

Note: If the Select option is activated and you are working in the Molecules editor, none of the drawing options will function, even if the status line shows that one of them is activated. Similarly, working on the Processing screen, it will not be possible to move the synthesis tree nor change the active molecule. The option "Select" must be disactivated before performing any of these activities.

Note: The program does not allow figures to be imported from other programs ("Paste" option), as these figures would lack the structural information needed for the CHAOS program to perceive the functional groups, rings, etc.

2.4. Limitations of the CHAOS program

In its present versions, the menus "Page Setup" and "Print" cannot be used.

3. RUNNING THE CHAOSBASE PROGRAM

3.1. Introduction

The CHAOSBASE program has been designed to *create retrosynthetic reactions data bases*, i.e. *transforms data bases*. These *transforms* can be used by the CHAOS program to create synthetic pathways. As many data bases as are needed can be created, but CHAOS can only use a maximum of 10 data bases simultaneously.

3.1.1. Features characteristic of the CHAOSBASE program

To introduce reactions in a file, do as follows:

1. First *create* a new data base using the option "New Database" (*File* menu) or *open* a pre-existing data base using the option "Open Database" (*File* menu).

2. Next *introduce reactions ("disconnections")* into this data base. The reactions are introduced in two stages:

a) In the first stage tell the program *which atoms are involved in THE PRODUCT* of the reaction and how they are connected: i.e. the *retron* (or *substructure)* is introduced.

b) In the second stage, the user processes these atoms in order to produce THE ATOMS INVOLVED IN THE REAGENTS, i.e. the *synthon* is introduced.

Therefore *the reactions are introduced in a retrosynthetic direction.* It is very important to remember that on creating the retron *you must only give the program the atoms involved in the reaction* (and not the *entire molecule* which the user will be thinking of in connection with the reaction).

The disconnections introduced into a data base will be used by the CHAOS program as follows: CHAOS will search for groupings of atoms (*substructures* or *retrons*) in the target molecule and if it finds one of these *retrons*, it will try to

disconnect the target molecule in order to produce the reagents.

3.1.2. Features that can be determined for transforms

The CHAOSBASE program can introduce the following features in the *transforms*:

1. *Special attributes* for each one of the atoms involved.

2. *Restrictions* on the application of the transform

These *attributes* and *restrictions* are discussed later on in the manual. *Sequences of disconnections* can also be defined, so that several *transforms* are applied successively to the target molecule. *Notes, bibliographic references,* etc., linked to each reaction, can also be introduced. The CHAOS program lets the references linked to a transform be seen when it manages to disconnect a molecule using this transform.

3.2. Functioning of the CHAOSBASE program

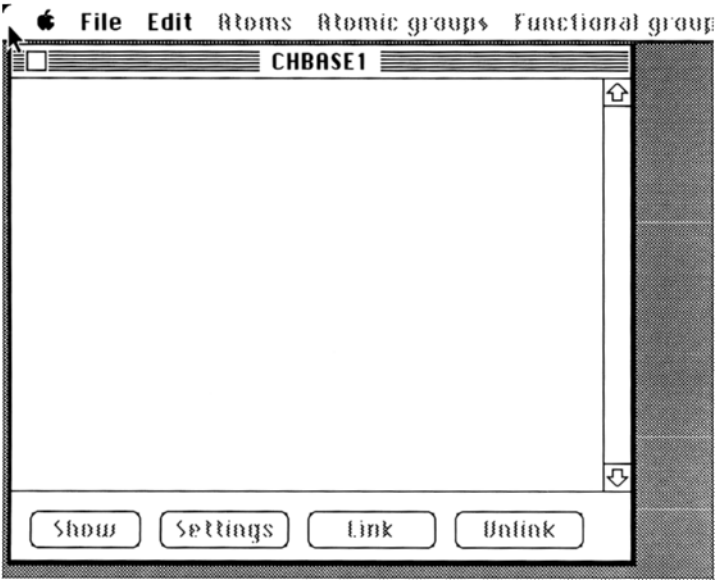
3.2.1. Starting up the program

On entering the program (by a double click on its icon), the only thing you will see is the *menu bar*. To begin work, you must bring up on screen the *window corresponding to a data base* by going to the options "New Database" or "Open Database" (*File* menu).

3.2.2 Creation of a new data base

a) Go to the option "New Database" (*File* menu). A dialog box, with which you can name your new data base and select its location, will come up.

b) Where it reads "UNTITLED," write "CHBASE1" and click *Save*. The screen will look like this:



Now you can begin to introduce reactions into the "CHBASE1" data base. If you want, go directly to *Heading 3.2.4.*

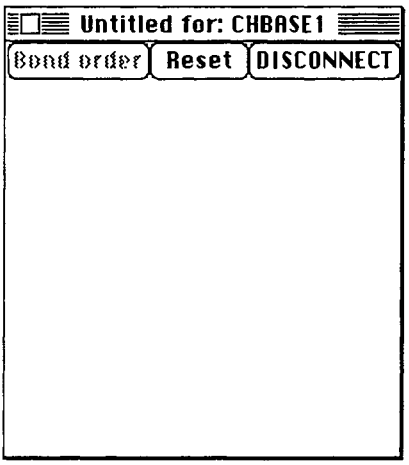
3.2.3. How to open a pre-existing data base

Go to the option "Open Database" (*File* menu), which will bring up a dialog box. Locate the file you desire to open and double click on its name or, with the file highlighted in black, click "Open".

3.2.4. How to define a reaction (disconnection)

3.2.4.1. Drawing a substructure or retron

With a data base window on screen, go to the option "New disconnection" (*File* menu), which will bring up a new window, whose appearance will look like this:



In this window the user can draw the *substructure* or *retron* associated with the disconnection to be introduced. We will call it the *window for defining substructures*. The substructures are drawn in a very similar way to the molecules in the CHAOS program (i.e. by pressing the button of the mouse where we want to locate an atom and dragging the mouse, without releasing the button, to where we want to locate an atom linked to the first one). On introducing a substructure, it is assumed that carbon atoms are being positioned. In general, the way of introducing any substructure is:

1. Draw a *skeleton of carbon atoms*. Carbon atoms must be drawn *even in the places where we want to introduce heteroatoms.*

2. Incorporate the heteroatoms, *converting* carbon atoms (whichever we want) into the heteroatoms we really want to introduce.

The main differences between *drawing a molecule* with the CHAOS program and *drawing a substructure* with CHAOSBASE are *the way of introducing double and triple bonds* and *the way of introducing heteroatoms*. As you will see, on introducing a substructure into the CHAOSBASE program, the following possibilities exist:

1. *Each bond can imply several bond orders at the same time.*

2. *Each atom can in fact be of several different kinds.*

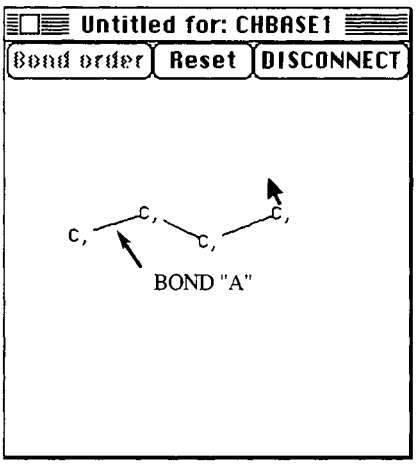
3. *Each atom can include "special attributes".*

4. *Each atom can be assigned the property of "forming a part or not of determined functional groups".*

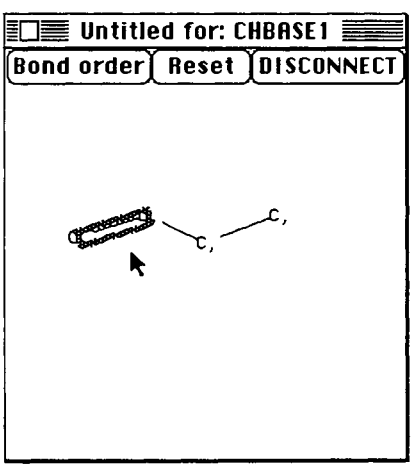
In the following sections, how to use these possibilities is explained.

3.2.4.1.1. Introduction of multiple bond orders

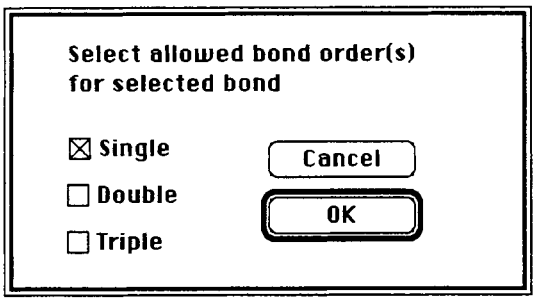
a) Draw in the *window for defining substructures* four carbon atoms joined to each other, as in the following figure:



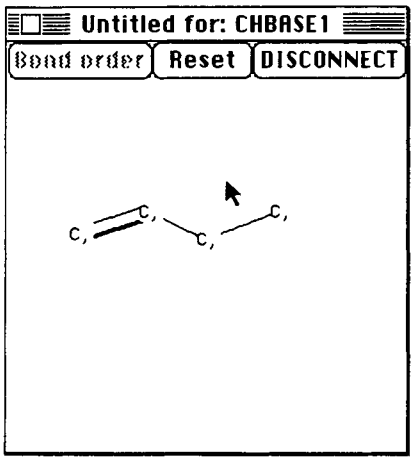
b) Click on bond "A" of the above figure. You will see that this bond is surrounded by a rectangle, at which point we can say the bond is *selected.*



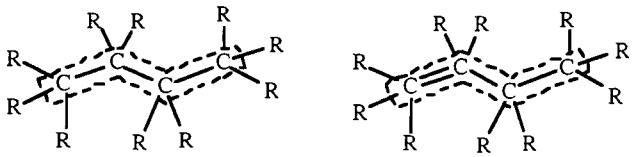
c) Click the command "Bond order" and the following dialog box will come up:



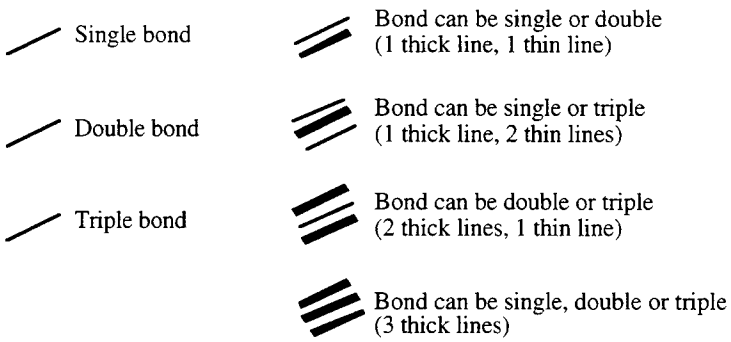
You can then choose what bond order you want for the selected bond. *You can select several bond orders at the same time.* Click "Double," leaving the orders *single* and *double* both *marked.* Click "OK". The dialog box will disappear. Observe, however, that the bond remains *selected.* Click anywhere in the *window for defining substructures* and the *rectangle* round the selected bond will vanish. The screen will now look like the following figure:



Observe how a double bond with one *thin* and one *thick* line has appeared, a graphic representation that this bond can be *single* or *double* in the target molecule. The CHAOS program will detect the presence of this substructure provided it finds either of the two atom groupings in the following figure:



For some disconnections it will probably make more sense to decide that a bond could be *double* or *triple*. CHAOSBASE allows any combination of the three possibilities (single, double or triple) to be determined for each bond. The different combinations are represented on screen by *different bar codes:*

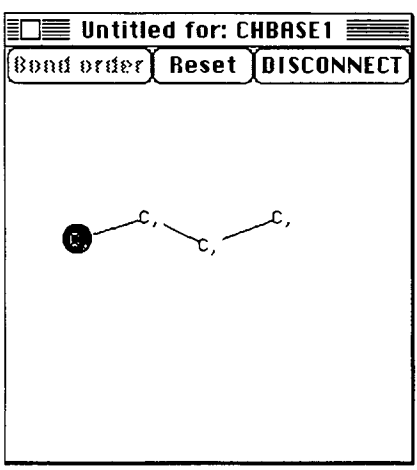


3.2.4.1.2. Clearing a substructure

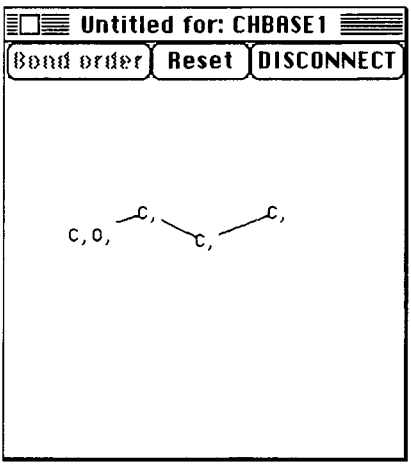
Click "Reset" and you will *eliminate the substructure you were drawing.* There is no option for clearing only one bond or atom. *A substructure cannot be recovered once it has been eliminated.*

