

Advanced Organic Chemistry

FIFTH
EDITION

Part B: Reactions and Synthesis

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PART A: Structure and Mechanisms

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Preface

The methods of organic synthesis have continued to advance rapidly and we have made an effort to reflect those advances in this Fifth Edition. Among the broad areas that have seen major developments are enantioselective reactions and transition metal catalysis. Computational chemistry is having an expanding impact on synthetic chemistry by evaluating the energy profiles of mechanisms and providing structural representation of unobservable intermediates and transition states.

The organization of Part B is similar to that in the earlier editions, but a few changes have been made. The section on introduction and removal of protecting groups has been moved forward to Chapter 3 to facilitate consideration of protecting groups throughout the remainder of the text. Enolate conjugate addition has been moved from Chapter 1 to Chapter 2, where it follows the discussion of the generalized aldol reaction. Several new sections have been added, including one on hydroalumination, carboalumination, and hydrozirconation in Chapter 4, another on the olefin metathesis reactions in Chapter 8, and an expanded discussion of the carbonyl-ene reaction in Chapter 10.

Chapters 1 and 2 focus on enolates and other carbon nucleophiles in synthesis. Chapter 1 discusses enolate formation and alkylation. Chapter 2 broadens the discussion to other carbon nucleophiles in the context of the generalized aldol reaction, which includes the Wittig, Peterson, and Julia olefination reactions. The chapter considers the stereochemistry of the aldol reaction in some detail, including the use of chiral auxiliaries and enantioselective catalysts.

Chapters 3 to 5 focus on some fundamental functional group modification reactions. Chapter 3 discusses common functional group interconversions, including nucleophilic substitution, ester and amide formation, and protecting group manipulations. Chapter 4 deals with electrophilic additions to double bonds, including the use of hydroboration to introduce functional groups. Chapter 5 considers reductions by hydrogenation, hydride donors, hydrogen atom donors, and metals and metal ions.

Chapter 6 looks at concerted pericyclic reactions, including the Diels-Alder reaction, 1,3-dipolar cycloaddition, [3,3]- and [2,3]-sigmatropic rearrangements, and thermal elimination reactions. The carbon-carbon bond-forming reactions are emphasized and the stereoselectivity of the reactions is discussed in detail.

Chapters 7 to 9 deal with organometallic reagents and catalysts. Chapter 7 considers Grignard and organolithium reagents. The discussion of organozinc reagents emphasizes their potential for enantioselective addition to aldehydes. Chapter 8 discusses reactions involving transition metals, with emphasis on copper- and palladium-mediated reactions. Chapter 9 considers the use of boranes, silanes, and stannanes in carbon-carbon bond formation. These three chapters focus on reactions such as nucleophilic addition to carbonyl groups, the Heck reaction, palladium-catalyzed cross-coupling, olefin metathesis, and allyl- boration, silylation, and stannylation. These organometallic reactions currently are among the more important for construction of complex carbon structures.

Chapter 10 considers the role of reactive intermediates—carbocations, carbenes, and radicals—in synthesis. The carbocation reactions covered include the carbonyl-ene reaction, polyolefin cyclization, and carbocation rearrangements. In the carbene section, addition (cyclopropanation) and insertion reactions are emphasized. Catalysts that provide both selectivity and enantioselectivity are discussed. The section on radicals considers both intermolecular and intramolecular (cyclization) addition reactions of radicals are dealt with. The use of atom transfer steps and tandem sequences in synthesis is also illustrated.

Chapter 11 focuses on aromatic substitution, including electrophilic aromatic substitution, reactions of diazonium ions, and palladium-catalyzed nucleophilic aromatic substitution. Chapter 12 discusses oxidation reactions and is organized on the basis of functional group transformations. Oxidants are subdivided as transition metals, oxygen and peroxides, and other oxidants.

Chapter 13 illustrates applications of synthetic methodology by multistep synthesis and perhaps provides some sense of the evolution of synthetic capabilities. Several syntheses of two relatively simple molecules, juvabione and longifolene, illustrate some classic methods for ring formation and functional group transformations and, in the case of longifolene, also illustrate the potential for identification of relatively simple starting materials by retrosynthetic analysis. The syntheses of Prelog-Djerassi lactone highlight the methods for control of multiple stereocenters, and those of the Taxol precursor Baccatin III show how synthesis of that densely functionalized tricyclic structure has been accomplished. The synthesis of epothilone A illustrates both control of acyclic stereochemistry and macrocyclization methods, including olefin metathesis. The syntheses of (+)-discodermolide have been added, illustrating several methods for acyclic stereoselectivity and demonstrating the virtues of convergency. The chapter ends with a discussion of solid phase synthesis and its application to syntheses of polypeptides and oligonucleotides, as well as in combinatorial synthesis.

