Cyclic Compounds

9-Membered Carbocycles: Strategies and Tactics for their Synthesis

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Abstract: Many natural products comprising a nine-membered carbocyclic core structure exhibit interesting biological effects. However, only a minority have succumbed to their synthesis in the past. The synthesis of functionalized nine-membered carbocycles still remains a challenging goal for synthetic chemists, mainly due to their high ring strain. Different strategies to overcome the unfavorable enthalpic and entropic factors associated with their formation are highlighted in this Concept article. The presented methods are classified into two different categories: (1) the ring-expansion of smaller rings or the ring-contraction of larger rings and (2) the direct cyclization of acyclic precursors.

1. Introduction

Functionalized nine-membered carbocyclic rings are incorporated in a variety of natural products with diverse biological activities. To date, their use in drug discovery is limited to enediyne anticancer antibiotics, such as neocarzinostatin, consisting of the labile chromophore 1, which is non-covalently bound to an apoprotein (Figure 1).[1] Other natural products with remarkable biological activities, such as rubratxin A (2),[2] α-viniferin (3)[3] and protoxenicin A (4),[4] exemplify the potential of nine-membered carbocyclic ring-containing natural products as lead compounds. The underrepresentation of these natural products can be mainly attributed to the difficulties associated with the synthesis of such ring systems. Besides their preparation by total synthesis, the modification of easily isolable nine-membered carbocyclic ring-containing natural products, such as caryophyllene, is another strategy for drug discovery and will not be covered in this article.

In general, carbocyclic rings are classified according to the number of atoms in their ring and their distinct properties. The group of medium-sized carbocycles, consisting of eight to eleven carbon atoms, is characterized by its relatively high ring strain compared to the most prevalent five-, six- and seven-membered rings and large rings (≥ twelve carbon atoms). The observed conformations of carbocyclic rings are a result of the system to minimize the angle and torsional strain. In medium-sized rings, additional transannular interactions of ring substituents on non-adjacent carbon atoms contribute significantly to the ring strain energy (Table 1).[5] Nine-membered carbocycles do not adopt a single low-energy conformation to relieve its ring strain. Instead, they have several conformations of similar energies, separated by low energy barriers, which can be interconverted by pseudorotation.[6]

Table 1. Strain energy of cycloalkanes.

| Ring size | Strain energy [kcal mol⁻¹] |
|-----------|--------------------------|
| 6         | 1.4                      |
| 7         | 7.6                      |
| 8         | 11.9                     |
| 9         | 15.5                     |
| 10        | 16.4                     |
| 11        | 15.3                     |
| 12        | 11.8                     |

It is noteworthy that planar chirality is commonly observed in constrained nine-membered carbocycles incorporating an E-configured olefin. In these molecules, the energy barrier of rotation about one or more C–C single bonds is high enough for the isolation of the conformers. The enantiomerically pure and optically active carbocycles can be either obtained by resolution of the racemic mixture or by synthesis from centrochiral precursors. For example, the two enantiomers of trans-cyclononene, 5 and ent-5, can be separated by coordination to a chiral platinum complex, followed by isolation of the two resulting diastereomeric complexes.[7] While enantiomerically pure trans-cyclononene (5) has a racemization half-life of about 4 min at 0°C, more constrained E-cyclononenes, such as enone 6,[8] maintain their planar chiral information at room temperature for longer periods and can be used as chiral precursors for further stereo- and regioselective transformations (Scheme 1).

Figure 1. Selected nine-membered carbocyclic ring-containing bioactive natural products. The nine-membered rings are highlighted with bold bonds.

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The synthesis of medium-sized rings is a long-standing challenge for synthetic chemists, mainly due to unfavorable enthalpic and entropic factors. About 100 years ago, it was commonly believed that carbocyclic rings containing more than eight carbon atoms were impossible to synthesize. In 1926, Ruzicka was the first to disregard this theory by elucidating the structures of the first macrocyclic natural products civetone, that exhibits a 17-membered ring, and muscone, bearing a 15-membered ring.

He also developed a method for the preparation of larger carbocycles containing between ten and 18 carbon atoms by vacuum pyrolysis of the thorium salts of acyclic dicarboxylic acids at 300–500 °C using a copper flask. Based on this method, the synthesis of nine-membered rings could only be achieved in very low yields. Ruzicka’s effort in exploring the synthesis and properties of larger rings was rewarded with the Nobel prize in chemistry in 1939, together with Butenandt, for his work on “polymethylene and higher terpenes.” In 1943, he reported the first efficient three-step synthesis of cyclononanone (8) via a Tiffenau–Demjanow rearrangement of 1-(aminomethyl)cyclooctan-1-ol (7), itself prepared from cyclooctanone in two steps, upon treatment with sodium nitrite and acetic acid (Scheme 2).

In 1947, Prelog and Stoll finally succeeded in developing the first reliable one-step procedure for the synthesis of medium-sized carbocycles, including nine-membered rings, from dicarboxylic acid esters by acyloin condensation (Scheme 3). Despite its harsh reaction conditions, this method has become a widely used transformation for the synthesis of medium-sized rings.

