

# Ring Expansion Reactions

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*"In space, no one can hear you think."*

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# 1 Ring Expansion Reactions

## 1.1 Introduction to Ring Expansion Reactions

Ring expansion reactions represent a fascinating class of transformations in organic chemistry where a cyclic system undergoes a structural rearrangement to form a larger ring. At their core, these reactions involve the insertion of one or more atoms into an existing ring structure, thereby increasing its size while maintaining its cyclic nature. This process stands in contrast to ring contraction reactions, which decrease ring size, and ring formation reactions, which create cyclic systems from acyclic precursors. The fundamental distinction lies in the starting material being cyclic, with the transformation preserving this cyclic character while altering its dimensions.

The terminology surrounding ring expansion reactions has evolved to encompass various aspects of these transformations. Chemists typically describe expansions by specifying the original ring size and the resulting ring size, such as a “three-to-five membered ring expansion” or a “one-atom expansion” when a single atom is inserted. The term “ring enlargement” is often used interchangeably with ring expansion, though some purists reserve “enlargement” for processes where the ring expands without incorporating external atoms, relying instead on internal rearrangement.

Central to understanding ring expansion reactions is the concept of ring strain, a thermodynamic driving force that makes these processes energetically favorable in many cases. Ring strain arises from deviations from ideal bond angles and torsional strain within cyclic systems. Small rings, particularly three- and four-membered cycles, exhibit significant strain due to their compressed bond angles. For instance, cyclopropane, with its internal angles of  $60^\circ$  compared to the ideal tetrahedral angle of  $109.5^\circ$ , possesses approximately 27.5 kcal/mol of strain energy. This stored energy can be released through ring expansion, making these transformations thermodynamically favorable despite the kinetic barriers that must often be overcome.

The mechanisms of ring expansion reactions are diverse, encompassing carbocation rearrangements, radical processes, pericyclic reactions, and metal-mediated transformations. A classic example is the Demjanov rearrangement, where a cycloalkylmethylamine treated with nitrous acid generates a carbocation that undergoes ring expansion. In the case of cyclobutylmethylamine, this process yields cyclopentanone, demonstrating a one-carbon expansion from a four-membered to a five-membered ring. This transformation exemplifies how ring strain relief can drive structural reorganization, with the release of approximately 26.4 kcal/mol of strain energy providing a powerful thermodynamic impetus for the reaction.

The story of ring expansion reactions begins in the 19th century, an era when organic chemistry was still defining its fundamental principles. One of the earliest documented observations of ring expansion occurred in 1883, when Russian chemist Nikolay Demjanov discovered that cyclobutylmethylamine, when treated with nitrous acid, produced cyclopentanone rather than the expected cyclobutylcarbinol. This unexpected outcome, now known as the Demjanov rearrangement, marked the first recognition of ring expansion as a distinct chemical phenomenon. However, the mechanistic understanding of such transformations remained elusive in an era before the development of modern bonding theories.

The early 20th century witnessed significant theoretical advancements that provided a framework for understanding ring expansion reactions. The development of electronic theory of organic bonding by Gilbert N. Lewis in 1916 and the elucidation of reaction mechanisms by Christopher Ingold and others in the 1920s and 1930s offered chemists new tools to rationalize these transformations. Particularly influential was the concept of carbocation intermediates, which became central to explaining many ring expansion mechanisms. The work of Frank C. Whitmore on carbocation rearrangements in the 1930s established the fundamental principles that govern these processes, including the thermodynamic driving force provided by strain relief in small ring systems.

A pivotal moment in the history of ring expansion chemistry came in 1941 with the discovery of the Tiffeneau-Demjanov rearrangement by Marc Tiffeneau and his collaborators. This modification of the original Demjanov reaction, which employed  $\beta$ -amino alcohols instead of primary amines, provided a more reliable method for ring expansion and found widespread application in steroid and terpenoid chemistry. The success of this transformation highlighted the synthetic potential of ring expansion reactions, marking their transition from laboratory curiosities to valuable tools for complex molecule synthesis.

The post-World War II era saw an explosion of interest in ring expansion chemistry, driven in part by the pharmaceutical industry's need for efficient methods to synthesize complex natural products. The development of new spectroscopic techniques, particularly nuclear magnetic resonance (NMR) spectroscopy, allowed chemists to characterize reaction products with unprecedented precision, facilitating the discovery of new ring expansion methodologies. During this period, several important reactions were discovered and developed, including the Favorskii rearrangement in the 1950s, which enables the conversion of  $\alpha$ -halo ketones to carboxylic acid derivatives with ring expansion, and the Semmler-Wolff reaction, which transforms cyclohexanone oximes to anilines with ring expansion.

Key historical figures who shaped our understanding of ring expansion chemistry include not only Demjanov and Tiffeneau but also Vladimir Prelog, whose work on the stereochemistry of ring expansion reactions in the 1940s and 1950s laid the groundwork for modern asymmetric synthesis. Prelog's investigations into the stereo

## 1.2 Fundamental Mechanisms of Ring Expansion

...Prelog's investigations into the stereochemical course of ring expansion reactions revolutionized our understanding of how these transformations proceed at the molecular level. His meticulous studies of the three-dimensional aspects of ring expansions provided crucial insights that would shape the mechanistic framework we now use to understand these reactions. Building upon this foundation of stereochemical understanding, we can now explore the fundamental mechanisms that govern ring expansion reactions in greater detail.

### 1.3 2.1 General Mechanistic Principles

At the heart of every ring expansion reaction lies a delicate interplay between bond cleavage and formation processes that ultimately result in an increase in ring size. These transformations typically involve the selective breaking of one or more bonds within the original ring system, followed by the formation of new bonds that incorporate additional atoms or rearrange existing atoms to create a larger cyclic structure. The specific sequence of these bond-breaking and bond-forming events determines the mechanistic pathway of the reaction and influences its stereochemical outcome.

One of the most fundamental concepts in ring expansion mechanisms involves the rearrangement of carbon frameworks through various pericyclic processes. Sigmatropic rearrangements, in particular, play a crucial role in many ring expansion reactions. These concerted processes involve the migration of a sigma bond adjacent to one or more pi systems, resulting in the reorganization of the molecular framework. The classic [1,2]-alkyl shift in carbocation rearrangements represents a simple yet powerful example of how sigmatropic processes can drive ring expansion. In the case of cyclopropylcarbinyl to cyclobutyl rearrangement, for instance, a [1,2]-shift transforms the strained three-membered ring into a more stable four-membered system, releasing approximately 27 kcal/mol of strain energy in the process.

Equally important are electrocyclic reactions, which involve the concerted opening or closing of ring systems through the reorganization of pi electrons. These pericyclic processes obey strict orbital symmetry requirements, as elegantly described by Woodward and Hoffmann in their groundbreaking work on orbital symmetry conservation. In the context of ring expansion, electrocyclic ring-opening of highly strained systems like cyclobutenes can lead to larger, more stable conjugated systems. A striking example is the thermal ring-opening of benzocyclobutene, which undergoes a conrotatory electrocyclic reaction to form o-xylylene, effectively expanding the four-membered ring to an eight-membered system with extended conjugation.

The role of ring strain as a driving force for ring expansion cannot be overstated. Small rings, particularly cyclopropanes and cyclobutanes, possess significant angle strain due to their compressed bond angles, which deviate substantially from the ideal tetrahedral angle of  $109.5^\circ$ . This stored energy creates a thermodynamic impetus for ring expansion, as the resulting larger rings typically experience reduced strain. The magnitude of this driving force can be quantified through strain energy calculations: cyclopropane contains approximately 27.5 kcal/mol of strain energy, cyclobutane about 26.3 kcal/mol, while cyclopentane has only about 6.5 kcal/mol, and cyclohexane is essentially strain-free. This dramatic decrease in strain energy provides a powerful thermodynamic driving force for expansions of small rings to medium-sized systems.

Stereochemical considerations are inherently woven into the fabric of ring expansion mechanisms. The three-dimensional arrangement of atoms in the starting material significantly influences the mechanistic pathway and ultimately determines the stereochemical outcome of the reaction. In many cases, ring expansion reactions proceed with high stereospecificity, meaning that the spatial relationships in the starting material dictate the stereochemistry of the product. This stereospecificity arises from the concerted nature of many ring expansion processes, where bond breaking and formation occur simultaneously through well-defined transition states that preserve certain stereochemical elements.

The stereochemical integrity of ring expansion reactions has profound implications for synthetic applications. For instance, in the synthesis of complex natural products where specific stereochemical arrangements are crucial for biological activity, the ability to predict and control stereochemistry during ring expansion becomes paramount. This understanding has enabled chemists to develop sophisticated strategies for constructing complex molecular architectures with precise control over three-dimensional structure, leveraging the inherent stereospecificity of ring expansion mechanisms to achieve desired stereochemical outcomes.

## 1.4 2.2 Types of Ring Expansion Mechanisms

Ring expansion reactions encompass a diverse array of mechanistic pathways, each with its own characteristic features, advantages, and limitations. These mechanisms can be broadly categorized based on the nature of the reactive intermediates involved or the conditions under which the transformations occur. Understanding these distinct mechanistic classes provides chemists with a versatile toolkit for designing ring expansion strategies tailored to specific synthetic challenges.

Electrophilic ring expansions, driven by carbocation intermediates, represent one of the most well-studied and widely applied classes of ring expansion reactions. The Demjanov rearrangement, first discovered in 1883 and later refined by Tiffeneau, stands as the prototypical example of this mechanistic class. In this transformation, a cycloalkylmethylamine treated with nitrous acid generates a diazonium intermediate that decomposes to produce a carbocation. This carbocation then undergoes migration of an adjacent bond, resulting in ring expansion. The case of cyclobutylmethylamine transforming into cyclopentanone illustrates this process beautifully, with the expansion driven by the relief of ring strain in the four-membered system. The mechanistic elegance of this reaction lies in the way the carbocation intermediate, formed at the exocyclic position, prompts the migration of a ring bond to form the larger ring system.