3.2.4.1.3. Introduction of heteroatoms and atomic groups

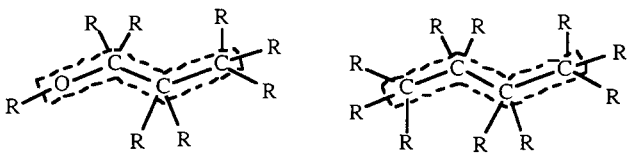
a) Draw again a substructure consisting of four carbon atoms joined to each other. Click on one of the atoms at the extremes, which will *select* this atom, placing it inside a circle:



b) Select the option "Oxygen" in the *Atoms* menu. Click anywhere in the *window for defining substructures* to eliminate the *circle*. The window will then look like this:



Observe that the fact of choosing a heteroatom on the *Atoms* menu does not clear selections already made for this atom, i.e. the selection of "oxygen" does not clear the selection of "carbon". Therefore, *we have an atom which includes two options: carbon and oxygen.* This reflects the possibility that the atom may be either *carbon* or *oxygen* in the target molecule. The CHAOS program will detect the presence of this substructure provided it finds either of the two following atom groupings:



This option makes the definition of a *transform* very versatile. However, more usually an atom will be of one type only, e.g. oxygen, in which case:

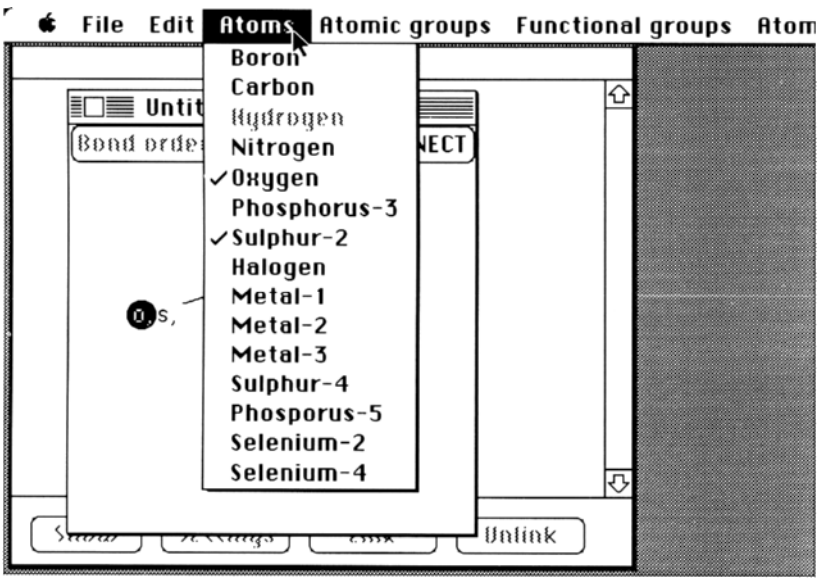
c) Select again the atom which can be "carbon or oxygen," so that the atom is inside a circle. Go to the option "Carbon" in the *Atoms* menu, which will eliminate the "carbon" possibility for this atom and just leave the *"oxygen"* possibility. In general, if you want to eliminate one of the elements chosen for an atom, you have

to select this atom and go to the element (on the *Atoms* menu) you wish to eliminate.

d) With the atom still selected, go to the option "Sulphur-2" (*Atoms* menu). By doing this *you will make this atom either oxygen or sulphur.* If you want, you can *assign more heteroatoms* to this atom.

The *atomic groups* defined in the *Atomic groups* menu are assigned and eliminated exactly the same as the heteroatoms on the *Atoms* menu. *It is possible to assign to the same atom simultaneously both heteroatoms and atomic groups.*

Observe that, *when an atom is selected* (ringed by a circle), some ticks appear on the *Atoms* and *Atomic groups* menus at the side of each one of the heteroatoms and atomic groups specified for this atom (see the following figure).



3.2.4.1.4. Assignation of "Belonging to a functional group"

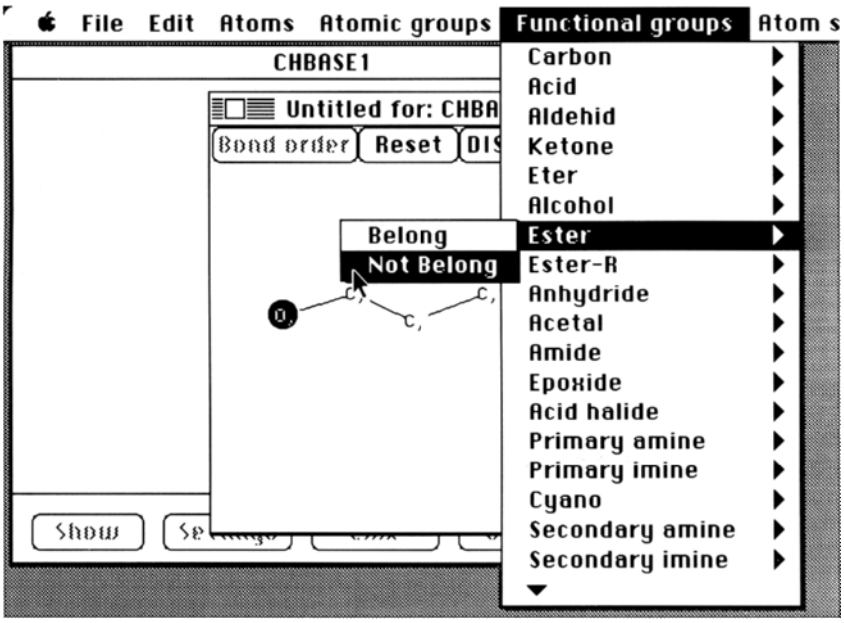
When an atom is selected (i.e. inside a circle), you can:

1. *Specify that this atom must form a part, in the target molecule, of one or various functional groups.*

2. *Specify that this atom must not form a part of certain functional groups.*

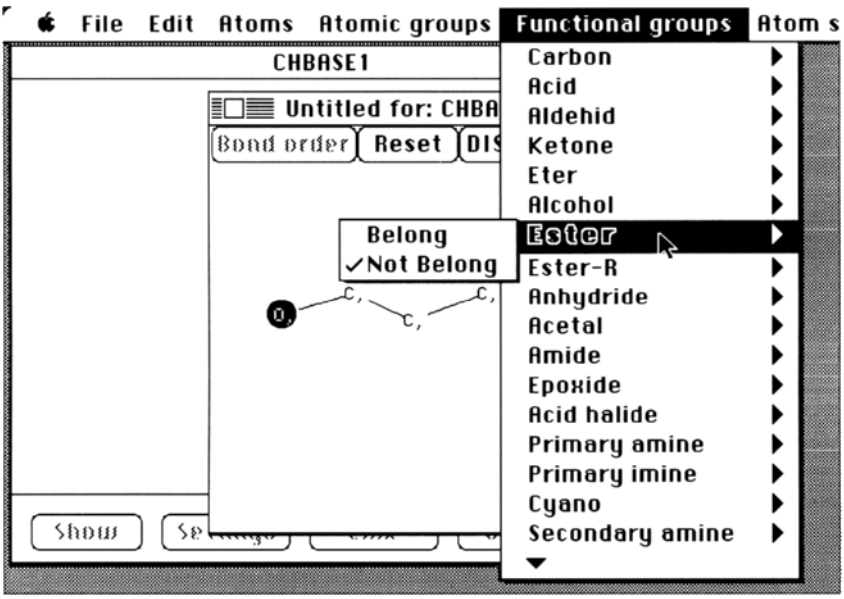
To do either of these, you *select* the atom and go to the *Functional groups* menu, where all the functional groups which the CHAOS program can perceive are displayed. Each one of them is accompanied by a "sub-menu" with two

options, "Belong" and "Not belong", either of which you can select (see the following figure).

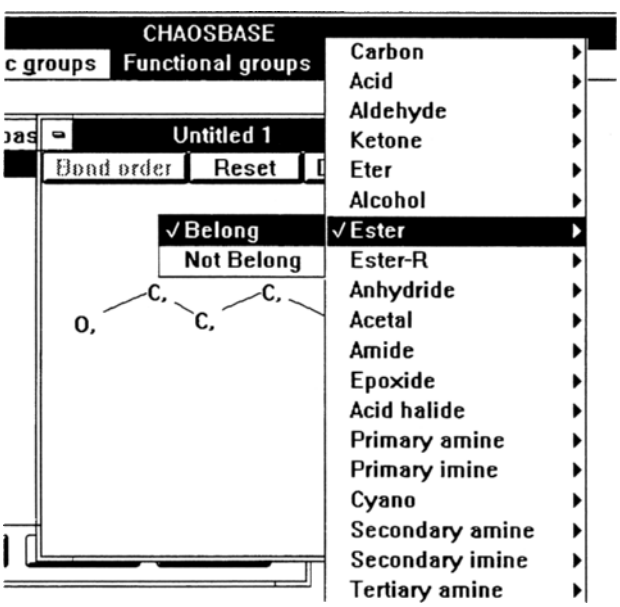


After specifying a functional group for a particular atom, no visual identification comes up on screen: just observing a *retron* in the *window for defining substructures* does not let us know which functional groups have been specified for each one of its atoms. How then do we find out which functional groups are assigned to an atom? By simply *selecting* this atom and going to the *Functional groups* menu. There is a slight variation in what we see, depending on which CHAOSBASE version we are using.

In the Macintosh version the functional group will be displayed in "Outline" and there will also be a *mark* at the side of the option chosen, as in the following figure:



In the Windows version, however, a *mark* will come up both at the side of the functional group chosen and at the side of the option for belonging or not belonging (see the following figure).

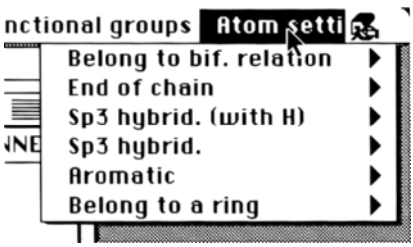


If you want to eliminate a previously established *relationship of* a specific atom*belonging to a functional group*, just *return to the appropriate menu* as if you were selecting this option again. This *eliminates the selection.*

Note: Observe that the option "Carbon" appears on the "Functional groups" menu. This option is used to specify that the atom marked is a carbon which is not connected to any heteroatom.

3.2.4.1.5. Assignation of "special attributes"

It is possible to specify whether an atom in a substructure *possesses or not certain special attributes*. This can be done by simply selecting an atom and going to the *Atom settings* menu, where different *special attributes* available in the present version of CHAOSBASE are displayed. Each one of these has a "sub-menu" with two options ("Belong" and "Not belong") for specifying the possession or otherwise of the attribute in question. These options are used in exactly the same way as the ones for *belonging or not to a determined functional group. Possession* or *non-possession* of one or several *attributes* can be specified for the same atom.



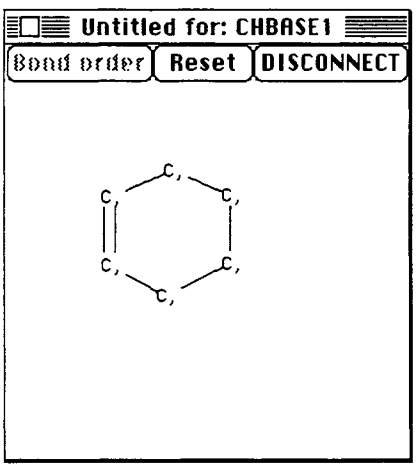
Note: CHAOSBASE does not prevent the introduction of substructures which are contradictory. It is possible, for example, to indicate that a nitrogen atom belongs to the functional group "Ketone". Nor does it prevent possible violations of valence. The consequences of defining an "impossible retron" are that the CHAOS program will never be able to detect its presence in the target molecule.

3.2.4.2. Producing the synthon: how to tell the program what procedures have to be performed on a transform to disconnect it and produce the precursors

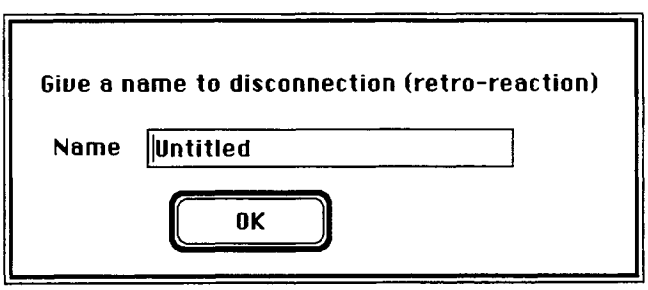
Some of the following exercises are aimed at creating a data base called

CHBASE1 where we will *introduce the Diels-Alder reaction*. It is important to do these exercises, as this data base is used in the part of the manual which deals with the CHAOS program.