There is increased emphasis throughout Part B on the representation of transition structures to clarify stereoselectivity, including representation by computational models. The current practice of organic synthesis requires a thorough knowledge of molecular architecture and an understanding of how the components of a structure can be assembled. Structures of enantioselective reagents and catalysts are provided to help students appreciate the three-dimensional aspects of the interactions that occur in reactions.

A new feature of this edition is a brief section of commentary on the reactions in most of the schemes, which may point out a specific methodology or application. Instructors who want to emphasize the broad aspects of reactions, as opposed to specific examples, may wish to advise students to concentrate on the main flow of the text, reserving the schemes and commentary for future reference. As mentioned in the

Acknowledgment and Personal Statement, the selection of material in the examples and schemes does not reflect priority, importance, or generality. It was beyond our capacity to systematically survey the many examples that exist for most reaction types, and the examples included are those that came to our attention through literature searches and reviews.

Several computational studies have been abstracted and manipulable three-dimensional images of reactants, transition structures, intermediates, and products provided. This material provides the opportunity for detailed consideration of these representations and illustrates how computational chemistry can be applied to the mechanistic and structural interpretation of reactivity. This material is available in the Digital Resource at springer.com/carey-sundberg.

As in previous editions, the problems are drawn from the literature and references are given. In this addition, brief answers to each problem have been provided and are available at the publishers website.

Acknowledgment and Personal Statement

The revision and updating of *Advanced Organic Chemistry* that appears as the Fifth Edition spanned the period September 2002 through December 2006. Each chapter was reworked and updated and some reorganization was done, as described in the Prefaces to Parts A and B. This period began at the point of conversion of library resources to electronic form. Our university library terminated paper subscriptions to the journals of the American Chemical Society and other journals that are available electronically as of the end of 2002. Shortly thereafter, an excavation mishap at an adjacent construction project led to structural damage and closure of our departmental library. It remained closed through June 2007, but thanks to the efforts of Carol Hunter, Beth Blanton-Kent, Christine Wiedman, Robert Burnett, and Wynne Stuart, I was able to maintain access to a few key print journals including the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Organic Letters*, *Tetrahedron*, and *Tetrahedron Letters*. These circumstances largely completed an evolution in the source for specific examples and data. In the earlier editions, these were primarily the result of direct print encounter or search of printed *Chemical Abstracts* indices. The current edition relies mainly on electronic keyword and structure searches. Neither the former nor the latter method is entirely systematic or comprehensive, so there is a considerable element of circumstance in the inclusion of specific material. There is no intent that specific examples reflect either priority of discovery or relative importance. Rather, they are interesting examples that illustrate the point in question.

Several reviewers provided many helpful corrections and suggestions, collated by Kenneth Howell and the editorial staff of Springer. Several colleagues provided valuable contributions. Carl Trindle offered suggestions and material from his course on computational chemistry. Jim Marshall reviewed and provided helpful comments on several sections. Michal Sabat, director of the Molecular Structure Laboratory, provided a number of the graphic images. My co-author, Francis A. Carey, retired in 2000 to devote his full attention to his text, *Organic Chemistry*, but continued to provide valuable comments and insights during the preparation of this edition. Various users of prior editions have provided error lists, and, hopefully, these corrections have

been made. Shirley Fuller and Cindy Knight provided assistance with many aspects of the preparation of the manuscript.

This Fifth Edition is supplemented by the *Digital Resource* that is available at springer.com/carey-sundberg. The *Digital Resource* summarizes the results of several computational studies and presents three-dimensional images, comments, and exercises based on the results. These were developed with financial support from the Teaching Technology Initiative of the University of Virginia. Technical support was provided by Michal Sabat, William Rourk, Jeffrey Hollier, and David Newman. Several students made major contributions to this effort. Sara Higgins Fitzgerald and Victoria Landry created the prototypes of many of the sites. Scott Geyer developed the dynamic representations using IRC computations. Tanmaya Patel created several sites and developed the measurement tool. I also gratefully acknowledge the cooperation of the original authors of these studies in making their output available. *Problem Responses* have been provided and I want to acknowledge the assistance of R. Bruce Martin, David Metcalf, and Daniel McCauley in helping work out some of the specific kinetic problems and in providing the attendant graphs.