Carbocation-mediated expansions often involve Wagner-Meerwein rearrangements, where alkyl or aryl groups migrate with their electron pairs to electron-deficient centers. These migrations are governed by the relative stability of the carbocation intermediates and the relief of ring strain. A particularly striking example is the expansion of bicyclo[2.2.1]heptane (norbornane) systems, where the rigid bicyclic framework facilitates specific migration patterns that lead to ring-expanded products. Such transformations have found extensive application in steroid chemistry, where controlled ring expansion enables access to derivatives with modified ring systems that may exhibit altered biological activities.

Radical-mediated ring expansions offer an alternative mechanistic pathway that often proceeds under milder conditions and with different selectivity profiles compared to their carbocation counterparts. These reactions typically involve the generation of carbon-centered radicals adjacent to ring systems, which then undergo ring expansion through bond migration or fragmentation. The remarkable versatility of radical chemistry allows for the development of ring expansion strategies that might be inaccessible through ionic pathways. For instance, the photolytic ring expansion of cyclic  $\alpha$ -diazoketones, pioneered by Meier and coworkers, involves the generation of carbenes that rapidly rearrange to ketenes, which can then be trapped to form expanded ring systems. This approach has proven particularly valuable in the synthesis of medium-sized rings, which are often challenging to construct through conventional methods.

Photochemical ring expansions harness the energy of light to drive ring expansion processes that might be thermally forbidden or prohibitively slow. These reactions often involve the excitation of molecules to electronically excited states, which then undergo pericyclic processes or other rearrangements leading to ring expansion. The photochemical ring expansion of cyclic ketones via  $\alpha$ -cleavage (Norrish type I reaction) represents a classic example. Upon irradiation, cyclic ketones undergo homolytic cleavage of the bond adjacent to the carbonyl group, generating biradical intermediates that can recombine in various ways, sometimes leading to ring-expanded products. The photochemical behavior of cyclic  $\beta,\gamma$ -unsaturated ketones provides another fascinating case study, where electrocyclic ring-opening followed by reclosure can result in ring expansion with impressive stereocontrol.

Thermal ring expansions, driven solely by heat energy without the need for photochemical excitation or reactive intermediates, rely on the inherent thermal energy of the system to overcome activation barriers. These transformations often involve pericyclic processes that are thermally allowed according to the Woodward-Hoffmann rules. The thermal ring expansion of vinylcyclopropanes to cyclopentenenes stands as a textbook example of this mechanistic class. This [3,3]-sigmatropic rearrangement, also known as the Cope rearrangement when applied to 1,5-dienes, proceeds through a concerted mechanism that maintains stereochemical integrity while expanding the ring system. The synthetic utility of such transformations has been dramatically enhanced through the development of catalytic variants, where Lewis acids or transition metal complexes can lower the activation barrier and improve selectivity.

Metal-mediated ring expansions have emerged as a powerful mechanistic class in recent decades, leveraging the unique reactivity patterns imparted by transition metal complexes. These reactions often involve the coordination of the metal center to the substrate, followed by insertion, migratory insertion, or oxidative addition/reductive elimination sequences that result in ring expansion. The ring expansion metathesis of cyclic alkenes, catalyzed by well-defined transition metal complexes such as Grubbs catalysts, represents a particularly impactful example. In this transformation, a strained cyclic alkene undergoes ring-opening metathesis followed by reclosure to form a larger ring system. This approach has revolutionized the synthesis of macrocyclic compounds, including natural products with large ring systems that were previously challenging to construct.

The rhodium-catalyzed ring expansion of diazo compounds offers another compelling example of metal-mediated ring expansion. In this process, a rhodium carbenoid generated from a diazo precursor can insert into C-H bonds or undergo cyclopropanation, followed by rearrangement to form expanded ring systems. The work of Davies and others has demonstrated the remarkable versatility of this approach, enabling the construction of complex molecular architectures with precise control over regiochemistry and stereochemistry. These metal-mediated processes often proceed under mild conditions with high functional group tolerance, making them particularly valuable for late-stage functionalization of complex molecules.

## 1.5 2.3 Thermodynamic and Kinetic Considerations

The successful implementation of ring expansion reactions requires a nuanced understanding of both thermodynamic and kinetic factors that govern these transformations. These considerations determine not only



whether a ring expansion will occur but also how rapidly it proceeds, what products are formed, and how various conditions might influence the outcome. By carefully analyzing energy profiles, substituent effects, and equilibrium considerations, chemists can predict and optimize ring expansion reactions for specific synthetic applications.

Energy profiles of ring expansion reactions typically feature characteristic transition states that reflect the mechanistic pathway of the transformation. In carbocation-mediated expansions, for instance, the energy profile often shows an initial energy barrier corresponding to the formation of the carbocation intermediate, followed by a lower barrier for the migration step that results in ring expansion. The relative heights of these barriers determine the rate-determining step of the reaction and influence the overall efficiency of the transformation. For example, in the Demjanov rearrangement of cyclopropylmethyl systems, the initial formation of the primary carbocation represents the highest energy barrier, while the subsequent [1,2]-shift to form the cyclobutyl system occurs with a much lower activation energy due to the significant strain relief that accompanies this step.

Substituent effects play a crucial role in modulating the energy profiles of ring expansion reactions. Electron-donating groups can stabilize carbocation intermediates, lowering activation barriers and accelerating rearrangement processes. Conversely, electron-withdrawing groups can destabilize these intermediates, potentially slowing the reaction or diverting the mechanistic pathway. The influence of substituents extends beyond simple electronic effects, however. Steric factors can dramatically impact the conformational preferences of transition states, while neighboring group participation can provide alternative mechanistic pathways that bypass high-energy intermediates. A fascinating illustration of these principles is found in the ring expansion of bicyclic systems, where substituents at bridgehead positions can exert profound influences on both the rate and regiochemistry of the expansion process.

Equilibrium considerations become particularly important in reversible ring expansion reactions, where the product distribution reflects the relative thermodynamic stability of various possible outcomes. In such cases, the reaction may proceed through kinetic control initially but eventually reach a thermodynamic equilibrium that favors the most stable product. The ring expansion of small to medium-sized rings often exemplifies this behavior, with the equilibrium shifting toward larger rings as the system minimizes strain energy. For instance, the equilibrium between cyclobutylmethyl and cyclopentyl systems strongly favors the latter due to the significant strain relief associated with the four-to-five membered ring expansion. Understanding these equilibrium relationships allows chemists to design reaction conditions that drive transformations toward desired products, either by exploiting kinetic control or by allowing the system to reach thermodynamic equilibrium.

Computational chemistry has emerged as an indispensable tool for understanding the mechanistic details of ring expansion reactions. Modern computational methods can model energy profiles with remarkable accuracy, providing insights into transition state geometries, activation barriers, and the relative stability of intermediates. Density functional theory (DFT) calculations, in particular, have proven valuable for elucidating the mechanisms of complex ring expansion processes that might be difficult to study experimentally. These computational approaches can predict stereochemical outcomes, identify potential side reactions, and

even suggest modifications to substrate structure that might improve reaction efficiency. The work of Houk and others in applying computational methods to pericyclic ring expansion reactions has provided profound insights into the orbital interactions that govern these transformations, complementing experimental observations and expanding our fundamental understanding of these processes.

The interplay between thermodynamic driving forces and kinetic accessibility represents a central theme in ring expansion chemistry. While thermodynamic factors often favor ring expansion of strained small rings to larger systems, kinetic barriers can sometimes prevent these transformations from occurring under mild conditions. This tension between thermodynamics and kinetics has inspired the development of catalytic strategies that lower activation barriers while preserving the thermodynamic driving force. Transition metal catalysis, in particular, has proven remarkably effective in this regard, enabling ring expansion reactions that would be prohibitively slow in the absence of the catalyst. The ring-closing metathesis of dienes to form cyclic alkenes, followed by ring expansion metathesis, exemplifies this approach, with ruthenium catalysts facilitating transformations that would require prohibitively high temperatures under thermal conditions.

Temperature effects on ring expansion reactions reflect the underlying kinetic and thermodynamic principles. Higher temperatures generally accelerate reactions by providing the energy needed to overcome activation barriers, but they can also shift equilibria and promote side reactions. In some cases, carefully controlled temperature profiles can be used to selectively promote certain mechanistic pathways over others. The photochemical ring expansion of cyclic ketones, for instance, often requires precise temperature control to maximize the yield of the desired expanded product while minimizing competing pathways. Similarly, thermal ring expansions of vinylcyclopropanes can exhibit dramatic temperature dependence, with different products dominating at different temperatures as the system navigates complex energy landscapes with multiple possible transition states and intermediates.

## 1.6 2.4 Stereochemical Aspects

The stereochemical dimensions of ring expansion reactions represent one of the most fascinating and practically important aspects of these transformations. Unlike many other organic reactions where stereochemistry might be secondary to the formation of the desired carbon skeleton, ring expansions often involve specific stereochemical relationships that can profoundly influence both the mechanism and the utility of the transformation. Understanding and controlling these stereochemical aspects has become essential for applying ring expansion strategies to the synthesis of complex natural products and other functionally important molecules.

Stereospecificity stands as a hallmark of many ring expansion reactions, particularly those proceeding through concerted mechanisms. In these transformations, the stereochemical configuration of the starting material directly determines the stereochemical outcome of the product. The electrocyclic ring expansion of cyclobutenes provides a classic example of this principle. According to the Woodward-Hoffmann rules, thermal electrocyclic reactions of  $4\pi$ -electron systems proceed through a conrotatory pathway, meaning that the terminal substituents rotate in the same direction during ring opening. This stereospecificity translates directly to the stereochemistry of the resulting cyclobutene to butadiene

## 1.7 Historical Development of Ring Expansion Chemistry

The profound understanding of stereospecificity in ring expansion reactions that we've explored did not emerge in a vacuum but represents the culmination of more than a century of scientific inquiry and discovery. The historical development of ring expansion chemistry reveals a fascinating narrative of scientific progress, marked by serendipitous discoveries, theoretical breakthroughs, and the relentless pursuit of synthetic utility. This rich historical tapestry not only illuminates how our current understanding evolved but also provides valuable context for appreciating the significance of modern ring expansion methodologies.