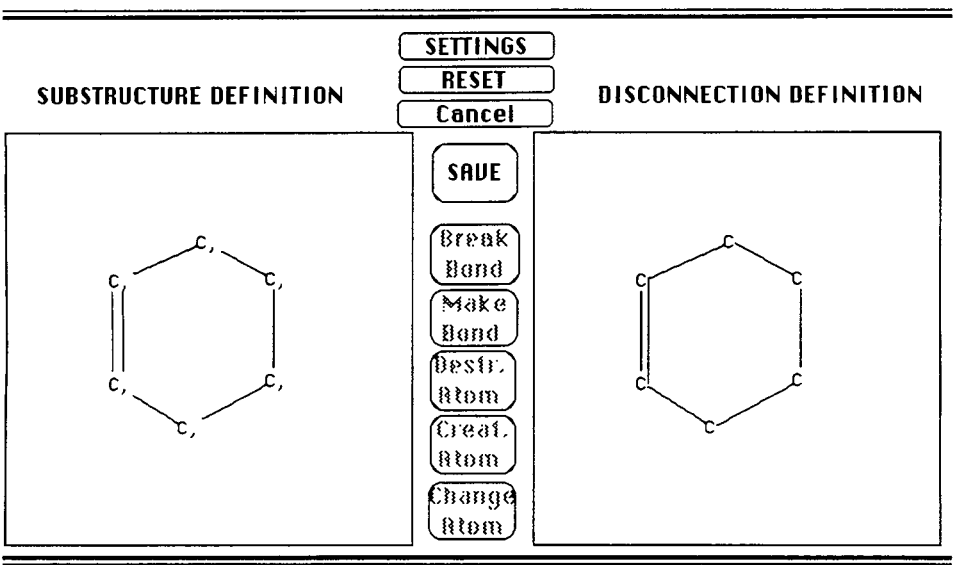
a) *Open* the CHBASE1 data base previously created. This must be *empty*. If you find a reaction in it, leave the CHAOSBASE program, clear this data base, re-enter the program and *create* the CHBASE1 data base again, using the option "New database" (*File* menu). Go to the option "New Disconnection" and introduce the substructure displayed in this figure:



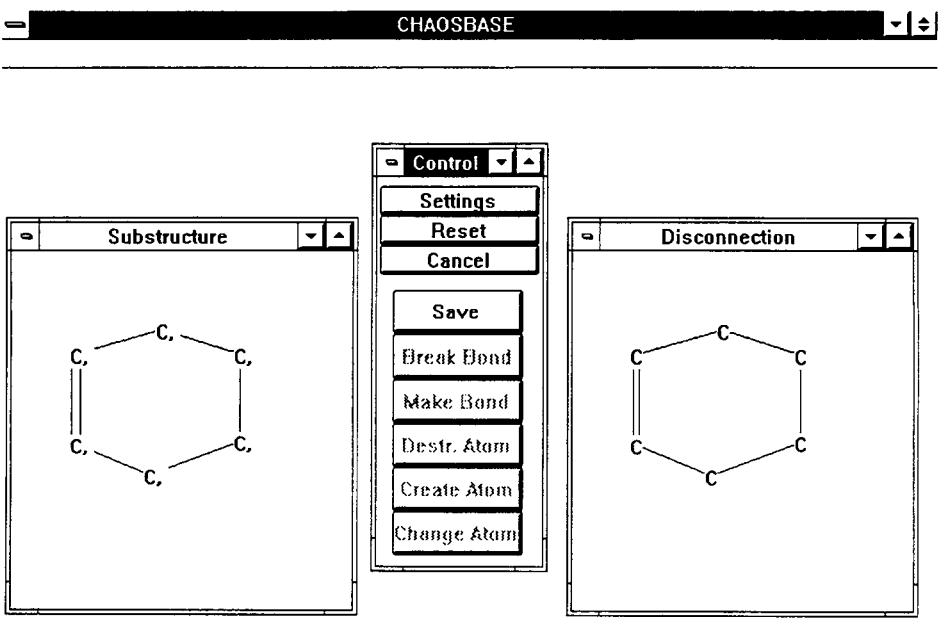
b) Click "Disconnect" and the following dialog box will come up:



On the line reading "Untitled," type *Diels-Alder* and click "OK". A dialog box, which will vary depending on whether you are using the Macintosh or Windows version of the CHAOSBASE program, will come up.



Macintosh version



Windows version

When we have this dialog box on screen, we say we are in *disconnection mode*. On both right and left you can see the *substructure* previously introduced. The left-hand box *remains to show the user how the retron looks like*. It is not possible to alter the content of this box. The user can *process* the figure on the right *to lead to the disconnection of the retron* (i.e. elaboration of the *synthon*). These procedures are basically for:

1. Clearing or creating bonds.

2. Eliminating or creating atoms.

3. Changing the *nature* of an atom: converting, for example, an oxygen into a sulphur atom.

To elaborate the *synthon* you want, you can combine the actions above in any way. With the exception of *creating new atoms*, all these actions require prior selection of an *atom* or *bond*, which is done by just clicking on the atom or bond you want.

When you have *selected an atom*, you can move to the commands.

1. "Destroy atom" *clears* the atom.

2. "Create atom" creates *an atom which is near the marked atom, but not joined to it.* The behaviour of "Create atom" may seem a little odd. It has been introduced because you may sometimes want to show, alongside the precursors, some reagent which, for example, acts as a catalyst. The fact that this atom is located *near in space to a previously marked atom* is so that the CHAOS program can assign it some coordinates.

3. "Change atom" converts the selected atom into another atom. On activating this option, a dialog box to select the new atom comes up.

When you have *selected* a bond, you can go to the commands "Break bond" and "Make bond," which are of course to *break* and *create* bonds, respectively.

To introduce new atoms, as already stated, you do not need to select any atom or bond: simply follow the technique explained above when discussing the CHAOS program (press the button of the mouse *near* the atom at which you want to start drawing and, *without releasing the button*, drag the mouse to where you want the new atom. Once there, release the button). This technique can also be used *to create bonds between atoms already on screen, but not joined directly.*

Other commands available are:

"RESET". Click "RESET" to eliminate all the procedures performed on the substructure, to go back to the *retron again*. It is useful if you want *to re-start* the

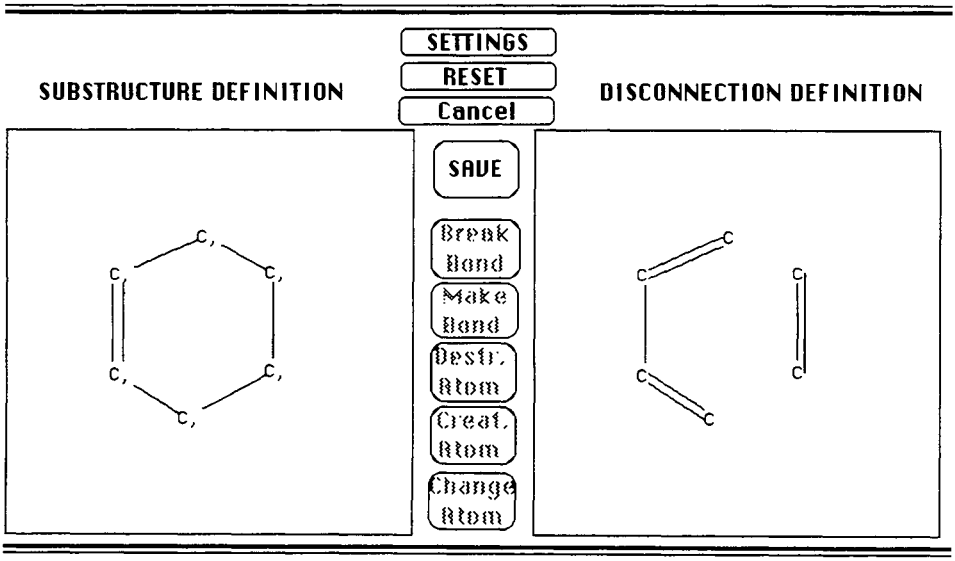
disconnection process because you have made mistakes.

"SETTINGS". This introduces *restrictions* on the application of the disconnection as well as *comments* on the disconnection, usually bibliographic references.

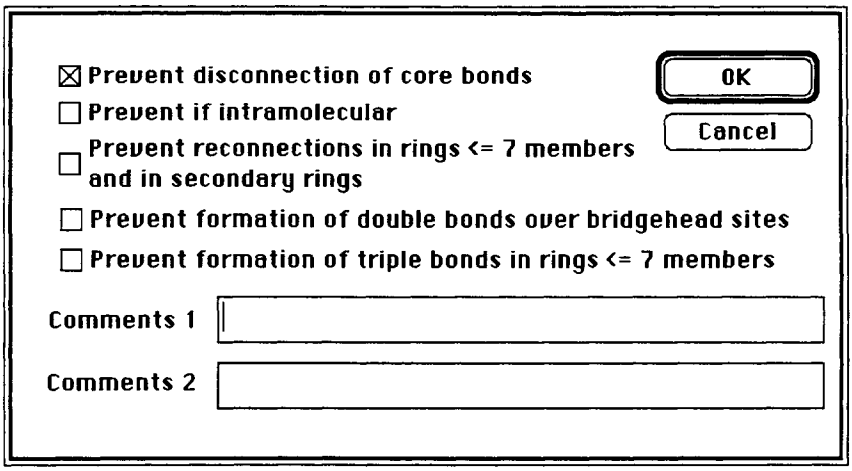
"SAVE" is to *save* the disconnection in the data base and leave the *disconnection mode.*

"CANCEL". By clicking this command, you can leave the *disconnection mode* without *saving* the disconnection in the data base.

c) *Disconnect* the cyclohexene substructure in line with the Diels-Alder reaction. To do this you must *select* those bonds which, in a retrosynthetic sense, *disappear;* and then go to the command "Break bond". You will also have to *select* those bonds which, *in a retrosynthetic sense*, change from singles to *doubles*. All these procedures should lead to a dialog box like the one in this figure:



d) Click "Settings" and the following dialog box will come up:

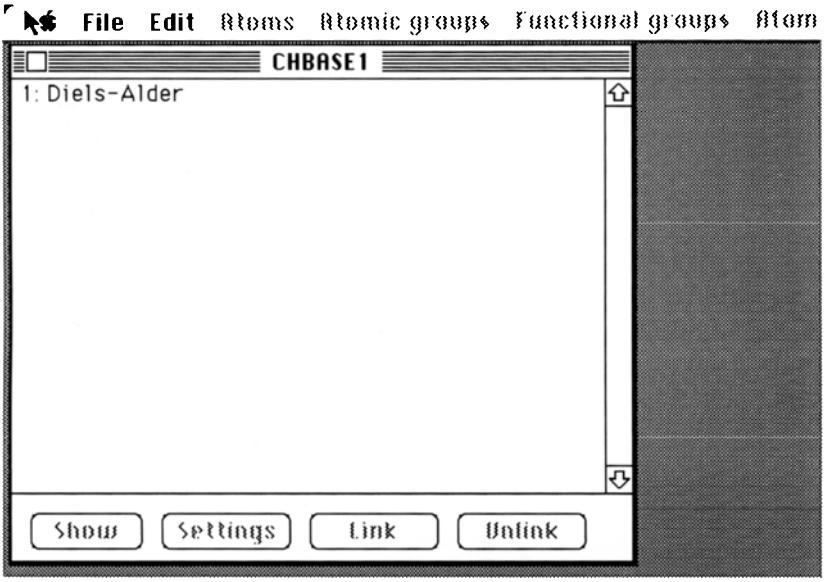


With this dialog box you can select the *restrictions* on disconnection which you want. Observe too that *prevention of disconnection of core bonds* comes up on screen automatically, as it is very often important that this option is active. If you want, you can disactivate it by clicking it. In the lower part there are two lines with the names "Comments 1" and "Comments 2," where *notes*, *bibliographic references*, etc., relevant to the disconnection being introduced can be written.

Click "OK" without modifying the contents of this dialog box. There is no need for further comments about it: just use it as you think best when defining a disconnection. And remember that, if you do not introduce *restrictions*, some disconnections could produce rather unsuitable results from the synthetic point of view.