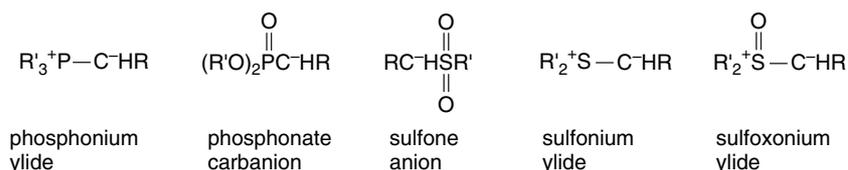
It is my hope that the text, problems, and other material will assist new students to develop a knowledge and appreciation of structure, mechanism, reactions, and synthesis in organic chemistry. It is gratifying to know that some 200,000 students have used earlier editions, hopefully to their benefit.

Richard J. Sundberg
Charlottesville, Virginia
June 2007

Introduction

The focus of Part B is on the closely interrelated topics of *reactions* and *synthesis*. In each of the first twelve chapters, we consider a group of related reactions that have been chosen for discussion primarily on the basis of their usefulness in synthesis. For each reaction we present an outline of the mechanism, its regio- and stereochemical characteristics, and information on typical reaction conditions. For the more commonly used reactions, the schemes contain several examples, which may include examples of the reaction in relatively simple molecules and in more complex structures. The goal of these chapters is to develop a fundamental base of knowledge about organic reactions in the context of synthesis. We want to be able to answer questions such as: What transformation does a reaction achieve? What is the mechanism of the reaction? What reagents and reaction conditions are typically used? What substances can catalyze the reaction? How sensitive is the reaction to other functional groups and the steric environment? What factors control the stereoselectivity of the reaction? Under what conditions is the reaction enantioselective?

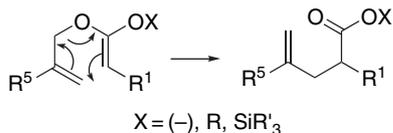
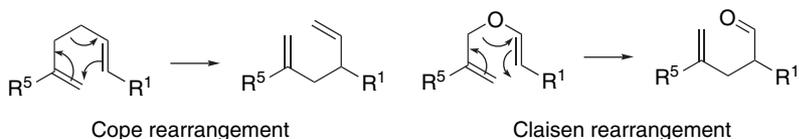
Synthesis is the application of one or more reactions to the preparation of a particular target compound, and can pertain to a single-step transformation or to a number of sequential steps. The selection of a reaction or series of reactions for a synthesis involves making a judgment about the most effective possibility among the available options. There may be a number of possibilities for the synthesis of a particular compound. For example, in the course of learning about the reactions in Chapter 1 to 12, we will encounter a number of ways of making ketones, as outlined in the scheme that follows.



Among the olefination reactions, those of phosphonium ylides, phosphonate anions, silylmethyl anions, and sulfone anions are discussed. This chapter also includes a section on conjugate addition of carbon nucleophiles to α, β -unsaturated carbonyl compounds. The reactions in this chapter are among the most important and general of the carbon-carbon bond-forming reactions.