### 1.8 3.1 Early Discoveries (19th Century)

The story of ring expansion chemistry begins in the 19th century, an era when organic chemistry was still establishing its fundamental principles and the very concept of molecular structure was being hotly debated. Among the earliest documented observations of ring expansion phenomena was the work of Russian chemist Nikolay Demjanov in 1883. While studying the reactions of amines with nitrous acid, Demjanov made an unexpected discovery that would later bear his name. When he treated cyclobutylmethylamine with nitrous acid, anticipating the formation of cyclobutylcarbinol, he instead obtained cyclopentanone as the major product. This unexpected outcome represented the first documented example of a ring expansion reaction, though Demjanov himself lacked the theoretical framework to fully comprehend the mechanistic implications of his discovery.

The significance of Demjanov's observation can only be fully appreciated when considered against the backdrop of 19th-century organic chemistry. At the time, the structural theory of organic compounds was still in its infancy. August Kekulé had proposed his revolutionary idea of cyclic structures for benzene in 1865, but the concept of ring strain and its implications for reactivity had not yet been developed. The tools available for characterizing organic compounds were primitive by modern standards, with chemists relying primarily on elemental analysis, determination of physical properties, and chemical degradation studies to elucidate structures. Despite these limitations, Demjanov correctly identified his product as cyclopentanone, demonstrating remarkable insight and experimental skill.

In the decades following Demjanov's discovery, several other European chemists made observations that would later be recognized as ring expansion reactions, though they lacked the unifying theoretical framework to connect these seemingly disparate phenomena. In 1893, German chemist Paul Fritsch reported that certain cyclic ketones could undergo expansion when treated with diazomethane, though the mechanism remained obscure. Similarly, the work of Russian chemist Alexander Butlerov on the rearrangements of terpenes provided early evidence for ring expansion processes in natural product chemistry, though the structural complexity of these compounds made definitive mechanistic interpretations challenging.

The late 19th century also witnessed important theoretical developments that would eventually enable a more sophisticated understanding of ring expansion reactions. The concept of tetrahedral carbon, proposed by Jacobus Henricus van 't Hoff and Joseph Achille Le Bel in 1874, provided a foundation for understanding the three-dimensional nature of organic molecules. This stereochemical insight would prove crucial for later

explanations of ring expansion mechanisms, particularly those involving carbocation intermediates where the spatial arrangement of atoms determines the course of rearrangement.

Perhaps the most significant limitation of 19th-century organic chemistry in the context of ring expansion reactions was the absence of electronic theory. Without an understanding of electron movement and bonding, chemists could only describe ring expansion phenomena in terms of atom migrations without explaining the driving forces behind these transformations. The term “rearrangement” was often used as a catch-all phrase for any unexpected reaction outcome, reflecting the limited mechanistic understanding of the era.

Despite these theoretical limitations, the experimental observations made during this period laid the groundwork for future developments. The recognition that cyclic systems could undergo structural transformations to form larger rings represented a conceptual breakthrough that would eventually inspire systematic investigation. These early discoveries also demonstrated the synthetic potential of ring expansion reactions, suggesting new pathways for the construction of complex molecular frameworks that would later prove invaluable in the synthesis of natural products and pharmaceuticals.

## 1.9 3.2 Mid-20th Century Advances

The mid-20th century marked a golden age for ring expansion chemistry, characterized by rapid theoretical advances, the development of powerful new experimental techniques, and the emergence of ring expansion as a valuable synthetic tool. This transformative period was catalyzed by several converging developments, including the maturation of electronic theory of organic chemistry, the advent of modern spectroscopic methods, and the growing demand from the pharmaceutical industry for efficient synthetic strategies to complex molecules.

The post-World War II era witnessed an explosion of interest in ring expansion chemistry, driven in part by the need for efficient methods to synthesize steroidal hormones and other medicinally important compounds. The structural complexity of these natural products, with their multiple fused ring systems, provided the perfect proving ground for ring expansion methodologies. During this period, several important ring expansion reactions were discovered and refined, expanding the synthetic chemist's toolkit and enabling access to previously challenging molecular architectures.

One of the most significant developments of this era was the refinement of the Demjanov rearrangement by French chemist Marc Tiffeneau in the 1940s. Recognizing the limitations of the original reaction, Tiffeneau modified the protocol by employing  $\beta$ -amino alcohols instead of primary amines. This modification, now known as the Tiffeneau-Demjanov rearrangement, provided a more reliable method for ring expansion and found immediate application in steroid chemistry. The transformation proved particularly valuable for expanding the D-ring of steroid frameworks, enabling the synthesis of novel derivatives with potential biological activity. The success of this methodology highlighted the synthetic potential of ring expansion reactions and inspired further investigation into related processes.

The 1950s saw the discovery and development of several other important ring expansion reactions. The Favorskii rearrangement, though first observed in the late 19th century, was thoroughly investigated and

mechanistically elucidated during this period. This transformation, which converts  $\alpha$ -halo ketones to carboxylic acid derivatives with ring expansion, proved particularly valuable for the synthesis of medium-sized rings that are difficult to access by other methods. The mechanism, involving a cyclopropanone intermediate, provided a fascinating example of how ring strain could be harnessed to drive structural reorganization.

Simultaneously, the Semmler-Wolff reaction, which transforms cyclohexanone oximes to anilines with ring expansion, was refined and optimized for synthetic applications. This reaction represented an important bridge between carbocyclic and heterocyclic chemistry, demonstrating how ring expansion could be used to introduce nitrogen into cyclic systems. The development of this methodology coincided with growing interest in nitrogen-containing heterocycles for pharmaceutical applications, further driving its adoption.

A pivotal moment in the history of ring expansion chemistry came with the introduction of spectroscopic techniques that allowed chemists to characterize reaction products with unprecedented precision. Nuclear magnetic resonance (NMR) spectroscopy, in particular, revolutionized the field by enabling detailed structural elucidation of complex molecules. The ability to determine carbon frameworks and stereochemical arrangements with confidence allowed chemists to study ring expansion reactions in greater detail than ever before, leading to more sophisticated mechanistic understanding and the discovery of new transformations.

Infrared spectroscopy and mass spectrometry also made significant contributions during this period. These techniques provided complementary information about functional groups and molecular weights, respectively, helping chemists to confirm the identity of ring expansion products and detect minor byproducts that might have gone unnoticed with earlier characterization methods. The combined application of these spectroscopic tools created a powerful analytical framework that accelerated the discovery and optimization of new ring expansion methodologies.

The theoretical understanding of ring expansion reactions also advanced dramatically during the mid-20th century. The development of molecular orbital theory, particularly the work of Robert Burns Woodward and Roald Hoffmann on orbital symmetry conservation, provided a rigorous framework for understanding pericyclic ring expansion reactions. Their formulation of the Woodward-Hoffmann rules in the 1960s offered a predictive model for the stereochemical course of electrocyclic reactions, including those involving ring expansion. This theoretical advance not only explained existing observations but also predicted new ring expansion pathways that were subsequently verified experimentally.

The work of Vladimir Prelog on the stereochemistry of ring expansion reactions during this period deserves special mention. Prelog's meticulous investigations into the three-dimensional aspects of these transformations provided crucial insights that would shape the mechanistic framework for decades to come. His studies of the stereochemical course of ring expansion reactions in complex molecules, particularly steroids and terpenes, demonstrated how the spatial arrangement of atoms could dictate the outcome of rearrangement processes. These insights proved invaluable for developing stereoselective synthetic strategies, a theme that would become increasingly important in the decades to follow.

The mid-20th century also witnessed the first applications of ring expansion reactions in industrial settings. Pharmaceutical companies recognized the value of these transformations for synthesizing complex drug candidates, particularly in the area of steroid derivatives. The ability to modify ring systems through expansion

methods offered new opportunities for structure-activity relationship studies, enabling the systematic exploration of how changes in molecular framework influenced biological activity. This industrial interest provided both financial support and practical motivation for continued research in ring expansion chemistry.

### 1.10 3.3 Modern Developments (Late 20th to 21st Century)

The late 20th and early 21st centuries have witnessed a remarkable evolution in ring expansion chemistry, characterized by the emergence of catalytic methods, integration with modern synthetic strategies, and the transformative impact of computational chemistry. This period has seen ring expansion reactions transition from specialized transformations to mainstream synthetic tools, with applications spanning natural product synthesis, medicinal chemistry, and materials science. The convergence of experimental innovation and theoretical sophistication has created a fertile environment for discovery, driving the field to new heights of efficiency, selectivity, and synthetic utility.

One of the most significant trends in modern ring expansion chemistry has been the rise of catalytic methods, which have dramatically improved the efficiency and sustainability of these transformations. Transition metal catalysis, in particular, has revolutionized the field by enabling ring expansion reactions under milder conditions with higher selectivity than their stoichiometric counterparts. The development of well-defined metal complexes with predictable reactivity patterns has given chemists unprecedented control over ring expansion processes. The ring-closing metathesis (RCM) reaction, pioneered by Robert Grubbs, Richard Schrock, and Yves Chauvin in the 1990s, stands as a landmark achievement in this area. This transformation, which employs ruthenium or molybdenum catalysts to form cyclic alkenes from dienes, can be adapted for ring expansion through ring-opening/ring-closing sequences. The ability to construct medium and large rings with high efficiency has had a profound impact on natural product synthesis, enabling the preparation of complex macrocyclic structures that were previously inaccessible.

Palladium catalysis has also made significant contributions to modern ring expansion chemistry. The work of Barry Trost and others on palladium-mediated transformations has expanded the scope of ring expansion reactions to include systems with sensitive functional groups and complex stereochemical arrangements. These methodologies often proceed through well-defined organopalladium intermediates, allowing for precise control over regiochemistry and stereochemistry. The development of chiral palladium catalysts has further enabled asymmetric ring expansion reactions, providing access to enantiomerically enriched building blocks for pharmaceutical synthesis.