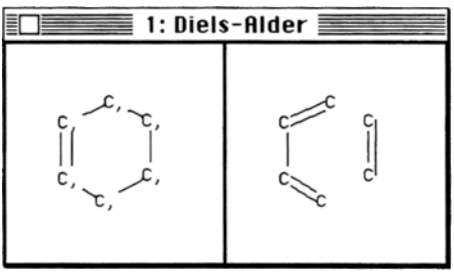
Note: Use the restrictions on "formation of triple bonds in small rings" and "formation of double bonds over bridgehead sites" only when strictly necessary. Their use can be very time-consuming, as the CHAOS program needs to search for the rings in the precursors generated to check whether a double bond on a bridgehead or a triple bond in a ring with less than 8 members has been formed.

e) Click *Save* and the dialog box will disappear, leaving the screen looking like this:



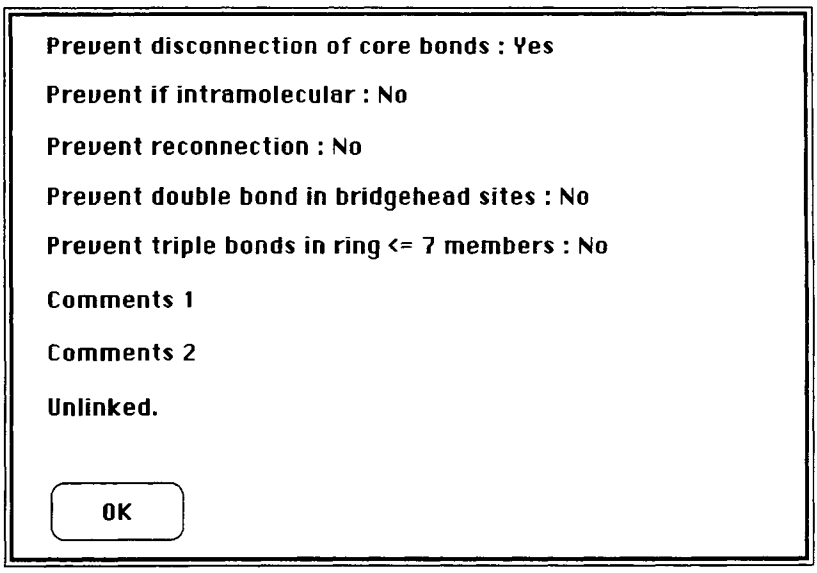
3.2.5. Studying what a previously introduced disconnection looks like

a) You should have the CHBASE1 data base with the Diels-Alder reaction on screen. If you do not, *open* this data base (Option "Open database" in the *File* menu). Make sure that the line reading "1:Diels-Alder" is *highlighted in black.* If it is not, click on the line to *activate* it. Then click "Show," which is in the bottom part. *A small window, where the disconnection introduced is shown, comes up*:



We will call this window *"Show" window. Close* this window by clicking the *close box* in the upper left corner.

b) Make sure that the line reading "1:Diels-Alder" is *highlighted in black.* Click on "Settings" and you will see the following dialog box:



With this dialog box you can both check what *restrictions* have been established for a specific *transform* and read the *comments* introduced. Additionally, in the lower part, there is information on whether or not it forms part of a *sequence of disconnections*. In this particular case it reads "Unlinked," which shows that it is an *individual* disconnection, not forming part of a *sequence*. Further on there is an exercise on *sequences of disconnection*. Click "OK".

c) Make sure that the line reading "1:Diels-Alder" is *highlighted in black*. Go to the option "Open disconnection" (*File* menu) or simply double click on this line. The *window for defining substructures* will come up again, with the *retron* which belongs to the Diels-Alder reaction. This window can be used for two purposes:

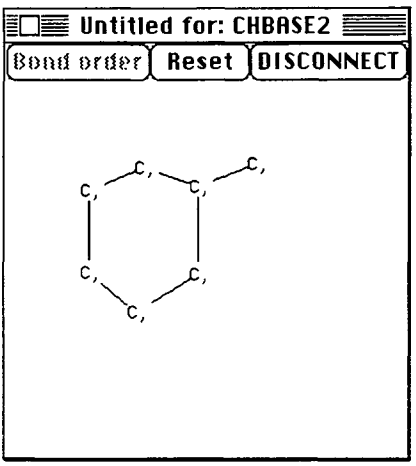
1. In order to check "belonging or not to functional groups" and "possession or not of special attributes" of each one of the atoms which form part of the *retron*, just select the atom you wish to check and go to the *Functional groups* or *Atom settings* menu. The options selected for the atom are *marked* on these menus.

2. To completely redefine a transform. More on this possibility later.

3.2.6. How to define sequences of disconnection

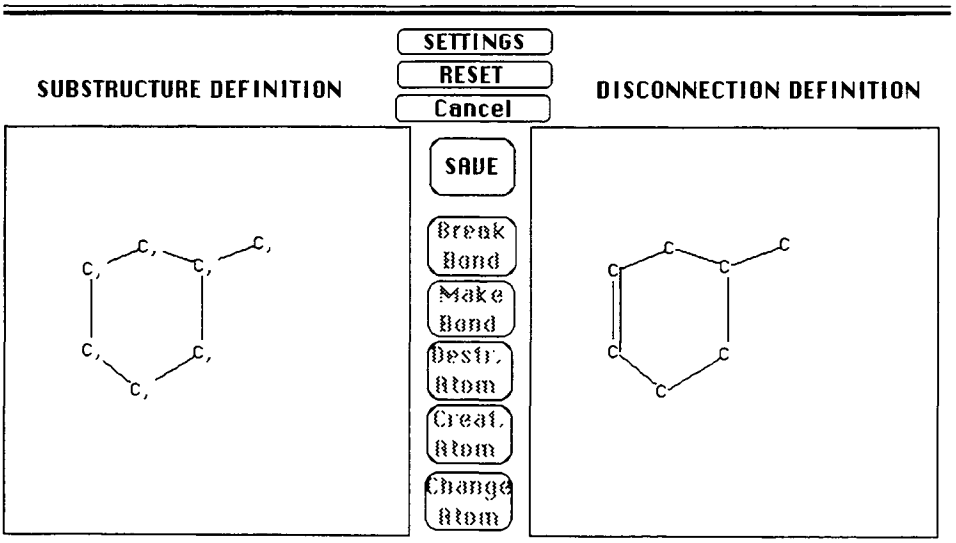
a) If you have any data base open, close it. *Create* a new *data base* ("New database" option in the *File* menu) and call it CHBASE2.

b) Go to "New disconnection" (*File* menu) and bring up the *window for defining substructures*. Draw the following substructure in it:



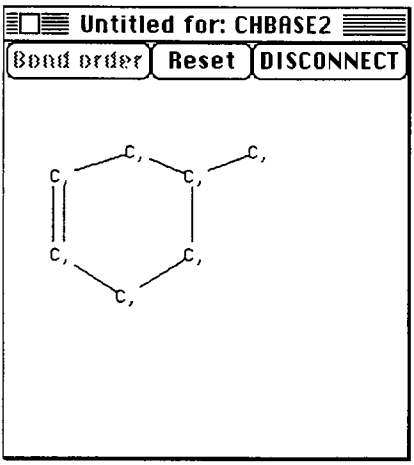
c) Click "DISCONNECT". Give the disconnection the name "Diels-Alder-1 activation" and click "OK". The program will automatically move into *disconnection mode*.

d) Once in disconnection mode, make *a bond between two carbon atoms*:



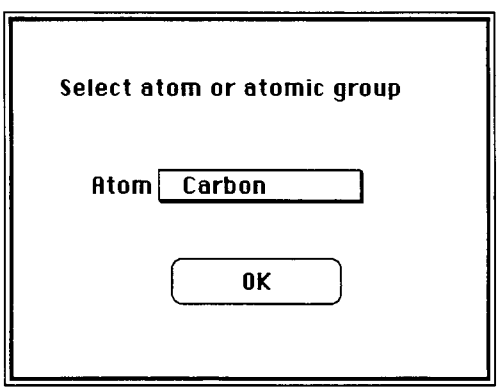
e) *Save* the disconnection (clicking *Save*).

f) To introduce *a second disconnection* in this same data base, you must still have on screen the window corresponding to CHBASE2. Bring up again the *window for defining substructures* (option "New disconnection" in the *File* menu). Draw as a substructure *exactly the result of the preceding disconnection*, i.e. the fragment of 4-methylcyclohexene.

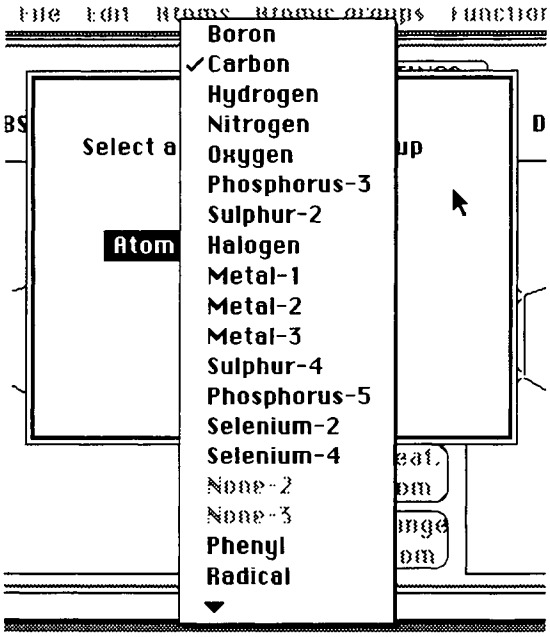


g) Click "DISCONNECT". Give the disconnection the name "Diels-Alder-2 activation" and click "OK," which will take you automatically to the *disconnection mode*.

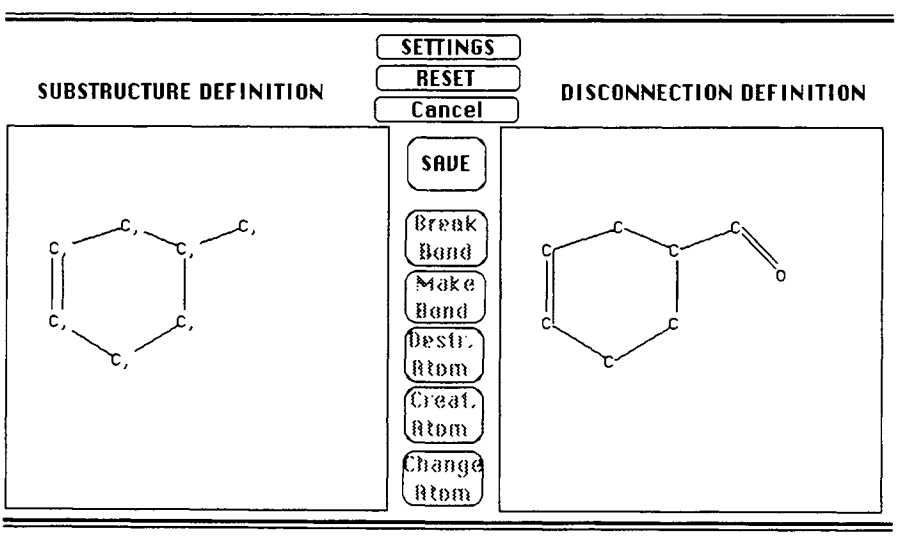
h) Now, for the first time in this manual, you have *the possibility of creating new atoms linked to a pre-existing one*. Go to the "methyl" and start drawing from it (press the button and, without releasing it, drag the mouse to where you wish to locate a new atom). When you release the button, the following dialog box will come up.