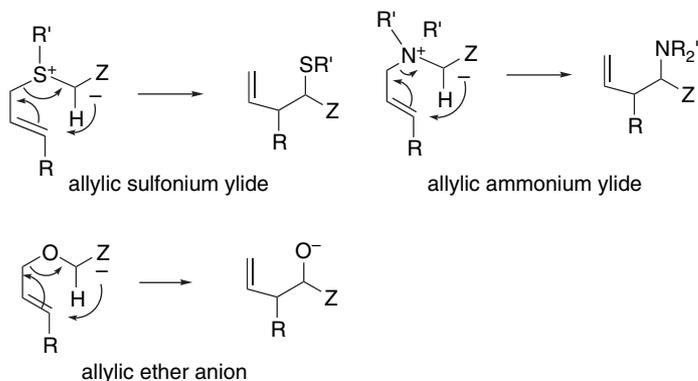
Chapters 3 to 5 deal mainly with introduction and interconversion of functional groups. In Chapter 3, the conversion of alcohols to halides and sulfonates and their subsequent reactions with nucleophiles are considered. Such reactions can be used to introduce functional groups, invert configuration, or cleave ethers. The main methods of interconversion of carboxylic acid derivatives, including acyl halides, anhydrides, esters, and amides, are reviewed. Chapter 4 discusses electrophilic additions to alkenes, including reactions with protic acids, oxymercuration, halogenation, sulfenylation, and selenylation. In addition to introducing functional groups, these reagents can be used to effect cyclization reactions, such as iodolactonization. The chapter also includes the fundamental hydroboration reactions and their use in the synthesis of alcohols, aldehydes, ketones, carboxylic acids, amines, and halides. Chapter 5 discusses reduction reactions at carbon-carbon multiple bonds, carbonyl groups, and certain other functional groups. The introduction of hydrogen by hydrogenation frequently establishes important stereochemical relationships. Both heterogeneous and homogeneous catalysts are discussed, including examples of enantioselective catalysts. The reduction of carbonyl groups also often has important stereochemical consequences because a new stereocenter is generated. The fundamental hydride transfer reagents $NaBH_4$ and $LiAlH_4$ and their derivatives are considered. Examples of both enantioselective reagents and catalysts are discussed, as well as synthetic applications of several other kinds of reducing agents, including hydrogen atom donors and metals.

In Chapter 6 the focus returns to carbon-carbon bond formation through cycloadditions and sigmatropic rearrangements. The Diels-Alder reaction and 1,3-dipolar cycloaddition are the most important of the former group. The predictable regiochemistry and stereochemistry of these reactions make them very valuable for ring formation. Intramolecular versions of these cycloadditions can create at least two new rings, often with excellent stereochemical control. Although not as broad in scope, [2 + 2] cycloadditions, such as the reactions of ketenes and photocycloaddition reactions of enones, also have important synthetic applications. The [3,3]- and [2,3]-sigmatropic rearrangements also proceed through cyclic transition structures and usually provide predictable stereochemical control. Examples of [3,3]-sigmatropic rearrangements include the Cope rearrangement of 1,5-dienes, the Claisen rearrangement of allyl vinyl ethers, and the corresponding reactions of ester enolate equivalents.



Claisen-type rearrangements of ester enolates, ketene acetals, and silyl ketene acetals

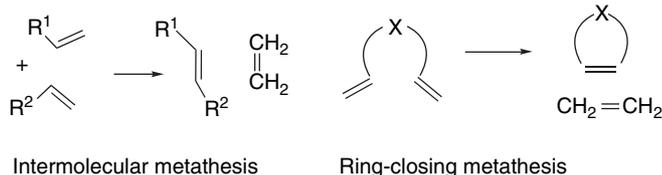
Synthetically valuable [2,3]-sigmatropic rearrangements include those of allyl sulfonium and ammonium ylides and α'-carbanions of allyl vinyl ethers.



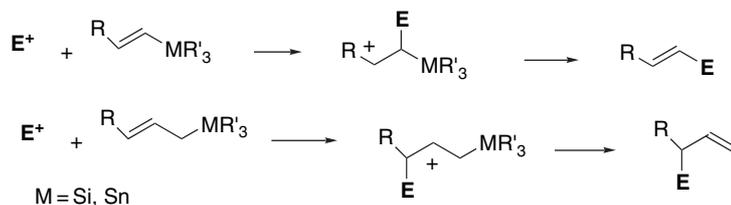
This chapter also discusses several β-elimination reactions that proceed through cyclic transition structures.

In Chapters 7, 8, and 9, the focus is on organometallic reagents. Chapter 7 considers the Group I and II metals, emphasizing organolithium, -magnesium, and -zinc reagents, which can deliver saturated, unsaturated, and aromatic groups as nucleophiles. Carbonyl compounds are the most common co-reactants, but imines and nitriles are also reactive. Important features of the zinc reagents are their adaptability to enantioselective catalysis and their compatibility with many functional groups. Chapter 8 discusses the role of transition metals in organic synthesis, with the emphasis on copper and palladium. The former provides powerful nucleophiles that can react by displacement, epoxide ring opening, and conjugate addition, while organopalladium compounds are usually involved in catalytic processes. Among the important applications are allylic substitution, coupling of aryl and vinyl halides with alkenes (Heck reaction), and cross coupling with various organometallic reagents including magnesium, zinc, tin, and boron derivatives. Palladium catalysts can also effect addition of organic groups to carbon monoxide (carbonylation) to give ketones, esters, or amides. Olefin metathesis reactions, also discussed in this chapter, involve ruthenium or molybdenum catalysts