Today, medium-sized rings are still the most difficult ones to access. Although several methods for the preparation of substituted nine-membered carbocycles have been reported in the past decades, no generally applicable method has been described. In this Concept article, strategies for accessing nine-membered carbocycles are classified into two categories: (1) ring-expansion/-contraction reactions and (2) cyclization reactions of acyclic precursors.

2. Ring-Expansion Reactions

Many published methods for the preparation of nine-membered carbocycles rely on ring-expansion strategies and the reactions associated with them are (1) fragmentation reactions, (2) radical ring-expansion/-contraction reactions and (3) pericyclic reactions.

2.1. Fragmentation reactions

Most ring-expansion reactions are fragmentation reactions of fused bicyclic compounds. Whereas classical head-to-tail cyclizations of acyclic precursors are often not predictable and suffer from low scalability, the synthesis of fused bicyclic substrates as precursors for ring-expansion reactions only requires the preparation of five- to seven-membered rings by cyclization reactions. A great variety of reliable methods for their formation exists, which facilitates synthetic planning.

The most famous fragmentation reaction for the synthesis of nine-membered carbocycles is the Grob fragmentation reaction, which is still widely used today. In this reaction, a molecule of the form is heterolytically cleaved into three fragments (Scheme 4). The choice of the leaving group Y thereby determines the thermodynamic driving force of this irreversible reaction.
This strong thermodynamic driving force makes the Grob fragmentation a powerful synthetic tool in compensating the high ring strains associated with the formation of nine-membered carbocyclic rings. In the last 50 years, mainly 1,3-diols incorporated in fused 5,6-bicyclic ring systems were employed for Grob fragmentation approaches of complex natural products containing a nine-membered carbocycle. In these rigid bicyclic systems, the bond that is broken and the leaving group are fixed in an anti-periplanar alignment. Thus, the fragmentation proceeds in a concerted and highly stereospecific fashion, allowing the prediction of the configuration of the product.

The total synthesis of the first nine-membered carbocyclic ring-containing natural product reported in 1964, was a significant milestone in the field. The Corey group reported the successful total synthesis of the sesquiterpene β-caryophyllene (18), where the E-configured cyclononene ring was installed by sodium hydride mediated ring-expansion of bicyclic monotosylated 1,3-diol 14 (Scheme 5).[20]

Another compelling example that demonstrates the applicability of Grob fragmentations for the total synthesis of complex natural products, is the total synthesis of the tricyclic diterpenoid jatrophatrine (21) by Paquette (Scheme 6). First, mesylation of the sterically less congested secondary alcohol in tetra- 

in cycle 19 resulted in the formation of a monomesylated 1,3-

diol, which was readily fragmented upon treatment with potassium tert-butoxide (KOTBu) to construct the Z-configured cyclononene fragment 20 of jatrophatrine (21).[21]

In recent years, the Grob fragmentation was applied to cascade reactions, thus allowing formation of the fragmentation precursor and fragmentation in one-pot. For example, Molander and co-workers accessed eight-, nine- and ten-membered rings by a samarium diiodide-mediated cyclization/fragmentation cascade of simple iodocycloalkanones.[22] In this domino reaction, samarium(III) alkoxide 23 was formed by a samarium diiodide-mediated intramolecular cyclization of δ-iodoketone 22, which then fragmented to afford cyclononene 24 (Scheme 7a). In a conceptually related approach, the Dudley group accessed highly strained cycloalkynes of medium ring size.[23] The first step was an iodine-lithium exchange of a vinyl or phenyl iodide 25 with n-butyllithium, followed by an intramolecular 1,2-addition of the generated organolithium species to the ketone (Scheme 7b). An ensuing alkynogenic fragmentation of the resultant lithium alkoxide 26 afforded the cycloalkynes 27. The formation of these strained products was likely driven by the release of a triflate anion.

While the rearrangement of oximes to their corresponding amides, known as the Beckmann rearrangement, is a widely used transformation, the Beckmann fragmentation is less commonly used in total synthesis.[24] It is a variant of the Beckmann

Scheme 4. General Grob fragmentation of 1,3-diheterosubstituted compounds.

Scheme 5. Grob fragmentation approach to β-caryophyllene (18).

Scheme 6. Paquette’s jatrophatrine (21) synthesis.

Scheme 7. Molander’s and Dudley’s cyclization/fragmentation cascades.
rearrangement for substrates that have a quaternary carbon atom in the anti-position to the hydroxyl group of an oxime. In this reaction, oximes are converted to nitriles instead of amides. The reaction was the key step in the total synthesis of (±)-byssochilamic acid (30) by Stork. Treatment of tetracyclic oxime 28 with phosphoryl trichloride (POCl₃) and pyridine resulted in the isolation of a mixture of Z-cyclononene 29 and its propylidene double bond isomer, which was isomerized with para-toluene sulfonic acid (p-TsOH) to give 29 in good yield (Scheme 8).