The program is ready to create a new atom, but *it needs to know what element in concrete it must create*. Click "Carbon" and *a pop-up menu will appear*:

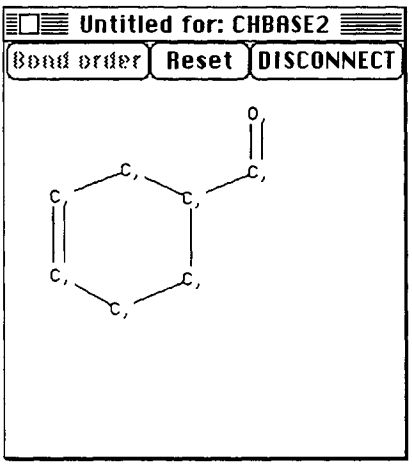


i) Select the option "Oxygen" from this menu. Click "OK" and *you have created an oxygen atom*. Next, *select the bond which joins the oxygen to the carbon atom* and click "Make bond". The screen should now look like this:



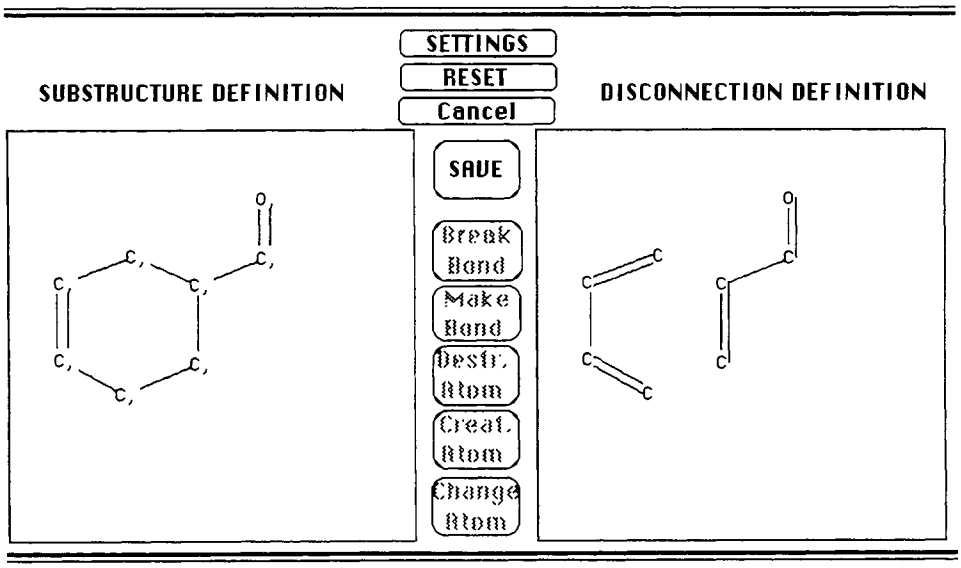
Click *Save* to save the disconnection.

j) To introduce a third disconnection into the data base, re-open the *window for defining substructures* and draw a substructure *equivalent to the result of the previous disconnection*, as is shown in the following figure:

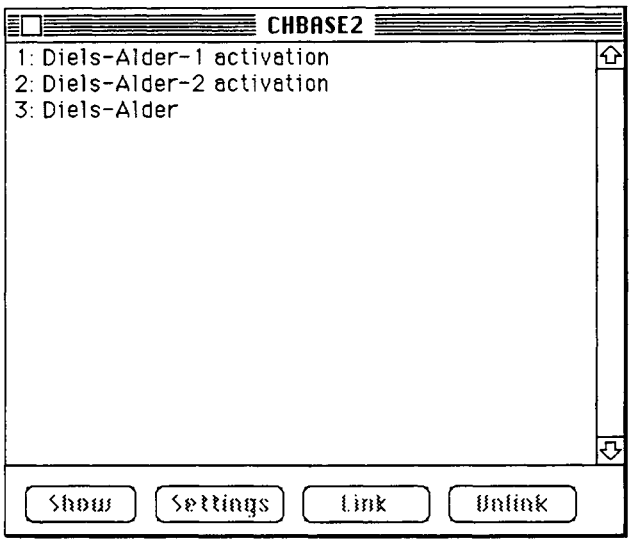


k) Click "DISCONNECT". Give the name "Diels-Alder" to the disconnection and click "OK".

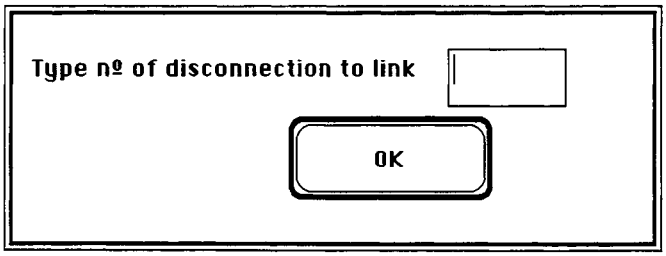
l) Next, disconnect the substructure as can be observed in the following figure. Click *Save*.



m) After clicking *Save*, your screen will probably look like this:

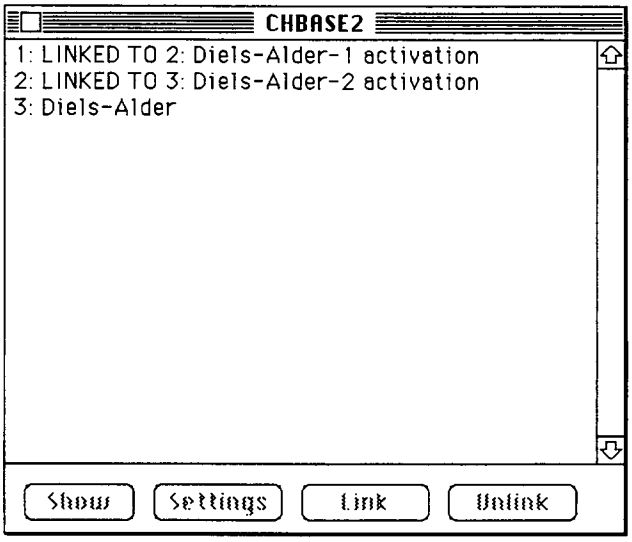


Click on the line "1:Diels-Alder-1 activation " to highlight it in black. Move to the "Link" button and the following dialog box will come up:



Write "2" (without the inverted commas) and click "OK".

n) Click on the line "2: Activation Diels-Alder 2" to *highlight it in black*. Go to "Link," type "3" in the dialog box and click "OK". Your screen should now look like this:



By taking all these steps *you have defined a sequence of disconnections. When you use this data base with the CHAOS program, CHAOS will perform the following actions*:

1. If the retron corresponding to disconnection n^{o} 1 is present in the target molecule, *disconnections 1, 2 and 3 will be applied sequentially*. The result will be the generation of various "levels" of precursors in just one step.

2. If the retron corresponding to disconnection 2 is present in the target molecule, *disconnections 2 and 3 will be applied sequentially*. Disconnection 1 will not be applied, since *it is only applied in the context of a sequence and not as an individual disconnection*. In this case too, various "levels" of precursors will be generated.

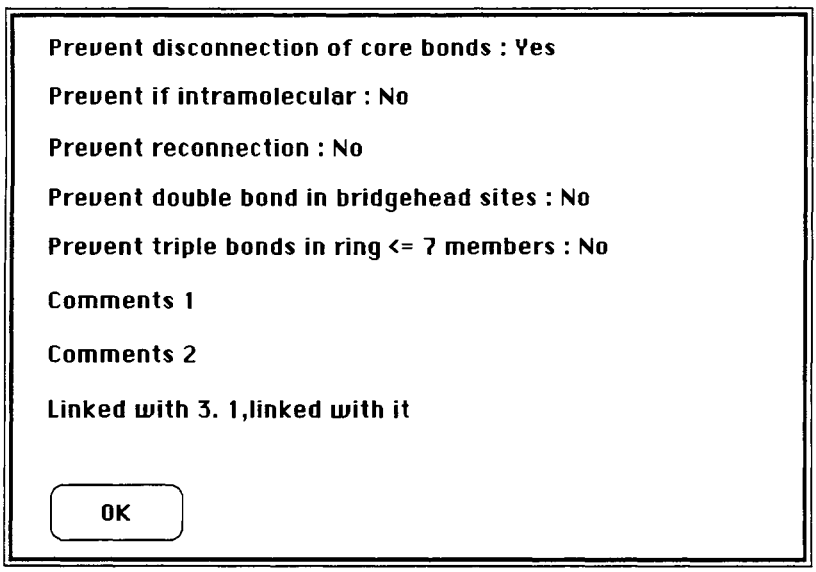
3. If the retron corresponding to disconnection n^{o} 3 is present in the target molecule, this disconnection will be applied individually and the result will be shown to the user. *Disconnections 1 and 2 are only applied in the context of a sequence and not as individual disconnections.*

In conclusion, the following should be kept in mind:

1. A sequence can be applied *from any of the intermediate stages until the end.*

2. The last stage of a sequence can be an *individual* disconnection: the rest can only be applied *in the context of a sequence.*

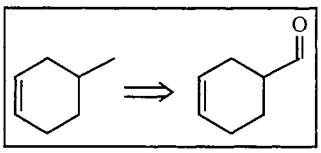
o) Click on the line "2: Activation Diels-Alder 2" to *highlight it in black.* Move to the command "Settings". Note that there is information in the lower part of the dialog box on the belonging of this disconnection to a sequence. Concretely "*linked with 3. 1, linked with it*" can be read.



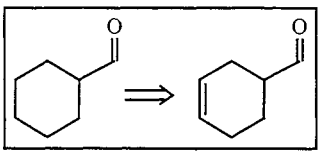
Note: For the CHAOS program to perform successfully a "sequence of disconnections", the result of the disconnection (synthon) corresponding to the "n" stage of the sequence must correspond exactly with the substructure (retron) of the "n+1" stage. The user must define and "link" (via the "Link" command) the disconnections correctly, in such a way that the resulting sequence makes sense to the CHAOS program.

Note: With the exception of the final stage, a transform must never be used in a sequence of disconnections which, on being applied, generates several fragments: the CHAOS program will be unable of carrying through such a sequence.

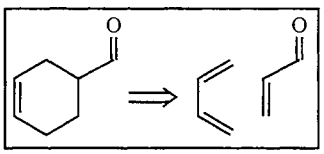
Note: It is not possible to link one disconnection to several other disconnections at the same time. However, it IS possible the opposite: to link several disconnections to the same one. For example, to link disconnections "X" and "Y" to "Z" makes sense and may be useful.



Disconnection"X"



Disconnection "Y"



Disconnection "Z"

Note: Sequences of up to ten linked disconnections can be defined. However, bear in mind that the time the CHAOS program needs to perform a sequence of this nature may be too long.

Note: "Sequences of disconnections" and "individual disconnections" can coexist in the same data base without any problem.

With everything stated above, the user is now ready to build *sequences of disconnections*. Finally, we will explain how the program is also able to *undo sequences*. This requires just these two steps:

1. In the data base window click the disconnection that you want to *unlink* from a sequence. This will then be *highlighted in black.*

2. Click the command "Unlink".

Note: It is only possible to "unlink" the first disconnection from a sequence. If you want to "undo" the entire sequence, you must apply the option "Unlink" to all the disconnections, but successively, beginning with the first: if we have the sequence "disconnection A linked to B" and "disconnection B linked to C", "Unlink" must first be applied to disconnection "A" and then to disconnection "B".

p) Problems in a sequence of disconnections: If the user builds a sequence of disconnections which is then not performed by the CHAOS program, it could be for the following reasons:

1. The *synthon* of one of the stages does not correspond exactly to the *retron* of the following stage.

2. The successive *synthons* and *retrons* correspond correctly, but one of the disconnections in the sequence was not done for a reason such as: violation of the valence of an atom, the existence of *restrictions* on the application of a disconnection, or *special attributes* not fulfilled by an atom.

Bear in mind that the CHAOS program views the sequences as a whole. Therefore, to show the user a sequence, the program *must have been capable of performing the sequence right through to the last stage.*

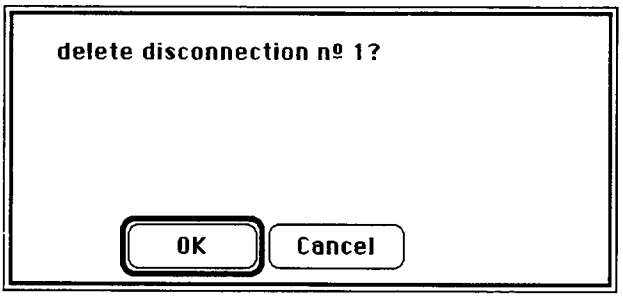
To find the reason why CHAOS does not perform a sequence, we recommend that the user *should test each of the stages individually*. To do this:

1. "Unlink" the sequence using the CHAOSBASE program (click *unlink* for each one of the stages in the sequence).

2. Go again to the CHAOS program and create a synthesis to test the unlinked disconnections. Introduce manually precursors with the appropriate *retrons*, so that, at least theoretically, all the disconnections in the sequence can be applied. Next, try to disconnect these precursors using the data base which the sequence (already *unlinked*) possesses. Make sure that all the steps are performed individually and that *various fragments are not generated* in any of them (remember that a disconnection which generates various fragments invalidates the application of the entire sequence). If one of the disconnections is not performed, it will probably be easy to identify the reason.

3.2.7. How to eliminate disconnections from a data base

If you wish to *eliminate* a disconnection from a data base, click on its name (in the window of this data base) and move to the option "Clear" (*Edit* menu), which will bring up the following dialog box:



Click "OK" to confirm you really wish to *clear* this disconnection. Click "Cancel" if you decide not to clear it.

Note: The program will not allow you to clear disconnections which form part of a sequence.

3.2.8. Transference of disconnections from one data base to another

a) *With a data base open*, click the name of the disconnection *which you wish to transfer to another data base.*

b) Go to the option "Cut" or "Copy," *depending on whether you want or not the disconnection eliminated from the present data base.* If you choose the option "Cut," a dialog box for confirming the elimination of the disconnection will come up.

c) *Close* the data base window by clicking on the *close box* in the top left corner.

d) Go to the *Edit* menu. At the end of the menu "In clipboard" can be read, followed by the name of the disconnection you have just copied. This informs the user *what disconnection is at present on the clipboard.*

e) *Open* the data base to which you want to incorporate the disconnection.

f) With the data base open, go to the option "Paste" (*Edit* menu). Observe how the disconnection on the clipboard has been incorporated into the data base, located at the end.