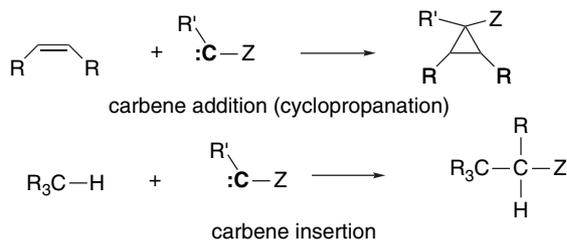
and both intermolecular and ring-closing metathesis have recently found applications in synthesis.



Chapter 9 discusses carbon-carbon bond-forming reactions of boranes, silanes, and stannanes. The borane reactions usually involve B → C migrations and can be used to synthesize alcohols, aldehydes, ketones, carboxylic acids, and amines. There are also stereoselective alkene syntheses based on organoborane intermediates. Allylic boranes and boronates provide stereospecific and enantioselective addition reactions of allylic groups to aldehydes. These reactions proceed through cyclic transition structures and provide a valuable complement to the aldol reaction for stereochemical control of acyclic systems. The most important reactions of silanes and stannanes involve vinyl and allyl derivatives. These reagents are subject to electrophilic attack, which is usually followed by demetallation, resulting in net substitution by the electrophile, with double-bond transposition in the allylic case. Both these reactions are under the regiochemical control of the β-carbocation-stabilizing ability of the silyl and stannyl groups.

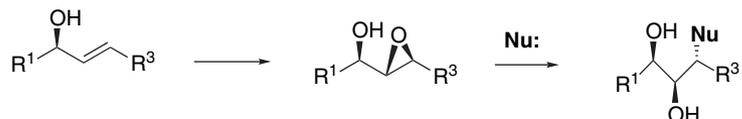


In Chapter 10, the emphasis is on synthetic application of carbocations, carbenes, and radicals in synthesis. These intermediates generally have high reactivity and short lifetimes, and successful application in synthesis requires taking this factor into account. Examples of reactions involving carbocations are the carbonyl-ene reaction, polyene cyclization, and directed rearrangements and fragmentations. The unique divalent character of the carbenes and related intermediates called carbenoids can be exploited in synthesis. Both addition (cyclopropanation) and insertion are characteristic reactions. Several zinc-based reagents are excellent for cyclopropanation, and rhodium catalysts have been developed that offer a degree of selectivity between addition and insertion reactions.



Radical reactions used in synthesis include additions to double bonds, ring closure, and atom transfer reactions. Several sequences of tandem reactions have been developed that can close a series of rings, followed by introduction of a substituent. Allylic stannanes are prominent in reactions of this type.

Chapter 11 reviews aromatic substitution reactions including electrophilic aromatic substitution, substitution via diazonium ions, and metal-catalyzed nucleophilic substitution. The scope of the latter reactions has been greatly expanded in recent years by the development of various copper and palladium catalysts. Chapter 12 discusses oxidation reactions. For the most part, these reactions are used for functional group transformations. A wide variety of reagents are available and we classify them as based on metals, oxygen and peroxides, and other oxidants. Epoxidation reactions have special significance in synthesis. The introduction of the epoxide ring can set the stage for subsequent nucleophilic ring opening to introduce a new group or extend the carbon chain. The epoxidation of allylic alcohols can be done enantioselectively, so epoxidation followed by ring opening can control the configuration of three contiguous stereocenters.



The methods available for synthesis have advanced dramatically in the past half-century. Improvements have been made in selectivity of conditions, versatility of transformations, stereochemical control, and the efficiency of synthetic processes. The range of available reagents has expanded. Many reactions involve compounds of boron, silicon, sulfur, selenium, phosphorus, and tin. Catalysis, particularly by transition metal complexes, has also become a key part of organic synthesis. The mechanisms of catalytic reactions are characterized by *catalytic cycles* and require an understanding not only of the ultimate bond-forming and bond-breaking steps, but also of the mechanism for regeneration of the active catalytic species and the effect of products, by-products, and other reaction components in the catalytic cycle.