The integration of ring expansion reactions with modern synthetic strategies represents another important trend in contemporary chemistry. Tandem and cascade reactions, where multiple bond-forming events occur in a single synthetic operation, have been particularly influential. These domino processes often incorporate ring expansion as a key step, enabling the rapid construction of complex molecular frameworks from relatively simple precursors. The work of K.C. Nicolaou on cascade ring expansion reactions in the synthesis of biologically active natural products exemplifies this approach, demonstrating how strategic ring expansion can streamline synthetic routes to challenging targets.



Click chemistry, a concept introduced by Barry Sharpless in the early 2000s, has also influenced modern ring expansion methodologies. The principles of click chemistry—modular, high-yielding reactions with minimal byproducts—have inspired the development of ring expansion reactions that proceed with exceptional efficiency and reliability. These transformations often employ highly reactive intermediates that undergo rapid ring expansion, minimizing side reactions and maximizing synthetic utility.

Computational chemistry has emerged as an indispensable tool for understanding and designing ring expansion reactions in the modern era. The application of density functional theory (DFT) calculations and other computational methods has provided unprecedented insights into the mechanisms of these transformations, including transition state geometries, activation energies, and the relative stability of intermediates. The work of Kendall Houk and others in applying computational methods to pericyclic ring expansion reactions has been particularly influential, offering detailed mechanistic pictures that complement experimental observations and guide the design of new reactions.

Machine learning and artificial intelligence have begun to play an increasingly important role in ring expansion chemistry. These computational approaches can analyze vast databases of chemical reactions to identify patterns and predict the outcomes of new transformations. In the context of ring expansion chemistry, machine learning algorithms have been used to predict the regiochemical and stereochemical outcomes of complex rearrangements, accelerating the discovery process and reducing the need for extensive experimental screening.

The late 20th and early 21st centuries have also witnessed the development of innovative ring expansion methodologies that push the boundaries of traditional reactivity. Photochemical ring expansion reactions, driven by electronic excitation rather than thermal energy, have undergone a renaissance with the development of new light sources and photocatalysts. These transformations often proceed through unique mechanistic pathways that are inaccessible under thermal conditions, enabling access to novel molecular architectures. The work of Tehshik Yoon and others on visible-light photocatalysis has expanded the scope of photochemical ring expansion reactions, making them more practical for synthetic applications.

Biocatalytic approaches represent another frontier in modern ring expansion chemistry. Enzymes have evolved over billions of years to catalyze complex transformations with remarkable efficiency and selectivity, including ring expansion reactions involved in natural product biosynthesis. The application of these biocatalysts in synthetic settings, either as isolated enzymes or in whole-cell systems, offers a sustainable alternative to traditional chemical methods. The engineering of enzymes to catalyze non-natural ring expansion reactions, through directed evolution and rational design, represents an exciting area of ongoing research.

The synthetic applications of ring expansion reactions have continued to expand in the modern era, with these transformations playing crucial roles in the synthesis of complex natural products, pharmaceuticals, and functional materials. In natural product synthesis, ring expansion strategies have enabled the efficient construction of challenging molecular frameworks, particularly those containing medium and large rings. The synthesis of macrolide antibiotics, for instance, has often benefited from ring expansion methodologies that provide efficient access to the macrocyclic core structure.

In medicinal chemistry, ring expansion reactions have proven valuable for the synthesis of compound libraries and the optimization of lead compounds. The ability to systematically modify ring systems through expansion methods allows medicinal chemists to explore structure-activity relationships and identify compounds with improved biological properties. Ring expansion has also been employed in the synthesis of constrained peptides and peptidomimetics, which are important targets for drug discovery due to their potential for enhanced metabolic stability and bioavailability.

### 1.11 3.4 Key Historical Figures

The historical development of ring expansion chemistry has been shaped by numerous brilliant scientists whose contributions have collectively advanced our understanding and application of these transformations. These key historical figures, through their insights, discoveries, and innovations, have transformed ring expansion from a chemical curiosity into a powerful synthetic tool. Their individual stories not only illuminate the scientific progress but also reflect the broader historical context in which they worked.

Nikolay Demjanov (1861-1938) stands as the foundational figure in ring expansion chemistry. A Russian chemist educated at the University of St. Petersburg, Demjanov made his landmark discovery while working as a laboratory assistant. His observation that cyclobutylmethylamine treated with nitrous acid produced cyclopentanone rather than the expected cyclobutylcarbinol was the first documented example of a ring expansion reaction. Despite the limited theoretical framework available at the time, Demjanov recognized the significance of this unexpected outcome and published his findings in 1883. His work laid the groundwork for future investigations into ring expansion phenomena, though the mechanistic implications would not be fully understood for decades. Demjanov's career was marked by scientific contributions beyond ring expansion chemistry, including important work on the chemistry of amines and diazo compounds, but his name remains inextricably linked to the rearrangement that bears his name.

Marc Tiffeneau (1873-1945), a French chemist and pharmacologist, made significant contributions to ring expansion chemistry through his refinement of the Demjanov rearrangement. Educated at the University of Paris, Tiffeneau developed a modification of the original reaction that employed  $\beta$ -amino alcohols instead of primary amines. This improvement, now known as the Tiffeneau-Demjanov rearrangement, provided a more reliable method for ring expansion and found immediate application in steroid chemistry. Tiffeneau's work exemplified the practical orientation of much French chemistry during this period, with a focus on developing synthetic methods useful for pharmaceutical applications. Beyond his contributions to ring expansion chemistry, Tiffeneau made significant advances in pharmacology and was a pioneer in the field

### 1.12 Classification of Ring Expansion Reactions

...pioneer in the field of medicinal chemistry. His development of the Tiffeneau-Demjanov rearrangement exemplifies how incremental improvements to fundamental reactions can dramatically enhance their synthetic utility, paving the way for more systematic approaches to ring expansion chemistry.



### 1.13 Section 4: Classification of Ring Expansion Reactions

The rich historical tapestry of ring expansion chemistry, woven by the contributions of Demjanov, Tiffeneau, and many others, has given rise to a diverse array of transformations that defy simple categorization. Yet, as the field has matured, chemists have found it increasingly necessary to develop systematic classification systems that bring order to this apparent complexity. These classifications serve not merely as organizational tools but as conceptual frameworks that illuminate the underlying principles governing ring expansion reactions, revealing patterns and relationships that might otherwise remain obscured. By examining ring expansion reactions through multiple complementary lenses—mechanism, ring type, methodology, and the number of atoms added—we gain a more nuanced understanding of this fascinating corner of organic chemistry.

#### 1.13.1 4.1 Classification Based on Reaction Mechanism

Perhaps the most fundamental approach to classifying ring expansion reactions is by their underlying mechanism, as this classification reveals the essential chemical processes driving the transformation. Mechanistic classification provides insights into the reactivity patterns, selectivity, and potential side reactions associated with each type of ring expansion, enabling chemists to make informed decisions when designing synthetic strategies.

Carbocation-mediated expansions represent one of the oldest and most extensively studied mechanistic classes, tracing their lineage back to Demjanov's original discovery. These reactions proceed through carbocation intermediates, which undergo bond migrations that result in ring expansion. The driving force for these transformations often lies in the relief of ring strain or the formation of more stable carbocation species. The Demjanov rearrangement itself, where a cycloalkylmethylamine treated with nitrous acid generates a carbocation that undergoes ring expansion, serves as the prototypical example. When cyclobutylmethylamine undergoes this transformation, the resulting primary carbocation rearranges to form the more stable cyclopentyl system, releasing approximately 26.4 kcal/mol of strain energy in the process. The Tiffeneau-Demjanov variant, employing  $\beta$ -amino alcohols, provides greater reliability and has found particular utility in steroid chemistry, where controlled expansion of the D-ring enables access to novel derivatives with potentially altered biological activities.

Beyond these classical examples, carbocation-mediated expansions encompass a rich diversity of transformations. The Wagner-Meerwein rearrangement, initially discovered in the context of camphene chemistry, involves the migration of alkyl or aryl groups with their electron pairs to electron-deficient centers, often resulting in ring expansion. A particularly fascinating example is the expansion of bicyclo[2.2.1]heptane systems, where the rigid bicyclic framework facilitates specific migration patterns that lead to ring-expanded products. The synthetic power of these transformations was dramatically demonstrated in the synthesis of the complex sesquiterpene illudin S, where a strategic Wagner-Meerwein rearrangement played a pivotal role in constructing the challenging tricyclic framework.

Carbanion-mediated expansions, while less common than their carbocation counterparts, offer unique re-

activity patterns and complementary synthetic utility. These reactions typically involve the generation of carbanionic species adjacent to ring systems, which then undergo ring expansion through bond migration or fragmentation. The Favorskii rearrangement stands as the quintessential example of this mechanistic class, transforming  $\alpha$ -halo ketones to carboxylic acid derivatives with ring expansion. The mechanism of this transformation involves the formation of a cyclopropanone intermediate, which then undergoes nucleophilic attack and ring opening to yield the expanded product. The strain inherent in the cyclopropanone ring provides a powerful driving force for the rearrangement, particularly when the original ring is small and highly strained. This reaction has proven invaluable for the synthesis of medium-sized rings, which are often challenging to construct by conventional methods. A striking application of the Favorskii rearrangement can be found in the synthesis of the antibiotic monensin, where a key ring expansion step enabled the efficient construction of the complex polyether framework.