The disconnections are transferred along with all the information they possess, including restrictions, bibliographic references, etc. It is also possible to transfer disconnections which form part of a sequence, but they must be transferred as *individual disconnections. It is not possible to transfer a whole sequence at once; you must transfer disconnection by disconnection and "link" once more the individual disconnections in the new data base.*

Note: The disconnections only remain on the clipboard while you do not leave the program. If you leave CHAOSBASE and then re-enter, you will have lost any information on the clipboard.

3.2.9. How to modify existing disconnections

Previously introduced disconnections can be modified. To do this:

a) *Open* the data base which contains the disconnection you wish to modify.

b) Bring up the name of this disconnection *highlighted in black*, by clicking it in the data base window.

c) Either go to the option "Open disconnection" (*File* menu) or double click on the name of the disconnection. This will bring up the *window for defining substructures*.

d) You can change the substructure at will by clicking "DISCONNECT", which will bring up a dialog box which will let you change the name of the disconnection. By clicking "OK," you will enter *disconnection mode*. Disconnect the substructure as you think best and click *Save* to save the modified disconnection or *Cancel* to discard the changes.

Note: The program will not let you modify disconnections belonging to a sequence.

3.2.10. Definition of "aromatic" disconnections

It requires some practice *to give the program the appropriate substructure for the disconnection which we want to introduce*. Disconnections which correspond to typically aromatic reactions can be introduced, but the following points must be borne in mind:

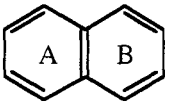
a) To represent the substructure corresponding to an aromatic ring, you must draw (in the *window for defining substructures*) a carbon atom ring with 6 members and you must specify that all the bonds in this ring can be simple or double. In addition, "aromatic" must be specified as a *special attribute* (via the *Atom settings* menu) of all the atoms of this ring. Then substitutes can be introduced into the ring, if you wish.

b) Depending on the concrete disconnection, often *it will not be necessary to introduce the entire benzene ring, but only two or three of its atoms* (for example, to express the reactions on introducing a functional group into *orto, meta or para* in relation to another group). Of course, the aromatic carbons should bear "aromatic" as a *special attribute* and the bonds between them should be catalogued as *simple* or *double*.

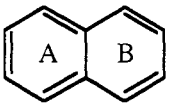
c) The CHAOSBASE program lets you *break or form bonds between carbons of an aromatic ring*, but this disconnection will not be performed by CHAOS, since there exist a *protection* against altering benzene rings.

d) The CHAOS program in its present version only interprets as aromatic those systems formed by a carbon atom ring with 6 members and alternating double bonds and, therefore, the *protection against altering benzene rings* will

only occur in these systems. This is illustrated in the following figure.



Both rings "A" and "B" are considered aromatics



Only ring "A" is recognized as aromatic

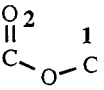
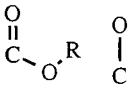
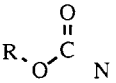
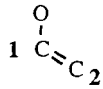
3.2.11. Limitations of the CHAOSBASE program

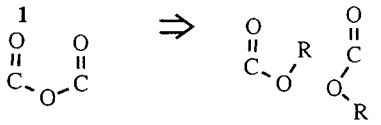
In the present versions of the CHAOSBASE program, the "Page Setup" and "Print" menus do not work. They have been included for use in future versions of the program.

Appendix B-3

CHAOS: TABLES OF DISCONNECTION GROUPS

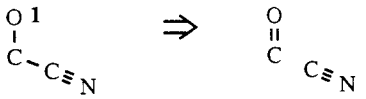
GROUP 1: PRELIMINARY

No.	RETRON		SYNTHON	NAME AND REMARKS
1.1		⇒		**Hydrolysis of carboxylic esters** 1: Must belong to an acid group
1.2		⇒		**Acetalation**
1.3		⇒		**Transesterification** 1: Carbon or phenyl 2: Must belong to an ester group
1.4		⇒		**Amination of esters** 1: Must belong to an amide group
1.5		⇒		**Metallation of alkyl or aryl halides**
1.6		⇒		**Formation of enol ethers from aldehydes or ketones** 1: Must belong to an ether group 2: Carbon without heteroatoms
1.7		⇒		**Conversion of esters to acyl halides** 1: Must belong to an acyl halide group
1.8		⇒		**Formation of enamines (addition of amines to aldehydes or ketones)** 1: Carbon without heteroatoms
1.9		⇒		**Formation of imines (addition of amines to aldehydes or ketones)** 1: Must belong to a primary or secondary imine group

1.10 

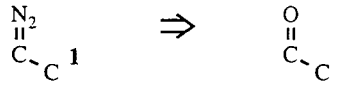
Formation of anhydrides from carboxylic acids or esters

1: Must belong to an anhydride group

1.11 

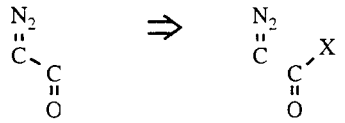
Formation of cyanohydrins

1: Oxygen or nitrogen
1: Must belong to an alcohol, primary amine or secondary amine group

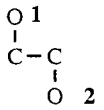
1.12 

Formation of hydrazones

1: Cannot belong to an aldehyde or ketone group

1.13 

Formation of diazo ketones

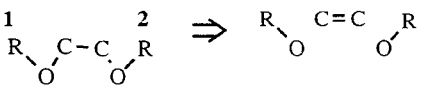
1.14 

Dihydroxylation, diamination or halogenation of olefins

1 and 2: Oxygen, nitrogen or halogen
1 and 2: Must belong to an alcohol, primary amine or halide

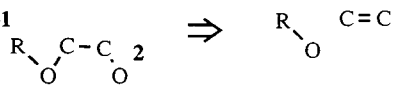
1.15 

Epoxidation of olefins

1.16 

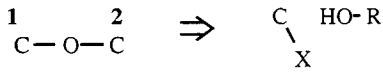
Dialcoxylation of olefins

1 and 2: Radical or carbon[52]

1.17 

Alcoxyhydroxylation of olefins

1: Radical or carbon
2: Must belong to an alcohol group

1.18 

Williamson reaction

1: Radical or carbon
2: Must belong to an ether group

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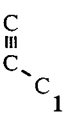
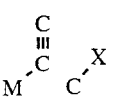
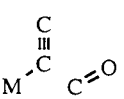
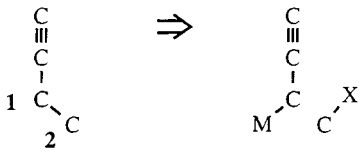
[52] "Radical" here means a "generic substituent". It is available in the CHAOS program through the "atomic groups" menu. "Radical" can be used when drawing a molecule, exactly in the same way as any of the "atoms" or "atomic groups", and is recognised in those disconnections in which it is indicated.

GROUP 2: MONOFUNCTIONAL (acts only on isolated functional groups)

No.	RETRON		SYNTHON	NAME AND REMARKS
2.1		⇒		**Formation of alkyl halides from alcohols** 1: Must belong to an halo derivative group 2: sp^3 Carbon
2.2		⇒		**Reduction of carbonyl compounds** 1: Must belong to an alcohol group
2.3		⇒		**Addition of organometallic compounds to aldehydes or ketones** 1: Must belong to an alcohol group
2.4		⇒		**Reduction of amides** 1: sp^3 Carbon 1: Cannot be a terminal atom
2.5		⇒		**Reduction of nitriles** 1: Must belong to a primary amine group
2.6		⇒		**Formation of nitriles from alkyl halides and cyanide ion**
2.7		⇒		**Alkylation at an alkynyl carbon** 1: Carbon without heteroatoms
2.8		⇒		**Formation of propargyl alcohols**
2.9		⇒		**Alcohols, amines or alkyl halides from esters** 1: Oxygen, halogen, nitrogen
2.10		⇒		**Reduction of imines** 1: Cannot be a terminal atom 1: sp^3 Carbon

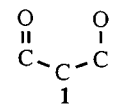
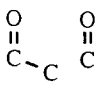
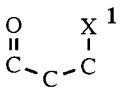
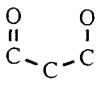
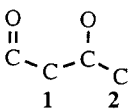
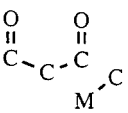
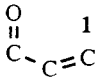
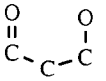
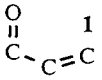
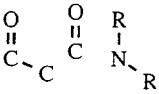
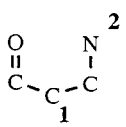
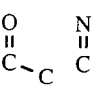
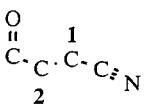
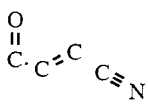
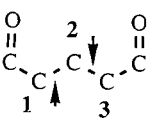
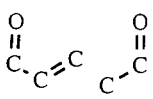
2.11



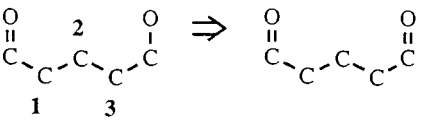
Propargylation of alkyl halides

1 and 2: Carbon without heteroatoms
1 and 2: sp^3 Carbons
Prevents intramolecular reaction

GROUP 3: CONSONANT

No.	RETRON		SYNTHON	NAME AND REMARKS
3.1		⇒		**Aldol condensation** 1: Carbon without heteroatoms 1: sp^3 Carbon Prevents disconnection of core bonds
3.2		⇒		**Formation of β-halocarbonyl compounds from aldols** 1: Must belong to an halo derivative group
3.3		⇒		**Addition of organometallic compounds to 1,3-dicarbonyl compounds** 1 and 2: Carbons without heteroatoms Prevents disconnection of core bonds Prevents intramolecular reaction
3.4		⇒		**Dehydration of aldols** 1: Cannot be a terminal atom **LINKED TO 3.1**
3.5		⇒		**Mannich reaction + deamination** 1: Must be a terminal atom
3.6		⇒		**Mannich reaction** 1: Carbon without heteroatoms 1: sp^3 Carbon 2: Must belong to a primary, secondary or tertiary amine group Prevents disconnection of core bonds
3.7		⇒		**Addition of HCN to α,β-unsaturated carbonyl compounds** 1 and 2: Carbons without heteroatoms 1: sp^3 Carbon
3.8		⇒		**Michael reaction** 1, 2 and 3: Carbons without heteroatoms 3: sp^3 Carbon The bonds indicated can be single or double Prevents disconnection of core bonds Prevents formation of triple bonds in rings with less than 8 members

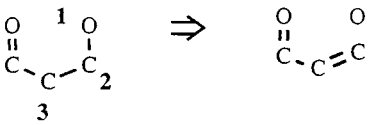
3.9



Reduction of 1,5-dicarbonyl compounds

1, 2 and 3: Carbons without heteroatoms

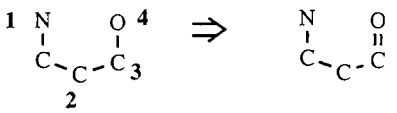
3.10



Addition of alcohols to α,β–unsaturated carbonyl compounds

1 and 2: Must belong to an ether group
2: sp^3 Carbon
3: Carbon without heteroatoms

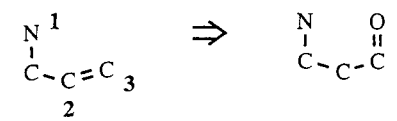
3.11



Reduction of β-amino carbonyl compounds

1 Must belong to a primary, secondary or tertiary amine group
2: Carbon without heteroatoms
3: sp^3 Carbon
4: Must belong to an alcohol group

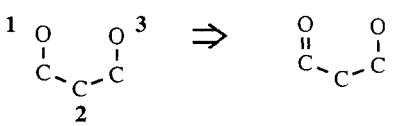
3.12



Reduction of β-amino carbonyl compounds + dehydration

1 Must belong to a primary, secondary or tertiary amine group
2 and 3: Carbons without heteroatoms

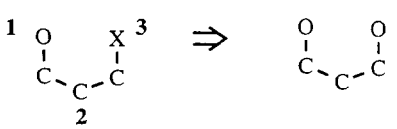
3.13



Reduction of aldols

1 and 3: Must belong to an alcohol group
2: Carbon without heteroatoms

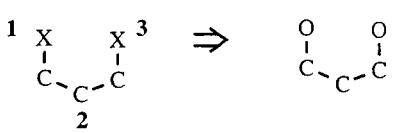
3.14



Formation of 1,3-haloalcohols from 1,3-diols

1: Must belong to an alcohol group
3: Must belong to an halo derivative group
2: Carbon without heteroatoms

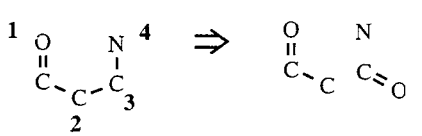
3.15



Formation of 1,3-dihalides from 1,3-diols

1 and 3: Must belong to an halo derivative group
2: Carbon without heteroatoms

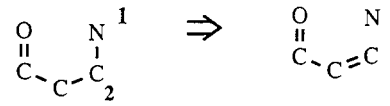
3.16



Mannich reaction

1: Must belong to an aldehyde or ketone group
2: Carbon without heteroatoms
3: sp^3 Carbon
4: Must belong to a secondary or tertiary amine group