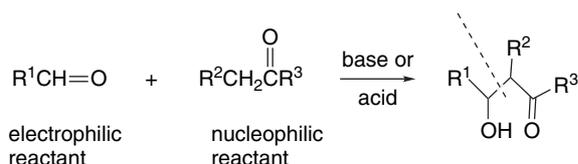
Over the past decade enantioselectivity has become a key concern in reactivity and synthesis. Use of *chiral auxiliaries* and/or *enantioselective catalysts* to control configuration is often a crucial part of synthesis. The analysis and interpretation of enantioselectivity depend on consideration of diastereomeric intermediates and transition structures on the reaction pathway. Often the differences in free energy of competing reaction pathways are on the order of 1 kcal, reflecting small and subtle differences in structure. We provide a number of examples of the structural basis for enantioselectivity, but a good deal of unpredictability remains concerning the degree of enantioselectivity. Small changes in solvent, additives, catalyst structure, etc., can make large differences in the observed enantioselectivity.

Mechanistic insight is a key to both discovery of new reactions and to their successful utilization in specific applications. Use of reactions in a synthetic context often entails optimization of reaction conditions based on mechanistic interpretations. Part A of this text provides fundamental information about the reactions discussed here. Although these mechanistic concepts may be recapitulated briefly in Part B, the details may not be included; where appropriate, reference is made to relevant sections in Part A. In addition to experimental mechanistic studies, many reactions of

synthetic interest are now within the range of computational analysis. Intermediates and transition structures on competing or alternative reaction pathways can be modeled and compared on the basis of MO and/or DFT calculations. Such computations can provide intricate structural details and may lead to mechanistic insight. A number of such studies are discussed in the course of the text.

A key skill in the practice of organic synthesis is the ability to recognize important aspects of molecular structure. Recognition of all aspects of stereochemistry, including conformation, ring geometry, and configuration are crucial to understanding reactivity and applying reactions to synthesis. We consider the stereochemical aspects of each reaction. For most reactions, good information is available on the structure of key intermediates and the transition structure. Students should make a particular effort to understand the consequences of intermediates and transition structures for reactivity.

Applying the range of reactions to synthesis involves planning and foreseeing the outcome of a particular sequence of reactions. Planning is best done on the basis of *retrosynthetic analysis*, the identification of key subunits of the target molecule that can be assembled by feasible reactions. The structure of the molecule is studied to identify bonds that are amenable to formation. For example, a molecule containing a carbon-carbon double bond might be disconnected at that bond, since there are numerous ways to form a double bond from two separate components. β -Hydroxy carbonyl units suggest the application of the aldol addition reaction, which assembles this functionality from two separate carbonyl compounds.

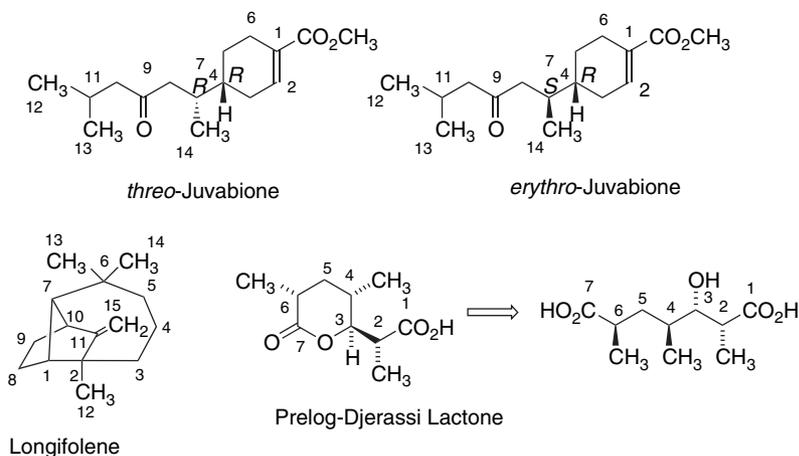


The construction of the overall molecular skeleton, that is, the carbon-carbon and other bonds that constitute the framework of the molecule, is the primary challenge. Molecules also typically contain a number of functional groups and they must be compatible with the projected reactivity at each step in the synthesis. This means that it may be necessary to modify or protect functional groups at certain points. Generally speaking, the protection and interconversion of functional groups is a less fundamental challenge than construction of the molecular framework because there are numerous methods for functional group interconversion.