Radical-mediated ring expansions offer an alternative mechanistic pathway that often proceeds under milder conditions and with different selectivity profiles compared to ionic transformations. These reactions typically involve the generation of carbon-centered radicals adjacent to ring systems, which then undergo ring expansion through bond migration or fragmentation. The remarkable versatility of radical chemistry allows for the development of ring expansion strategies that might be inaccessible through ionic pathways. For instance, the photolytic ring expansion of cyclic  $\alpha$ -diazoketones involves the generation of carbenes that rapidly rearrange to ketenes, which can then be trapped to form expanded ring systems. This approach has proven particularly valuable in the synthesis of medium-sized rings, which are often challenging to construct through conventional methods. A fascinating example is the ring expansion of cyclic  $\beta$ -keto esters via radical intermediates, developed by Dowd and coworkers, which provides efficient access to seven- and eight-membered rings with excellent functional group tolerance.

Pericyclic expansion reactions, governed by the principles of orbital symmetry conservation, represent a mechanistically distinct class characterized by their concerted nature and high stereospecificity. These transformations include electrocyclic reactions, sigmatropic rearrangements, and cycloadditions that result in ring expansion. The thermal ring expansion of vinylcyclopropanes to cyclopentenenes stands as a textbook example of this mechanistic class. This [3,3]-sigmatropic rearrangement, also known as the Cope rearrangement when applied to 1,5-dienes, proceeds through a concerted mechanism that maintains stereochemical integrity while expanding the ring system. The synthetic utility of such transformations has been dramatically enhanced through the development of catalytic variants, where Lewis acids or transition metal complexes can lower the activation barrier and improve selectivity. A particularly elegant application of pericyclic ring expansion can be found in the synthesis of the complex natural product endiandric acid, where a cascade of electrocyclic reactions, including ring expansion, enables the efficient construction of the challenging polycyclic framework.

Metal-catalyzed expansions have emerged as a powerful mechanistic class in recent decades, leveraging the unique reactivity patterns imparted by transition metal complexes. These reactions often involve the coordination of the metal center to the substrate, followed by insertion, migratory insertion, or oxidative addition/reductive elimination sequences that result in ring expansion. The ring expansion metathesis of cyclic alkenes, catalyzed by well-defined transition metal complexes such as Grubbs catalysts, represents a partic-

ularly impactful example. In this transformation, a strained cyclic alkene undergoes ring-opening metathesis followed by reclosure to form a larger ring system. This approach has revolutionized the synthesis of macrocyclic compounds, including natural products with large ring systems that were previously challenging to construct. The rhodium-catalyzed ring expansion of diazo compounds offers another compelling example of metal-mediated ring expansion. In this process, a rhodium carbenoid generated from a diazo precursor can insert into C-H bonds or undergo cyclopropanation, followed by rearrangement to form expanded ring systems. The work of Davies and others has demonstrated the remarkable versatility of this approach, enabling the construction of complex molecular architectures with precise control over regiochemistry and stereochemistry.

### 1.13.2 4.2 Classification Based on Ring Type

Another valuable approach to classifying ring expansion reactions is based on the type of ring system undergoing expansion. This classification reflects the structural diversity of cyclic systems and highlights how ring architecture influences the mechanistic pathways and synthetic outcomes of expansion reactions. By understanding how different ring types behave during expansion, chemists can select the most appropriate strategies for specific synthetic challenges.

Homocyclic ring expansions involve carbocyclic systems composed exclusively of carbon atoms. These transformations represent the most extensively studied category of ring expansion reactions, owing to the prevalence of carbocyclic frameworks in natural products and pharmaceuticals. The expansion of small carbocyclic rings, particularly cyclopropanes and cyclobutanes, often proceeds with remarkable efficiency due to the significant strain relief that accompanies these transformations. A classic example is the expansion of cyclopropylcarbinyl systems to cyclobutyl derivatives, a process that releases approximately 27 kcal/mol of strain energy. This transformation has been elegantly applied in the synthesis of the sesquiterpene  $\beta$ -vetivone, where a strategic cyclopropane expansion enabled the efficient construction of the challenging bicyclic framework. Medium-sized carbocyclic rings (7-12 members) present unique challenges for expansion due to their conformational flexibility and transannular interactions, which can complicate the reaction pathway. The ring expansion of cyclodecane derivatives, for instance, often requires carefully designed substrates to control the regiochemistry of bond migration and minimize competing side reactions.

Heterocyclic ring expansions incorporate heteroatoms such as nitrogen, oxygen, or sulfur into the ring system being expanded. These transformations are particularly valuable in medicinal chemistry, where heterocyclic frameworks are prevalent in biologically active compounds. The expansion of nitrogen-containing heterocycles has been extensively studied, with the Beckmann rearrangement of cyclohexanone oximes to caprolactam representing one of the most industrially important examples. This transformation, which produces the monomer for nylon-6, proceeds through a nitrilium ion intermediate that undergoes ring expansion with migration of an anti-periplanar substituent. Oxygen-containing heterocycles also undergo fascinating expansion reactions, as exemplified by the acid-catalyzed expansion of tetrahydrofuran derivatives to oxepanes. These transformations often proceed through oxocarbenium intermediates and have been applied in the synthesis of complex polyether natural products such as brevetoxin. Sulfur-containing heterocycles

exhibit their own unique expansion chemistry, with the ring expansion of thiiranes and thietanes providing efficient access to larger sulfur-containing rings that are valuable as ligands in coordination chemistry.

Fused ring system expansions involve polycyclic structures where two or more rings share a common bond. These transformations are particularly challenging due to the architectural complexity of the substrates, often requiring precise control over regiochemistry and stereochemistry. The expansion of decalin systems, for instance, can proceed through multiple mechanistic pathways depending on which bonds migrate and whether the fusion is *cis* or *trans*. The synthetic utility of fused ring expansions was dramatically demonstrated in the synthesis of the complex diterpene taxol, where a strategic ring expansion of a fused bicyclic system enabled the efficient construction of the challenging eight-membered B-ring. Fused heterocyclic systems undergo equally fascinating expansion reactions, as exemplified by the ring expansion of indole derivatives, which has been applied in the synthesis of numerous alkaloid natural products.

Spiro compound expansions involve ring systems where two rings share a single carbon atom. These transformations present unique mechanistic challenges due to the quaternary nature of the spiro center, which often necessitates specific geometric arrangements for successful expansion. The ring expansion of spiro[2.4]heptane derivatives, for instance, typically requires careful control of the conformation to ensure that the migrating bond is properly aligned for expansion. Despite these challenges, spiro ring expansions have proven valuable in the synthesis of complex natural products containing spirocyclic frameworks, such as the sesquiterpene acorenone B. The work of Wiesner and others on the synthesis of morphine alkaloids demonstrated how strategic spiro ring expansion could enable the construction of the challenging pentacyclic framework characteristic of these compounds.

Bridged compound expansions involve polycyclic systems where two rings are connected by a bridge containing one or more atoms. These transformations are particularly intriguing due to the geometric constraints imposed by the bridged architecture, which can dramatically influence the course of the expansion. The ring expansion of norbornane systems, for instance, typically involves migration of the bridge bonds, leading to specific expanded products that reflect the underlying symmetry of the starting material. bridged heterocyclic systems undergo equally fascinating expansion reactions, as exemplified by the ring expansion of 7-oxabicyclo[2.2.1]heptane derivatives, which has been applied in the synthesis of complex carbohydrate analogs with potential biological activity. The synthesis of the complex diterpene ingenol showcased the power of bridged ring expansion strategies, where a carefully designed sequence of expansions enabled the efficient construction of the challenging [3.3.1]bicyclic framework.

### 1.13.3 4.3 Classification Based on Expansion Methodology

A third approach to classifying ring expansion reactions focuses on the specific methodology employed to achieve the expansion, reflecting the diverse synthetic strategies that chemists have developed to increase ring size. This classification highlights the creativity and ingenuity that characterize modern synthetic organic chemistry, revealing how different approaches can be tailored to specific structural challenges and synthetic objectives.

Insertion-based expansions add atoms to existing rings without breaking the original ring bonds, effectively inserting new atoms into the cyclic framework. These transformations often involve highly reactive intermediates such as carbenes, nitrenes, or metal carbenoids that can insert into C-H or C-C bonds. The insertion of dichlorocarbene into cycloalkanes, for instance, generates homologated cycloalkanes with one additional carbon atom, providing a straightforward method for ring expansion. This approach has been elegantly applied in the synthesis of the musk odorant exaltone, where dichlorocarbene insertion into cyclododecanone followed by dehalogenation yielded the expanded 13-membered ring. Metal-mediated insertion reactions offer even greater control and selectivity, as exemplified by the rhodium-catalyzed insertion of diazo compounds into cyclic systems, which enables the efficient construction of complex molecular architectures with precise control over regiochemistry and stereochemistry.

Fragmentation/recombination expansions create new ring systems through the cleavage of existing bonds followed by recombination in an expanded configuration. These transformations often leverage ring strain as a driving force, with the energy released upon fragmentation providing the impetus for recombination in the expanded form. The Grob fragmentation represents a classic example of this approach, where the fragmentation of cyclic systems with appropriately positioned electron-donating and electron-withdrawing groups leads to ring-expanded products. This strategy has been particularly valuable in the synthesis of medium-sized rings, which are often challenging to construct by conventional methods. A fascinating application of fragmentation-based ring expansion can be found in the synthesis of the complex macrolide antibiotic erythromycin, where a strategic fragmentation/recombination sequence enabled the efficient construction of the challenging 14-membered lactone ring.

Ring-walking expansions involve the migration of substituents around rings, effectively expanding the ring system through a series of bond migrations. These transformations often proceed through pericyclic mechanisms or metal-mediated processes that enable the “walking” of substituents to new positions. The ring expansion of vinylcyclopropanes to cyclopentenones via Cope rearrangement represents a classic example of this approach, where the vinyl group effectively “walks” around the cyclopropane ring to form the larger cyclopentene system. Metal-catalyzed ring-walking processes offer even greater versatility, as exemplified by the rhodium-catalyzed expansion of cyclobutanols to cyclohexanones, where the metal catalyst facilitates the migration of carbon substituents around the ring framework. These transformations have been elegantly applied in the synthesis of complex terpenoids, where strategic ring-walking expansions enable the efficient construction of challenging polycyclic frameworks.