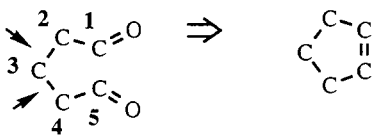
3.17



Addition of amines to α,β-unsaturated carbonyl compounds

1: Must belong to a primary, secondary or tertiary amine group
2: sp^3 Carbon
Prevents disconnection of core bonds

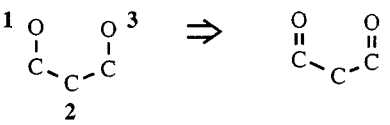
3.18



Cleavage of cyclopentenes to 1,5-dicarbonyl compounds

1 and 5: Cannot belong to an "Ester-R" group
2, 3 and 4: Carbons without heteroatoms
The bonds indicated can be single or double
Prevents reconection if it gives a strained system
Prevents formation of double bonds over bridgehead atoms

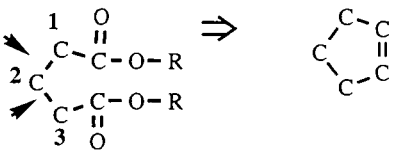
3.19



Reduction of 1,3-dicarbonyl compounds to 1,3-diols

1 and 3: Must belong to an alcohol group
2: Carbon without heteroatoms

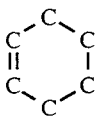
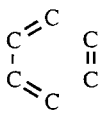
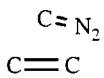
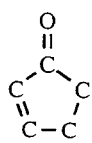
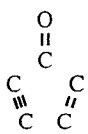
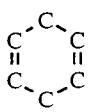
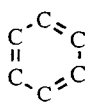
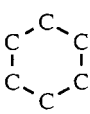
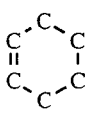
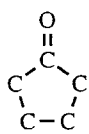
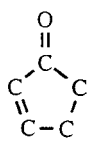
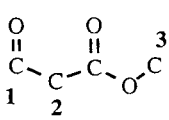
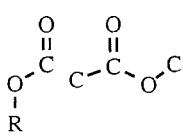
3.20



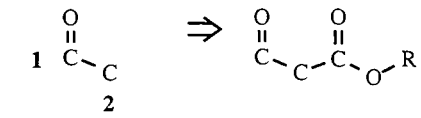
Cleavage of cyclopentenes to 1,5-dicarboxylic acids and esters

1, 2 and 3: Carbons without heteroatoms
The bonds indicated can be single or double
Prevents reconection if it gives a strained system

GROUP 4: RINGS

No.	RETRON		SYNTHON	NAME AND REMARKS
4.1		⇒		**Diels-Alder reaction** All of the atoms in the ring may be carbon, nitrogen, oxygen or sulphur (II) None of the atoms in the ring may belong to a ketone or an alcohol group
4.2		⇒		**[2+2]-cycloaddition** All of the atoms in the ring must be carbons without heteroatoms, or must belong to a ketone or ester group
4.3		⇒		**Addition of carbenes to olefins** All of the atoms in the ring must be carbons without heteroatoms
4.4		⇒		**Pauson-Khand reaction** Prevents formation of triple bonds in rings with less than 8 members
4.5		⇒		**Birch reduction** All of the atoms in the ring must be carbons without heteroatoms
4.6		⇒		**Reduction of cyclohexenes to cyclohexanes** All of the atoms in the ring may be carbon, nitrogen, oxygen or sulphur (II) All of the atoms in the ring are sp^3 Prevents formation of double bonds over bridgehead atoms **LINKED TO 4.1**
4.7		⇒		**Reduction of cyclopentenones to cyclopentanones** **LINKED TO 4.4**
4.8		⇒		**Dieckmann condensation** 1: Must belong to a ring 2: Carbon without heteroatoms 2: sp^3 Carbon 3: Carbon or radical

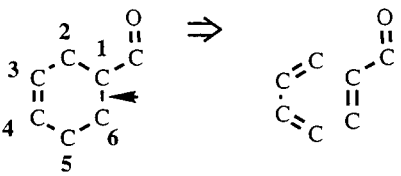
4.9



Hydrolysis and decarboxylation (or dealcoxycarbonylation) of β-keto esters

1: Must belong to a ring
2: Carbon without heteroatoms
LINKED TO 4.8

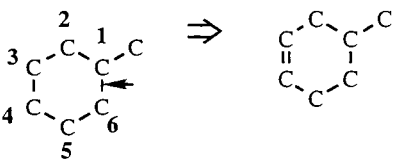
4.10



Diels-Alder reaction

1, 2, 3, 4, 5, 6: Cannot belong to an alcohol or ketone group
Prevents intramolecular reaction
The bond indicated can be single or double

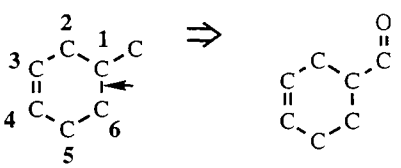
4.11



Reduction of cyclohexenes to cyclohexanes

1, 2, 3, 4, 5, 6: Cannot belong to an alcohol or ketone group
2, 3, 4, 5: sp^3 Carbons
The bond indicated can be single or double
LINKED TO 4.12

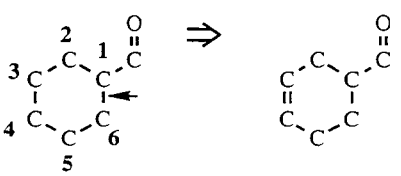
4.12



Reduction of carbonyl groups

1, 2, 3, 4, 5, 6: Cannot belong to an alcohol or ketone group
The bond indicated can be single or double
LINKED TO 4.10

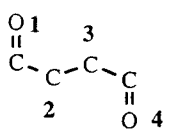
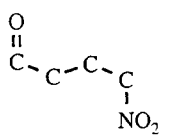
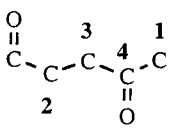
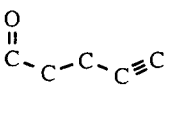
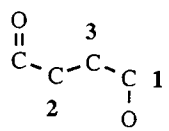
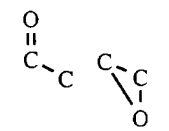
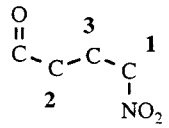
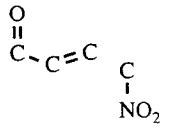
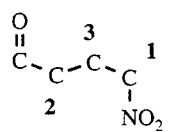
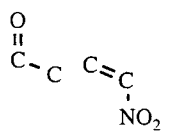
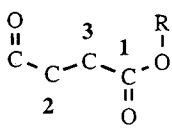
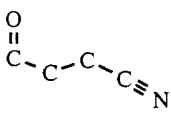
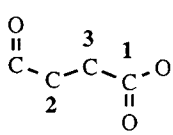
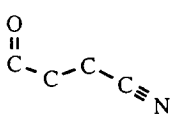
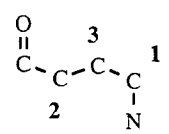
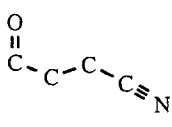
4.13



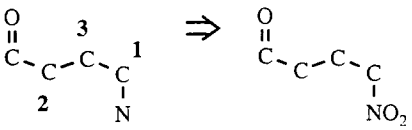
Reduction of cyclohexenes to cyclohexanes

1, 2, 3, 4, 5, 6: Cannot belong to an alcohol or ketone group
2, 3, 4, 5: sp^3 Carbons
The bond indicated can be single or double
LINKED TO 4.10

GROUP 5: DISSONANT

No.	RETRON	SYNTHON	NAME AND REMARKS
5.1			**Nef reaction (Formation of 1,4-dicarbonyl compounds)** 1 and 4: Must belong to an aldehyde or ketone group 2 and 3: Carbons without heteroatoms
5.2			**Hydration of terminal alkynes (Formation of 1,4-dicarbonyl compounds)** 1: Terminal atom 1, 2 and 3: Carbons without heteroatoms 4: Must belong to a ketone group
5.3			**Addition of enolates to epoxides** 1: Must belong to an alcohol group 2 and 3: Carbons without heteroatoms
5.4			**Michael reaction** 1: Must belong to a nitro group 2 and 3: Carbons without heteroatoms
5.5			**Michael reaction** 1: Must belong to a nitro group 2 and 3: Carbons without heteroatoms
5.6			**Alcoholysis of 4-keto nitriles** 1: Must belong to an "Ester-R" group 2 and 3: Carbons without heteroatoms
5.7			**Hydrolysis of 4-keto nitriles** 1: Must belong to an acid group 2 and 3: Carbons without heteroatoms
5.8			**Reduction of 4-keto nitriles** 1: Must belong to a primary amine group 2 and 3: Carbons without heteroatoms

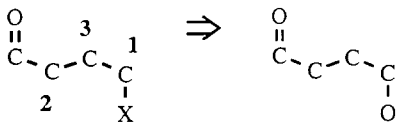
5.9



Reduction of 4-nitroketones

1: Must belong to a primary amine group
2 and 3: Carbons without heteroatoms

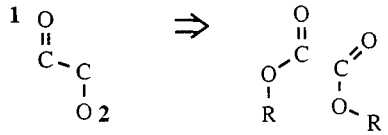
5.10



Conversion of 4-hydroxy ketones into 4-halo ketones

1: Must belong to an halo derivative group
2 and 3: Carbons without heteroatoms

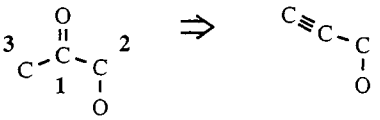
5.11



Acyloin condensation

1: Must belong to an aldehyde or ketone group
2: Must belong to an alcohol group

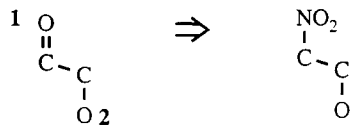
5.12



Hydration of propargyl alcohols

1: Must belong to a ketone group
2: Must belong to an alcohol group
3: Carbon without heteroatoms
3: Terminal carbon

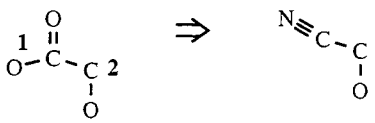
5.13



Nef reaction of α-hydroxy nitro compounds

1: Must belong to an aldehyde or ketone group
2: Must belong to an alcohol group

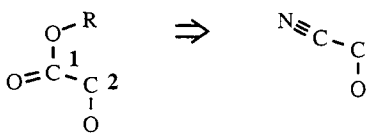
5.14



Hydrolysis of α-hydroxy nitriles

1: Must belong to an acid group
2: Must belong to an alcohol group

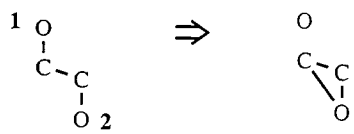
5.15



Alcoholysis of α-hydroxy nitriles

1: Must belong to an "Ester-R" group
2: Must belong to an alcohol group

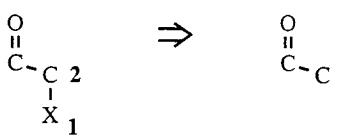
5.16



Alcoholysis or amination of epoxides

1: Oxygen or nitrogen
1: Must belong to an ether, primary, secondary or tertiary amine group
2: Must belong to an alcohol group

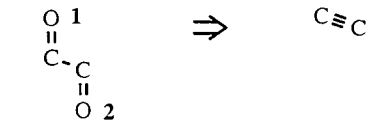
5.17



α-Halogenation of carbonyl compounds

1: Must belong to an halo derivative group
2: sp^3 Carbon

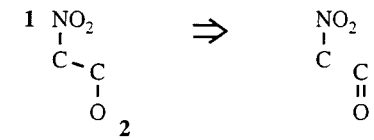
5.18



Oxidation of alkynes to α-dicarbonyl compounds

1 and 2: Must belong to an aldehyde or ketone group

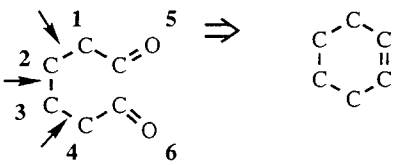
5.19



Knoevenagel reaction

1: Must belong to a nitroderivative
2: Must belong to an alcohol group
Prevents disconnection of core bonds

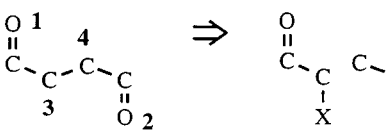
5.20



Cleavage of cyclohexenes to 1,6-dicarbonyl compounds

1, 2, 3 and 4: Carbons without heteroatoms
5 and 6: Must belong to an aldehyde or ketone group
The bonds indicated can be single or double
Prevents reconnection to strained systems
Prevents formation of double bonds over bridgehead atoms