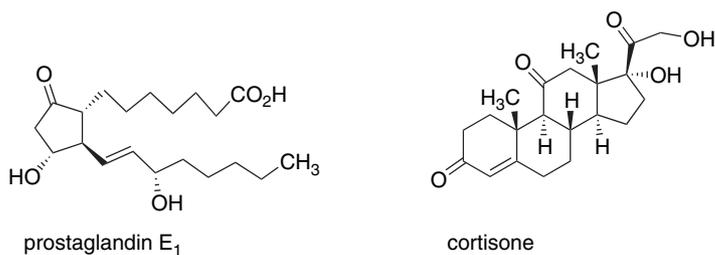
As the reactions discussed in Chapters 1 to 12 illustrate, the methodology of organic synthesis is highly developed. There are many possible means for introduction and interconversion of functional groups and for carbon-carbon bond formation, but putting them together in a multistep synthesis requires more than knowledge of the reactions. A plan that orchestrates the sequence of reactions toward the final goal is necessary.

In Chapter 13, we discuss some of the generalizations of multistep synthesis. Retrosynthetic analysis identifies bonds that can be broken and key intermediates. Various methods of stereochemical control, including intramolecular interactions. Chiral auxiliaries, and enantioselective catalysts, can be used. Protective groups can be utilized to prevent functional group interferences. Ingenuity in synthetic planning can lead to efficient construction of molecules. We take a retrospective look at the synthesis of six molecules of differing complexity. Juvabione is an oxidized terpene

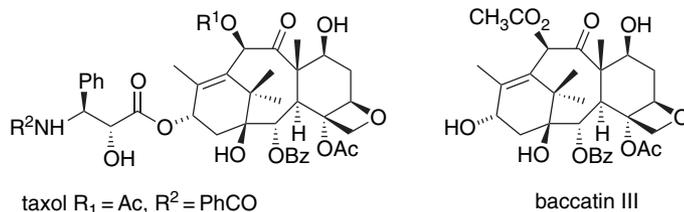
with one ring and two stereocenters. Successful syntheses date from the late 1960s to the present. Longifolene is a tricyclic sesquiterpene and its synthesis poses the problem of ring construction. The Prelog-Djerassi lactone, the lactone of (2*R*,3*S*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethylheptanedioic acid, is a degradation product isolated from various antibiotics. Its alternating methyl and hydroxy groups are typical of structural features found in many antibiotics and other natural substances biosynthetically derived from polypropionate units. Its synthesis illustrates methods of acyclic stereochemical control.



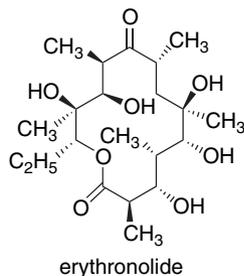
Synthetic methodology is applied to molecules with important biological activity such as the prostaglandins and steroids. Generally speaking, the stereochemistry of these molecules can be controlled by relationships to the ring structure.



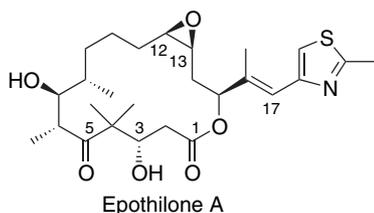
A somewhat more complex molecule, both in terms of the nature of the rings and the density of functionality is Baccatin III, a precursor of the antitumor agent Taxol[®]. We summarize syntheses of Baccatin III that involve sequences of 40–50 reactions. Baccatin III is a highly oxygenated diterpene and these syntheses provide examples of ring construction and functional group manipulations. Despite its complexity, the syntheses of Baccatin III, for the most part, also depend on achieving formation of rings and use of the ring structure to control stereochemistry.



Macrocyclic antibiotics such as the erythronolide present an additional challenge.

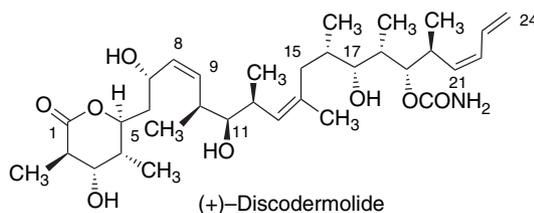


These molecules contain many stereogenic centers and they are generally constructed from acyclic segments, so the ability to control configuration in acyclic systems is necessary. Solutions to this problem developed beginning in the 1960s are based on analysis of transition structures and the concepts of cyclic transition structure and facial selectivity. The effect of nearby stereogenic centers has been studied carefully and resulted in concepts such as the Felkin model for carbonyl addition reactions and Cram's model of chelation control. In Chapter 13, several syntheses of epothilone A, a 16-membered lactone that has antitumor activity, are summarized. The syntheses illustrate methods for both acyclic stereochemical control and macrocyclization, including the application of the olefin metathesis reaction.