Tandem/cascade expansions combine multiple reaction steps in a single synthetic operation, often resulting in dramatic increases in molecular complexity from relatively simple starting materials. These transformations leverage the inherent reactivity of intermediates formed in one step to drive subsequent ring expansion steps, creating a domino effect that culminates in the formation of complex ring systems. The work of Nicolaou on cascade ring expansion reactions in the synthesis of biologically active natural products exemplifies this approach, demonstrating how strategic design can enable the rapid construction of challenging molecular frameworks. A particularly striking example is the cascade expansion of cyclic enyne systems, where a sequence of pericyclic reactions, including electrocyclic ring openings and closings, can transform simple monocyclic precursors into complex polycyclic products with multiple ring-expanded components.

These transformations highlight the power of strategic design in synthetic organic chemistry, where carefully orchestrated sequences of reactions can achieve remarkable efficiency in the construction of complex molecular architectures.

Multi-component ring expansions involve several reactants that come together to form expanded ring systems in a single synthetic operation.

### 1.14 Ring Expansion of Small Rings

...multi-component ring expansions involve several reactants that come together to form expanded ring systems in a single synthetic operation, offering unparalleled efficiency in the construction of complex molecular architectures. These transformations often combine elements of cycloadditions, insertions, and rearrangements in a carefully orchestrated sequence that results in ring expansion. The power of this approach was dramatically demonstrated in the synthesis of the complex alkaloid aspidophytine, where a multi-component ring expansion reaction enabled the efficient construction of the challenging pentacyclic framework in a single synthetic operation.

### 1.15 Section 5: Ring Expansion of Small Rings

The diverse classification systems we have explored provide a conceptual framework for understanding the rich tapestry of ring expansion chemistry, yet they merely set the stage for a deeper examination of how these transformations manifest across different ring systems. Among the most fascinating and synthetically valuable are the ring expansion reactions involving small rings (3-6 members), which occupy a special place in organic chemistry due to their unique reactivity patterns, high ring strain, and prevalence in biologically active natural products. The expansion of these small rings represents not only a powerful synthetic strategy but also a window into the fundamental principles that govern molecular reactivity and structural transformations.

#### 1.15.1 5.1 Cyclopropane and Cyclobutane Expansions

The extraordinary reactivity of three- and four-membered rings stems from their substantial ring strain, which creates a powerful thermodynamic driving force for expansion reactions. Cyclopropane, with its internal angles of  $60^\circ$  compared to the ideal tetrahedral angle of  $109.5^\circ$ , possesses approximately 27.5 kcal/mol of strain energy, while cyclobutane contains about 26.3 kcal/mol despite its larger size. This stored energy, released during ring expansion, provides the impetus for numerous transformations that would otherwise be energetically prohibitive. The unique bonding in these small rings—characterized by bent bonds with significant p-character in cyclopropane and eclipsing interactions in cyclobutane—further contributes to their distinctive reactivity patterns.

Cyclopropane derivatives undergo a remarkable array of expansion reactions, often proceeding through mechanisms that exploit the ring's inherent strain. One of the most well-studied transformations is the



cyclopropylcarbinyl to cyclobutyl rearrangement, which can proceed through either carbocation or radical intermediates. The carbocation-mediated version, first systematically studied by Julius Bredt in the early 20th century, involves the formation of a cyclopropylcarbinyl cation that rapidly rearranges to the more stable cyclobutyl system. The rate of this rearrangement is extraordinarily fast—approximately  $10^{11}$  times faster than the rearrangement of a typical secondary carbocation—highlighting the profound influence of ring strain on reactivity. The radical-mediated counterpart, studied extensively by Paul Dowd and others, exhibits similarly accelerated kinetics and has been exploited in synthetic applications where radical conditions are preferred.

The vinylcyclopropane to cyclopentene rearrangement represents another cornerstone of cyclopropane expansion chemistry. This [3,3]-sigmatropic rearrangement, a specific case of the Cope rearrangement, proceeds through a concerted mechanism that maintains stereochemical integrity while expanding the three-membered ring to a five-membered system. The synthetic utility of this transformation was dramatically demonstrated in the synthesis of the complex sesquiterpene  $\beta$ -vetivone, where a strategic vinylcyclopropane rearrangement enabled the efficient construction of the challenging bicyclic framework. The work of Larry Overman and others has extended this methodology to include catalytic variants, where transition metal complexes can lower the activation barrier and improve selectivity, further expanding the synthetic scope of this transformation.

Cyclobutane expansions, while less extensively studied than their cyclopropane counterparts, offer equally fascinating reactivity patterns and synthetic opportunities. The classic Demjanov rearrangement of cyclobutylmethylamine to cyclopentanone stands as one of the earliest documented examples of ring expansion and continues to inspire modern synthetic strategies. This transformation, proceeding through a carbocation intermediate, releases approximately 26.4 kcal/mol of strain energy, providing a powerful thermodynamic driving force. The Tiffeneau-Demjanov modification, employing  $\beta$ -amino alcohols rather than primary amines, offers improved reliability and has found particular utility in steroid chemistry, where controlled expansion of four-membered rings enables access to novel derivatives with potentially altered biological activities.

The Favorskii rearrangement of  $\alpha$ -halo cyclobutanones represents another powerful strategy for cyclobutane expansion. This transformation proceeds through a cyclopropanone intermediate, which then undergoes nucleophilic attack and ring opening to yield the expanded cyclopropanecarboxylic acid derivative. The strain inherent in both the cyclobutanone and cyclopropanone rings provides a powerful driving force for the rearrangement. A particularly elegant application of this methodology can be found in the synthesis of the complex macrolide antibiotic monensin, where a key Favorskii rearrangement enabled the efficient construction of the challenging polyether framework. The work of Robert Ireland and others has demonstrated how careful control of reaction conditions can direct the regiochemistry of the rearrangement, enabling selective expansion of unsymmetrical cyclobutanones.

Photochemical approaches to cyclobutane expansion offer unique mechanistic pathways that complement thermal reactions. The photochemical ring-opening of cyclobutenes to butadienes, governed by the Woodward-Hoffmann rules, proceeds through a conrotatory mechanism that results in stereospecific formation of the

diene product. This transformation has been elegantly applied in the synthesis of complex natural products containing conjugated diene systems, such as the sesquiterpene lactone artemisinin, where a strategic photochemical ring expansion enabled the efficient construction of the challenging peroxide bridge. The work of Nicholas Turro and others has extended this methodology to include catalytic photochemical variants, where sensitizers can enable the reaction to proceed under milder conditions and with improved selectivity.

The synthetic applications of cyclopropane and cyclobutane expansions extend far beyond natural product synthesis, finding utility in medicinal chemistry, materials science, and polymer chemistry. In pharmaceutical research, these transformations have been employed to generate novel heterocyclic frameworks with potential biological activity, as exemplified by the synthesis of  $\beta$ -lactam antibiotics through cyclobutane expansion strategies. In materials science, ring expansion of strained cyclic systems has been used to generate novel polymers with unique mechanical properties, as demonstrated by the work of Robert Grubbs on ring-opening metathesis polymerization of strained cyclic alkenes. The versatility of these transformations, combined with their fundamental mechanistic interest, ensures that cyclopropane and cyclobutane expansions will continue to occupy a central place in the synthetic chemist's toolkit.

### 1.15.2 5.2 Cyclopentane Expansions

Five-membered rings occupy a unique position in ring expansion chemistry, representing a balance between the high strain of smaller rings and the conformational flexibility of larger systems. With approximately 6.5 kcal/mol of strain energy, cyclopentanes possess sufficient thermodynamic driving force for expansion while maintaining enough stability to allow for selective functionalization and manipulation. The characteristic envelope conformation of cyclopentane, with one carbon atom bent out of the plane formed by the other four, creates unique stereoelectronic effects that influence the course of expansion reactions, often leading to regioselective outcomes that would be difficult to achieve in other ring systems.

The mechanisms specific to five-membered ring expansion often involve the strategic placement of functional groups that can facilitate bond cleavage and reorganization. One of the most well-studied transformations is the expansion of cyclopentanones to cyclohexanones via the Tiffeneau-Demjanov rearrangement. This process, which involves the conversion of a cyclopentanone derivative containing an  $\omega$ -aminoalkyl side chain to an expanded cyclohexanone, has proven particularly valuable in steroid chemistry. The synthesis of 19-norsteroids, important pharmaceutical agents with modified biological activity, often relies on strategic expansion of the five-membered D-ring of steroid frameworks. The work of William Johnson and others demonstrated how careful control of stereochemistry in the starting material could translate to predictable stereochemical outcomes in the expanded product, enabling the synthesis of specific steroid derivatives with desired biological properties.

Tropone and related systems formed through cyclopentane expansion represent another fascinating area of study. The transformation of cyclopentadienones to tropones, first systematically investigated by E. P. Kohler in the early 20th century, involves a remarkable rearrangement that converts the five-membered ring to a seven-membered system with extended conjugation. This transformation proceeds through a series of



pericyclic reactions, including electrocyclic ring openings and closings, that ultimately result in the formation of the tropone system. The synthetic utility of this methodology was dramatically demonstrated in the synthesis of the complex natural product colchicine, where a strategic cyclopentane expansion enabled the efficient construction of the challenging seven-membered tropolone ring. The work of Gilbert Stork and others has extended this approach to include catalytic variants, where transition metal complexes can facilitate the rearrangement under milder conditions.

The applications of cyclopentane expansion in natural product synthesis are particularly noteworthy, as five-membered rings are prevalent in numerous biologically active compounds. In terpenoid chemistry, the expansion of cyclopentane derivatives has been employed to access complex polycyclic frameworks that would be difficult to construct by other methods. The synthesis of the sesquiterpene patchouli alcohol, for instance, utilized a strategic ring expansion of a cyclopentane intermediate to efficiently construct the challenging tricyclic framework characteristic of this compound. Similarly, in alkaloid chemistry, cyclopentane expansion has proven valuable for the synthesis of indole alkaloids containing modified ring systems, as exemplified by the synthesis of the complex Strychnos alkaloid akuammicine, where a key cyclopentane expansion enabled the efficient construction of the pentacyclic framework.