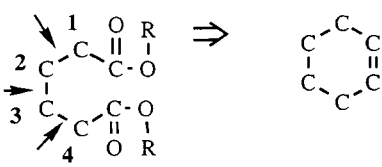
5.21



Alkylation of enolates with α-halo carbonyl compounds. (Formation of 1,4-dicarbonyl compounds)

1 and 2: Must belong to an aldehyde or ketone group
3 and 4: Carbons without heteroatoms
Prevents disconnection of core bonds

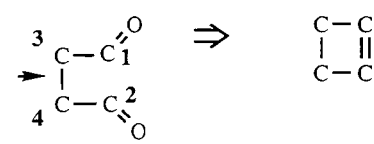
5.22



Cleavage of cyclohexenes to 1,6-dicarboxylic acids or esters

1, 2, 3 and 4: Carbons without heteroatoms
The bonds indicated can be single or double
Prevents reconnection to strained systems

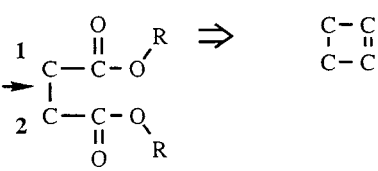
5.23



Cleavage of cyclobutenes to 1,4-dicarbonyl compounds

1 and 2: Cannot belong to an "Ester-R" group
3 and 4: Carbons without heteroatoms
The bond indicated can be single or double
Prevents reconnection to strained systems

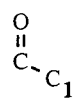
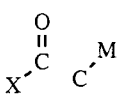
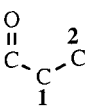
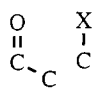
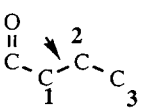
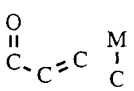
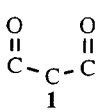
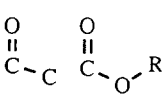
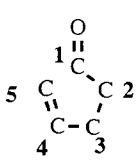
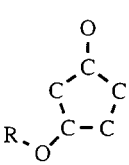
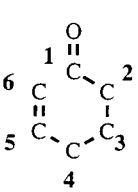
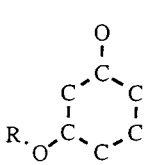
5.24



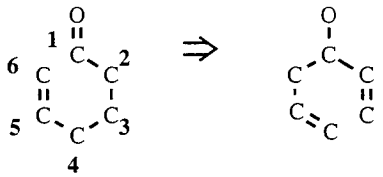
Cleavage of cyclobutenes to 1,4-dicarboxylic acids or esters

1 and 2: Carbons without heteroatoms
The bond indicated can be single or double
Prevents reconnection to strained systems

GROUP 6: FINALS

No.	RETRON		SYNTHON	NAME AND REMARKS
6.1		⇒		**Reaction of acyl halides or other acid derivatives with organometallic compounds** 1: Carbon without heteroatoms 1: sp^3 Carbon Prevents intramolecular reaction
6.2		⇒		**α-Alkylation of carbonyl compounds** 1 and 2: Carbons without heteroatoms 1 and 2: sp^3 Carbon Prevents disconnection of core bonds
6.3		⇒		**Conjugate addition of organometallic compounds to unsaturated carbonyl compounds** 1, 2 and 3: Carbons without heteroatoms 3: sp^3 Carbon The bond indicated can be single or double Prevents intramolecular reaction
6.4		⇒		**Claisen condensation** 1: sp^3 Carbon with hydrogen 1: Carbon without heteroatoms
6.5		⇒		**Hydration of olefins** 1 and 2: Carbons without heteroatoms
6.6		⇒		**Fragmentation of 1,3-diols** 1: Must belong to a ketone group 2, 3, 4 and 5: Carbons without heteroatoms
6.7		⇒		**Fragmentation of 1,3-diols** 1: Must belong to a ketone group 2, 3, 4, 5 and 6: Carbons without heteroatoms

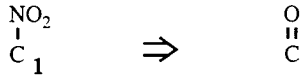
6.8



Oxy-Cope Rearrangement

1: Must belong to a ketone group
2, 3, 4, 5 and 6: Carbons without heteroatoms
2, 3 and 4: sp^3 Carbons

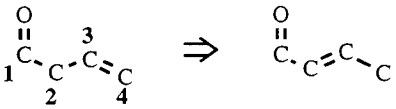
6.9



Conversion carbonyl-nitro

1: Must belong to a nitro derivative

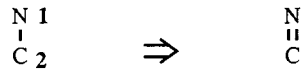
6.10



Stork conjugation

1: Must belong to an aldehyde or ketone group
2, 3 and 4: Carbons without heteroatoms

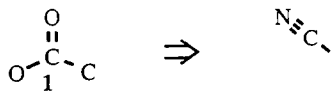
6.11



Reduction of carbon-nitrogen double bond

1: Must belong to a primary or secondary amine group
2: Cannot be a terminal atom
2: sp^3 Carbon

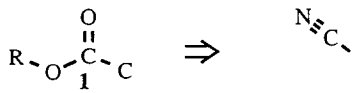
6.12



Hydrolysis of nitriles

1: Must belong to an acid group

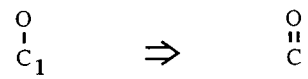
6.13



Alcoholysis of nitriles

1: Must belong to an "ester-R" group

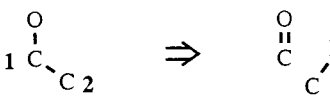
6.14



Reduction of carbonyl group

1: Must belong to an alcohol group

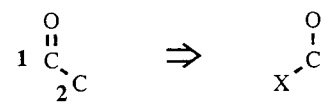
6.15



Addition of organometallic compounds to aldehydes or ketones

1: Must belong to an alcohol group
2: Carbon without heteroatoms
Prevents disconnection of core bonds

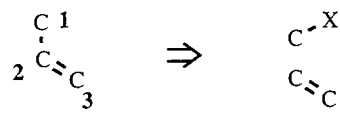
6.16



Friedel-Crafts acylation

1: Must belong to a ketone group
2: Must belong to a benzene ring

6.17



Friedel-Crafts alkylation

1: Carbon without heteroatoms
2 and 3: Must belong to a benzene ring

6.18

Friedel-Crafts alkylation

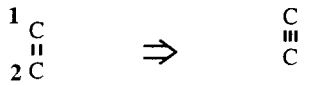
1: Terminal atom
1 and 2: Carbons without heteroatoms
3 and 4: Must belong to a benzene ring

6.19

Wittig-type reaction

1 and 2: Carbons without heteroatoms
2: Cannot be a terminal atom

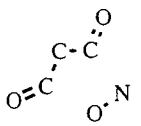
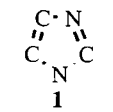
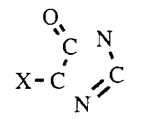
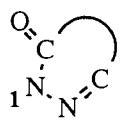
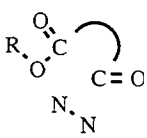
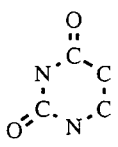
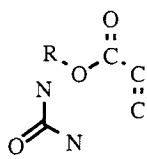
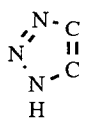
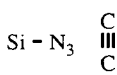
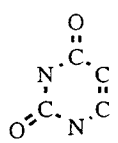
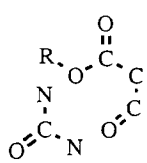
6.20



Reduction of a triple bond to a double bond

1 and 2: Carbons without heteroatoms
Prevents formation of triple bonds in small rings

GROUP 7: HETEROCYCLIC DISCONNECTIONS

No.	RETRON	SYNTHON	NAME AND REMARKS
7.1			**Formation of five-membered 1,2-diheteroaromatic rings** 1: Carbon without heteroatoms 2: Oxygen, nitrogen
7.2			**Formation of five-membered 1,3-diheteroaromatic rings** 1: Oxygen, nitrogen or sulphur -2
7.3			**Formation of five- and six-membered 1,2-diheteroaromatic rings** 1: Oxygen, nitrogen
7.4			**Formation of dioxy-1,3-diazines. Reaction of urea with α,β-unsaturated esters**
7.5			**Formation of 1,2,3-triazoles. 1,3-Dipolar cycloaddition**
7.6			**Formation of dioxy-1,3-diazines. Reaction of urea with 1,3-dicarbonyl compounds**

HERETOATOMS RECOGNIZED BY CHAOS:

Boron, carbon, nitrogen, oxygen, phosphorus-3, sulphur-2, halogen (generic), metal-1, metal-2, metal-3, sulphur-4, phosphorus-5, selenium-2, selenium-4.

ATOMIC GROUPS RECOGNIZED BY CHAOS

Phenil, radical (a generic substituent), nitro, sulphonic acid, diazo, azide, trialkylsilyl.

FUNCTIONAL GROUPS RECOGNIZED BY CHAOS

Carboxylic acid, aldehyde, ketone, ether, alcohol, ester, ester-R (the chain attached to the oxygen atom being a generic substituent), anhydride, acetal, amide, epoxide, acid halyde, primary amine, primary imine, cyano, secondary amine, secondary imine, tertiary amine, nitro derivative, metal-1, metal-2, carbene, halo derivative.

A *carbon with no heteroatoms attached* is considered as a kind of functional group, and recognized by the CHAOSBASE program when defining substructures (it appears on the Functional groups menu).

REMARKS

"Carbene" and "Metal-2" functional groups consist of a generic divalent metal joined to a carbon atom by a double bond.

In the disconnection tables, when we refer to "prevention against strained system", we mean that "prevents reconnection to rings of less than 8 members and secondary rings".

Appendix B-4

SUGGESTED EXERCISES TO BE SOLVED BY CHAOS

Remember the limitations of CHAOS and "ignore" the disconnections you realise are too "odd".

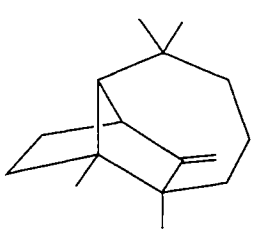
1. Try to elaborate "synthesis trees" of most of the exercises found in Warren's book "Designing Organic Syntheses. A Programmed Introduction to the Synthon Approach" (John Wiley & Sons, Chichester, 1978) and compare the different synthetic sequences with the solutions proposed therein.

2. Draw the structures of the bicyclo[3.1.0]hex-2-ene-2-carboxaldehyde, *cis*-jasmone, the Wieland-Miescher ketone and the bis-nor-analogue -which you may find through the "Subject index"- and:

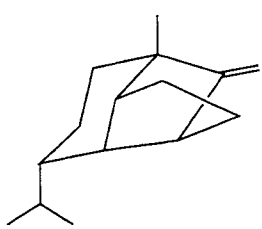
i) Search the bifunctional relationships, rings and synthetically significant rings, as well as the "core bonds".

ii) Process them automatically and grow the corresponding "synthesis trees". In order to have a limited and logical "synthesis tree" you must "Save" only some disconnections and "Ignore" the rest. You should be able to find the synthetic sequences outlined in the book (see Scheme 4.15, Schemes 5.3 and 5.4, and Schemes 6.3 and 6.4, respectively).

3. Draw the structures of twistane, tropinone, *exo*-brevicomin, patchouli alcohol, longifolene, sativene, luciduline and porantherine and search: bifunctional relationships, rings, synthetically significant rings, bridgeheads, core bonds and strategic bonds of each one of them.



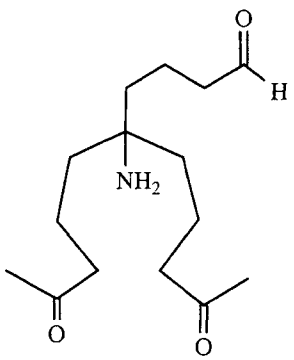
Longifolene



Sativene

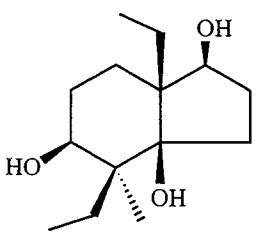
4. Process automatically the structure of tropinone, *exo*-brevicomin and luciduline.

5. Process automatically the structure of the alkaloid porantherine, first with the "default-order" of disconnections and then giving priority to "consonant" over "rings" disconnections. In the latter case you should "Save" only the intermediate precursors leading to the same synthetic sequence and the same starting material (A) used in Corey's synthesis, which was actually found by LHASA (see ref. 19, Chapter 12).



A

6. Draw the structure of *Cecropia* juvenile hormone and process it automatically. Save only the intermediate precursors which finally lead to the bicyclic compound B used by the Syntex group.



B

Since the drawing resulting from the "Wharton-Grob reconnections" appears in the screen completely distorted, correct it as shown in B by the "Modify Precursor" option.

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SUBJECT INDEX