We also discuss the synthesis of (+)-discodermolide, a potent antitumor agent isolated from a deep-water sponge in the Caribbean Sea. The first synthesis was reported in the mid-1990s, and synthetic activity is ongoing. Discodermolide is a good example of the capability of current synthetic methodology to produce complex molecules. The molecule contains a 24-carbon chain with a single lactone ring connecting C(1) and C(5). There are eight methyl substituents and six oxygen substituents, one of which is carbamoylated. The chain ends with a diene unit. By combining and refining elements of several earlier syntheses, it was possible to carry

out a 39-step synthesis. The early stages were done on a kilogram scale and the entire effort provided 60 grams of the final product for preliminary clinical evaluation.



There is no synthetic path that is uniquely “correct,” but there may be factors that recommend particular pathways. The design of a synthesis involves applying one’s knowledge about reactions. Is the reaction applicable to the particular steric and electronic environment under consideration? Is the reaction compatible with other functional groups and structures that are present elsewhere in the molecule? Will the reaction meet the regio- and stereochemical requirements that apply? Chemists rely on mechanistic considerations and the precedent of related reactions to make these judgments. Other considerations may come into play as well, such as availability and/or cost of starting materials, and safety and environmental issues might make one reaction preferable to another. These are critical concerns in synthesis on a production scale.

Certain types of molecules, especially polypeptides and polynucleotides, lend themselves to synthesis on solid supports. In such syntheses, the starting material is attached to a small particle (bead) or a surface and the molecule remains attached during the course of the synthetic sequence. Solid phase synthesis also plays a key role in creation of combinatorial libraries, that is, collections of many molecules synthesized by a sequence of reactions in which the subunits are systematically varied to create a range of structures (*molecular diversity*).

There is a vast amount of knowledge about reactions and how to use them in synthesis. The primary source for this information is the published chemical literature that is available in numerous journals, and additional information can be found in patents, theses and dissertations, and technical reports of industrial and governmental organizations. There are several means of gaining access to information about specific reactions. The series *Organic Syntheses* provides examples of specific transformations with detailed experimental procedures. Another series, *Organic Reactions*, provides fundamental information about the scope and mechanism as well as comprehensive literature references to many examples of a specific reaction type. Various review journals, including *Accounts of Chemical Research* and *Chemical Reviews*, provide overviews of particular reactions. A traditional system of organization is based on *named reactions*. Many important reactions bear well-recognized names of the chemists involved in their discovery or development. Other names such as dehydration, epoxidation, enolate alkylation, etc., are succinct descriptions of the structural changes associated with the reaction. This vocabulary is an important tool for accessing information about organic reactions. There are large computerized databases of organic reactions, most notably those of *Chemical Abstracts* and *Beilstein*. Chemical structures can be uniquely described and these databases can be searched for complete or partial structures. Systematic ways of searching for reactions are also incorporated into the databases. Another database, *Science Citation Index*, allows search for subsequent citations of published work.

A major purpose of organic synthesis at the current time is the discovery, understanding, and application of biological activity. Pharmaceutical laboratories, research foundations, and government and academic institutions throughout the world are engaged in this research. Many new compounds are synthesized to discover useful biological activity, and when activity is discovered, related compounds are synthesized to improve it. Syntheses suitable for production of drug candidate molecules are developed. Other compounds are synthesized to explore the mechanisms of biological processes. The ultimate goal is to apply this knowledge about biological activity for treatment and prevention of disease. Another major application of synthesis is in agriculture for control of insects and weeds. Organic synthesis also plays a part in the development of many consumer products, such as fragrances.

The unique power of synthesis is the ability to create new molecules and materials with valuable properties. This capacity can be used to interact with the natural world, as in the treatment of disease or the production of food, but it can also produce compounds and materials beyond the capacity of living systems. Our present world uses vast amounts of synthetic polymers, mainly derived from petroleum by synthesis. The development of nanotechnology, which envisions the application of properties at the molecular level to catalysis, energy transfer, and information management has focused attention on multimolecular arrays and systems capable of self-assembly. We can expect that in the future synthesis will bring into existence new substances with unique properties that will have impacts as profound as those resulting from syntheses of therapeutics and polymeric materials.

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