Stereochemical considerations play a crucial role in cyclopentane expansion reactions, as the three-dimensional arrangement of atoms in the starting material significantly influences the course of the transformation. The envelope conformation of cyclopentane creates distinct stereochemical environments that can lead to diastereoselective outcomes in expansion reactions. This stereochemical control has been elegantly exploited in the synthesis of complex natural products, where specific stereoisomers often exhibit distinct biological activities. The work of Samuel Danishefsky on the synthesis of the complex macrolide rapamycin demonstrated how careful control of stereochemistry in cyclopentane expansion reactions could enable the efficient construction of the challenging macrocyclic framework with the correct stereochemical arrangement.

The development of catalytic methods for cyclopentane expansion has significantly expanded the synthetic utility of these transformations. Transition metal catalysis, in particular, has enabled ring expansion reactions under milder conditions with improved selectivity compared to traditional methods. The rhodium-catalyzed expansion of cyclopentanone derivatives via carbenoid intermediates, pioneered by Huw Davies and others, offers remarkable control over regiochemistry and stereochemistry, enabling the synthesis of complex molecular architectures that would be difficult to access by other methods. Similarly, palladium-catalyzed cyclopentane expansions have proven valuable for the synthesis of medium-sized rings, which are often challenging to construct by conventional cyclization strategies.

The mechanistic understanding of cyclopentane expansion reactions has been greatly enhanced by modern computational methods. Density functional theory calculations have provided detailed insights into the transition states and intermediates involved in these transformations, enabling chemists to predict and optimize reaction outcomes with remarkable precision. The work of Kendall Houk and others on the computational study of pericyclic cyclopentane expansions has revealed subtle stereoelectronic effects that govern the course of these reactions, complementing experimental observations and guiding the design of new synthetic strategies. This synergy between computational and experimental approaches continues to drive innovation

in cyclopentane expansion chemistry, opening new avenues for the synthesis of complex molecular architectures.

### 1.15.3 5.3 Cyclohexane Expansions

Six-membered rings represent a unique case in ring expansion chemistry, as they occupy a position of relative stability compared to smaller rings yet still undergo fascinating expansion reactions that offer valuable synthetic opportunities. With minimal ring strain due to their ability to adopt chair conformations with staggered bonds and tetrahedral angles, cyclohexane derivatives require different strategies for expansion compared to their more strained counterparts. The expansion of these systems typically relies on the strategic placement of functional groups that can facilitate bond cleavage and reorganization, rather than the strain-driven processes that dominate the chemistry of smaller rings. Despite their relative stability, cyclohexane expansions play a crucial role in synthetic chemistry, particularly in the modification of steroid and terpenoid frameworks where six-membered rings are prevalent.

The expansion strategies for six-membered carbocyclic systems often involve the introduction of functional groups that can generate reactive intermediates capable of initiating ring expansion. One of the most well-established methodologies is the Beckmann rearrangement of cyclohexanone oximes to caprolactam, a transformation of immense industrial importance as it produces the monomer for nylon-6. This reaction proceeds through a nitrilium ion intermediate that undergoes ring expansion with migration of an anti-periplanar substituent. The stereospecific nature of this migration has been elegantly exploited in synthetic applications, where the stereochemistry of the starting material can be used to control the configuration of the expanded product. The work of Gilbert Stork on the synthesis of complex alkaloids demonstrated how strategic Beckmann rearrangements could enable the efficient construction of nitrogen-containing heterocycles with precise control over stereochemistry.

Chair-to-chair transitions represent a fundamental aspect of cyclohexane expansion reactions, as the conformational flexibility of six-membered rings allows for multiple pathways during the expansion process. The ability of cyclohexane derivatives to undergo chair flipping creates dynamic stereochemical environments that can influence the course of expansion reactions. This conformational flexibility has been exploited in the development of stereoselective expansion strategies, where the preferred conformation of the starting material can direct the regiochemistry and stereochemistry of the transformation. The synthesis of the complex diterpene taxol, for instance, utilized a strategic cyclohexane expansion that relied on conformational control to achieve the correct stereochemical arrangement in the eight-membered B-ring. The work of Robert Holton and others demonstrated how careful design of the substrate could exploit conformational preferences to achieve the desired expansion outcome.

The applications of cyclohexane expansion in steroid chemistry are particularly noteworthy, as the steroid framework contains multiple six-membered rings that can be selectively expanded to generate novel derivatives with potentially altered biological activities. The expansion of the A-ring of steroid frameworks, for example, has been employed to synthesize 19-norsteroids, which exhibit modified hormonal activities compared to their natural counterparts. Similarly, the expansion of the C-ring has been used to generate novel

steroid derivatives with enhanced pharmacological properties. The work of Carl Djerassi and others pioneered many of these methodologies, demonstrating how strategic ring expansion could provide access to novel steroid architectures for structure-activity relationship studies. These transformations often proceed with remarkable stereochemical fidelity, preserving the complex stereochemical arrangements characteristic of steroid frameworks while introducing structural modifications that can dramatically alter biological activity.

Control of stereochemistry in cyclohexane expansion reactions presents unique challenges and opportunities. The chair conformation of cyclohexane derivatives creates distinct stereochemical environments that can lead to diastereoselective outcomes in expansion reactions. This stereochemical control has been elegantly exploited in the synthesis of complex natural products, where specific stereoisomers often exhibit distinct biological activities. The work of K.C. Nicolaou on the synthesis of the complex marine

## 1.16 Ring Expansion of Medium-Sized Rings

The work of K.C. Nicolaou on the synthesis of complex marine natural products demonstrates the power of strategic ring expansion in constructing intricate molecular architectures. However, as we move beyond the well-trodden territory of small ring systems, we encounter a distinct set of challenges and opportunities that characterize the chemistry of medium-sized rings (7-12 members). These cyclic systems occupy a fascinating middle ground in organic chemistry, exhibiting properties that are neither fully small-ring-like nor truly macrocyclic in nature. The unique conformational behavior, strain patterns, and synthetic accessibility of medium-sized rings have made them both challenging targets and valuable tools in the synthetic chemist's arsenal, particularly in the context of natural product synthesis where these ring systems are prevalent.

### 1.16.1 6.1 Challenges in Medium-Sized Ring Synthesis

The synthesis of medium-sized rings presents a constellation of challenges that distinguish them from both smaller and larger cyclic systems. Perhaps the most significant of these challenges stems from the transannular interactions that characterize these ring systems. Unlike small rings, where angle strain dominates, or large rings, where transannular interactions become negligible, medium-sized rings exhibit substantial transannular strain due to non-bonded interactions between atoms separated by three or more bonds. This phenomenon, often referred to as “medium-ring strain,” reaches its maximum in systems containing 8-11 atoms, where the ring is large enough to allow significant folding but not large enough to avoid unfavorable interactions between distal atoms.

The conformational flexibility of medium-sized rings creates additional complications for their synthesis and manipulation. Unlike cyclohexane, which predominantly adopts the well-defined chair conformation, or cyclopentane, with its characteristic envelope conformation, medium-sized rings exist as complex mixtures of rapidly interconverting conformers. Cyclononane, for instance, has been shown to adopt at least eight distinct conformations of comparable energy, including crown, twist-chair, and boat-chair forms. This con-

formational flexibility complicates both the synthesis of these systems and the prediction of their reactivity, as the preferred conformation can dramatically influence the course of chemical reactions.

Entropic considerations further compound the challenges associated with medium-sized ring synthesis. The direct cyclization of acyclic precursors to form medium-sized rings faces significant entropic penalties due to the loss of rotational freedom that accompanies ring closure. According to the Jacobson-Stockmayer theory, the effective concentration of chain ends decreases with increasing chain length for acyclic precursors, reaching a minimum in the medium-sized ring region. This entropic barrier explains why direct cyclization methods, which work well for small and large rings, often fail for medium-sized systems, yielding only trace amounts of the desired cyclic product.

Competing reaction pathways present yet another obstacle in medium-sized ring chemistry. The conformational flexibility of medium-ring precursors often allows for multiple modes of ring closure, leading to mixtures of products rather than the desired single compound. Additionally, the transannular interactions that characterize these systems can promote alternative reaction pathways, such as transannular cyclizations or fragmentations, that compete with the desired ring expansion or formation processes. These competing pathways not only reduce the yield of the desired product but also complicate the purification and characterization of the reaction mixture.

The synthetic challenges associated with medium-sized rings were vividly illustrated in the early attempts to synthesize cyclodecanone, a 10-membered cyclic ketone. Traditional methods that worked well for smaller ketones, such as the Dieckmann condensation or intramolecular alkylation, proved ineffective for this medium-sized system, yielding primarily polymeric material rather than the desired cyclic product. It was not until the development of specialized methodologies, such as the acyloin condensation and later ring-closing metathesis, that efficient routes to medium-sized rings became available.

The physical properties of medium-sized rings further reflect their unique status in organic chemistry. Unlike smaller rings, which tend to have elevated melting and boiling points due to their compact structures, or larger rings, which behave more like their acyclic counterparts, medium-sized rings often exhibit anomalous physical properties. For example, cyclodecane has a melting point significantly lower than either cyclononane or cycloundecane, reflecting the particularly unfavorable transannular interactions in the 10-membered ring system. These anomalous properties not only complicate the handling and purification of medium-sized rings but also provide diagnostic tools for their identification and characterization.

### 1.16.2 6.2 Specific Methodologies for Medium-Sized Rings

The unique challenges posed by medium-sized rings have inspired the development of specialized methodologies tailored to their synthesis and expansion. Among the most impactful of these approaches is ring-closing metathesis (RCM), a transformation that has revolutionized the synthesis of medium and large rings since its development in the 1990s. Pioneered by Robert Grubbs, Richard Schrock, and Yves Chauvin, RCM employs transition metal catalysts, typically based on ruthenium or molybdenum, to effect the cyclization of diene substrates through the formation of new carbon-carbon double bonds. The power of this method-

ology lies in its ability to overcome the entropic penalties that plague traditional cyclization methods, as the metathesis process effectively brings the reacting centers into proximity through coordination to the metal center.

The application of RCM to medium-sized ring synthesis was dramatically demonstrated in the synthesis of the macrolide antibiotic erythromycin, where a key ring-closing metathesis step enabled the efficient construction of the challenging 14-membered lactone ring. The work of Steven Ley and others showed that carefully designed diene precursors could undergo high-yielding RCM to form the medium-sized macrocycle, providing a convergent and efficient approach to this complex natural product. The development of increasingly sophisticated ruthenium catalysts, such as the Grubbs second-generation catalyst and the Hoveyda-Grubbs catalyst, has further expanded the scope of RCM for medium-sized ring synthesis, enabling the formation of increasingly complex and functionalized systems.

Fragmentation-based expansions represent another powerful strategy for constructing medium-sized ring systems. These transformations leverage the strain energy present in bicyclic or polycyclic precursors to drive ring expansion through bond cleavage and reorganization. The Grob fragmentation, first systematically studied by Cyril Grob in the 1950s, stands as a prototypical example of this approach. In this transformation, a cyclic system containing appropriately positioned electron-donating and electron-withdrawing groups undergoes fragmentation to yield an expanded ring system. The power of this methodology was elegantly demonstrated in the synthesis of the complex sesquiterpene caryophyllene, where a strategic Grob fragmentation enabled the efficient construction of the challenging nine-membered ring characteristic of this natural product.

The development of fragmentation-based methodologies specifically tailored for medium-sized rings has been particularly fruitful. The work of Larry Overman on the fragmentation of bicyclic lactams, for instance, has provided efficient access to medium-sized nitrogen heterocycles, which are prevalent in numerous biologically active natural products. Similarly, the vinylcyclopropane rearrangement, which converts three-membered rings to five-membered systems, has been extended to include substrates that yield medium-sized rings through sequential fragmentation processes. These transformations often proceed with remarkable stereochemical fidelity, preserving the complex stereochemical arrangements characteristic of natural product frameworks while introducing the desired medium-sized ring system.

Lactam and lactone expansions in heterocyclic chemistry offer specialized methodologies for constructing nitrogen- and oxygen-containing medium rings. The Beckmann rearrangement, which converts cyclohexanone oximes to caprolactam, represents one of the oldest and most industrially important examples of this approach, producing the monomer for nylon-6 on a massive scale. However, the application of this methodology to medium-sized rings requires careful optimization due to the conformational flexibility of these systems. The work of Albert Eschenmoser on the synthesis of corrin systems demonstrated how strategic Beckmann rearrangements could be employed to construct the challenging medium-sized rings characteristic of vitamin B12 and related compounds.

The development of specialized lactone expansion methodologies has been equally impactful. The Baeyer-Villiger oxidation, which converts ketones to esters with insertion of an oxygen atom, has been adapted for

the construction of medium-sized lactones through the oxidation of cyclic ketones. The work of Barry Trost on the synthesis of the complex macrolide bryostatin demonstrated how strategic Baeyer-Villiger oxidations could be integrated into synthetic sequences to construct medium-sized lactone rings with precise control over stereochemistry. Similarly, the nucleophilic expansion of lactones, often involving the attack of carbon nucleophiles on lactone carbonyls followed by ring expansion, has proven valuable for the synthesis of complex polyketide natural products containing medium-sized rings.

Electrocyclic ring expansions, governed by the principles of orbital symmetry conservation, represent a mechanistically distinct class of transformations particularly well-suited for medium-sized ring synthesis. These pericyclic processes often proceed with remarkable stereospecificity and can be triggered by thermal or photochemical conditions. The electrocyclic ring opening of benzocyclobutenes, for instance, proceeds through a conrotatory mechanism under thermal conditions to yield o-quinodimethanes, which can be trapped to form eight-membered rings. This transformation has been elegantly applied in the synthesis of the complex natural product endiandric acid, where a cascade of electrocyclic reactions, including ring expansion, enabled the efficient construction of the challenging polycyclic framework.

The photochemical electrocyclic ring opening of cyclobutenes represents another powerful strategy for medium-sized ring synthesis. Under photochemical conditions, these transformations proceed through a disrotatory mechanism, yielding diene products that can undergo subsequent cyclizations to form medium-sized rings. The work of Nicholas Turro and others has demonstrated how carefully designed cyclobutene precursors can undergo sequential electrocyclic reactions to yield complex medium-sized ring systems with precise control over stereochemistry. These photochemical methodologies offer complementary reactivity to their thermal counterparts, expanding the synthetic chemist's toolkit for medium-sized ring construction.

### 1.16.3 6.3 Applications in Natural Product Synthesis

The unique challenges presented by medium-sized rings are matched by their profound importance in natural product synthesis, where these systems serve as key structural elements in numerous biologically active compounds. Alkaloid synthesis, in particular, has benefited tremendously from the development of medium ring expansion strategies, as many alkaloids contain medium-sized nitrogen heterocycles that are crucial for their biological activity. The synthesis of the complex indole alkaloid ervitsine, for instance, employed a strategic medium ring expansion to construct the challenging eight-membered lactam ring characteristic of this compound. The work of Samuel Danishefsky on this synthesis demonstrated how carefully designed ring expansion reactions could overcome the synthetic hurdles associated with medium-sized nitrogen heterocycles, providing efficient access to this biologically active natural product.

The synthesis of the macrocyclic alkaloid manzamine A represents another striking example of the power of medium ring expansion strategies in alkaloid chemistry. This complex natural product, which exhibits potent antimalarial and anticancer activities, contains a challenging 13-membered carbocyclic ring that presented a significant synthetic hurdle. The work of Paul Wender on the synthesis of manzamine A employed a strategic ring expansion of a bicyclic precursor to efficiently construct this medium-sized ring, demonstrating how ring expansion methodologies could provide convergent and efficient routes to complex alkaloid frameworks.



This approach not only simplified the synthesis of manzamine A but also provided a general strategy for constructing medium-sized carbocyclic rings in complex molecular settings.

Macrocyclic terpenoid synthesis has also been revolutionized by the application of medium ring expansion methods. The complex diterpene taxol, one of the most important anticancer agents discovered in recent decades, contains a challenging eight-membered B-ring that proved difficult to construct by traditional methods. The synthesis of taxol by Robert Holton employed a strategic ring expansion of a bicyclic precursor to efficiently construct this medium-sized ring, demonstrating how ring expansion methodologies could overcome the synthetic hurdles associated with complex terpenoid frameworks. Similarly, the synthesis of the complex sesquiterpene avermectin, a potent anthelmintic agent, utilized a strategic ring expansion to construct the challenging 16-membered macrolactone ring characteristic of this compound.

The work of K.C. Nicolaou on the synthesis of the complex marine natural product brevetoxin B exemplifies the power of medium ring expansion strategies in constructing highly oxygenated polycyclic frameworks. This natural product, which is responsible for neurotoxic shellfish poisoning, contains multiple medium-sized ether rings that presented formidable synthetic challenges. Nicolaou's synthesis employed a series of carefully orchestrated ring expansion reactions to construct these challenging rings, demonstrating how strategic ring expansion could provide efficient access to complex polycyclic frameworks that would be difficult to access by traditional methods. This synthesis not only provided a route to brevetoxin B but also established general principles for the construction of medium-sized cyclic ethers in complex molecular settings.

Peptide and depsipeptide synthesis has also benefited tremendously from the application of medium ring expansion methodologies. Many biologically active peptides contain medium-sized lactam or lactone rings that are crucial for their biological activity and conformational stability. The synthesis of the cyclic peptide cyclosporin A, a potent immunosuppressant, employed a strategic medium ring expansion to construct the challenging 11-membered subunit characteristic of this compound. The work of Dieter Seebach on this synthesis demonstrated how ring expansion methodologies could overcome the synthetic hurdles associated with medium-sized peptide rings, providing efficient access to this clinically important natural product.

The synthesis of the depsipeptide antibiotic actinomycin D represents another striking example of the application of medium ring expansion strategies in peptide chemistry. This complex natural product, which exhibits potent antibacterial and anticancer activities, contains two challenging medium-sized depsipeptide rings that presented significant synthetic challenges. The work of R.B. Woodward on the synthesis of actinomycin D employed strategic ring expansion reactions to construct these challenging rings, demonstrating how ring expansion methodologies could provide convergent and efficient routes to complex peptide frameworks. This approach not only simplified the synthesis of actinomycin D but also provided a general strategy for constructing medium-sized depsipeptide rings in complex molecular settings.

The case study of the synthesis of the macrolide antibiotic erythromycin provides a compelling illustration of the power of medium ring expansion strategies in complex molecule synthesis. This natural product, which contains a challenging 14-membered lactone ring, presented formidable synthetic challenges due to the conformational flexibility of medium-sized rings and the presence of multiple stereocenters. The syn-

thesis of erythromycin by Steven Ley employed a strategic ring-closing metathesis to efficiently construct the medium-sized lactone ring, demonstrating how modern catalytic methods could overcome the synthetic hurdles associated with medium-sized macrocycles. This synthesis not only provided an efficient route to erythromycin but also established ring-closing metathesis as a general strategy for constructing medium-sized lactone rings in complex molecular settings.

#### **1.16.4 6.4 Stereochemical Control in Medium Ring Expansions**

The stereochemical control of medium ring expansions presents unique challenges that distinguish these transformations from those involving smaller or larger ring systems. The conformational flexibility of medium-sized rings, while complicating their synthesis, also offers opportunities for stereochemical control that are not available in more rigid systems. The dynamic stereochemical effects that characterize medium rings arise from their ability to adopt multiple conformations of comparable energy, each with distinct stereochemical environments. This conformational flexibility can be exploited to achieve stereoselective outcomes in ring expansion reactions, provided that the reaction conditions can be carefully controlled to favor specific con