2.2. Radical ring-expansion reactions

Free radical-mediated ring-expansion reactions have been frequently utilized in the synthesis of medium-sized rings in the past. Radical fragmentations can usually be conducted under mild reaction conditions and are operationally simple. Furthermore, a variety of functional groups are tolerated. The drawbacks of radical reactions are the formation of side products. Besides quenching of the generated radical, competing intramolecular 1,5-hydrogen atom abstraction followed by radical quenching is the main undesired reaction pathway. In order to circumvent these unwanted pathways, the reactions are often carried out in highly diluted solutions along with slow addition of the reagents.

Dowd and Beckwith were the pioneers of radical ring-expansion reactions and their synthetic strategy, known as the Dowd–Beckwith reaction, and variants thereof are the most widely used radical fragmentation strategies. Their method was described as a one-, three-, or four-carbon ring-expansion and is shown in Scheme 9. These early examples allowed the efficient preparation of rings containing up to eleven carbon atoms. As starting materials, they used β-keto esters, which were readily accessible by Dieckmann condensation of linear diesters.

Mechanistically, the reaction commences with the generation of the primary alkyl radical 35 from the halide or selenide substituent (Scheme 10). Subsequent intramolecular cyclization results in the formation of the high-energy oxygen-centered radical 36. Radical ring-opening of bicycle 36 leads to 37 with the tertiary radical stabilized by the ester group, providing the driving force for the fragmentation. Hydrogen abstraction from tributyltin hydride finally gives the nine-membered cyclic ketone 34 and generates at ributylstannyl radical, which propagates the radical chain reaction. The use of β-keto esters as substrates thereby not only facilitated the preparation of the radical precursors by alkylation, but also rendered the cyclic ketone more electron-deficient and thus activated it for the radical cyclization.

In a modern variant of the Dowd–Beckwith reaction, Liu reported the synthesis of benzannulated medium-sized ketones by radical fragmentation. Addition of azide, difluoromethyl, trifluoromethyl, tosyl or perfluoroalkyl radicals to the terminal alkenefunctionality of a cyclic α-hydroxy ketone 38 results in the formation of secondary radical 39 (Scheme 11). The generation of the respective radicals was realized using either hypervalent iodine(III) reagents and catalytic amounts of copper(I) iodide (R = CF₃, N₃) or single-electron reduction under photoredox catalysis (R = Ts, CF₃, CF₂H). The following reversible intramolecular attack of the ketone affords the 6,6,5-tricyclic system 40, which is fragmented to medium-sized carbocycle 41. The radical fragmentation is thermodynamically driven by the formation of a stabilized α-hydroxy benzylic radical 41. A final single-electron transfer (SET) to the photoredox or copper(I) catalyst and the loss of a proton affords the cyclic diketone 42.
The presented examples for radical ring-expansion reactions were so far based on alkyl radical cyclizations onto ketones to form highly reactive oxygen-centered radicals, followed by fragmentation reactions. The next two examples describe high-energy carbon-centered radicals as intermediates in radical fragmentation reactions. The Harrowven group reported a procedure for the synthesis of eight- and nine-membered β-keto esters by radical ipso-substitution (Scheme 12).[32] First, generation of an aryl radical and subsequent 5-exo-trig cyclization via radical ipso-substitution at C3 position gives the delocalized radical. Rearomatization of the acceptor ring by radical fragmentation affords tertiary radical, which is stabilized by the ester functionality. The eight- and nine-membered β-keto esters are then obtained by hydrogen abstraction from tributyltin hydride. The yields for the nine-membered carbocycles were only moderate, which the authors attributed to the formation of significant amounts of the corresponding ortho-cyclization products, formed via a 6-endo-trig cyclization of the aryl radical to the tetralone ring.

Building upon their previous work on the construction of benzannulated medium-sized rings via ring-expansion, the Liu group reported on the synthesis of carboxycles of medium and large size by using a radical ipso-substitution strategy in 2016.[33] Generation of the radicals was realized by using hypervalent iodine(III) reagents and copper(I) cyanide to form reactive oxygen-centered radicals, followed by fragmentation reactions. The first step of their procedure is the addition of the generated radicals to the terminal alkene of substrate (Scheme 13). The secondary radical undergoes a 1,4- or 1,5-aryl migration/ring-expansion sequence to afford neutral ketyl radical. The migration presumably proceeds through spiro radical intermediate. Oxidation of the tertiary radical to the ketone by the copper or silver catalyst and loss of a proton gives the ring-expanded medium-sized cyclic or macrocyclic ketones. Furthermore, the authors demonstrated that the use of enantiomerically pure alcohols enabled isolation of enantioenriched medium-sized rings through radical chirality transfer during the ring-expansion.

2.3. Pericyclic ring-expansion reactions

2.3.1. Sigmatropic reactions

Sigmatropic rearrangements were well explored for the synthesis of medium-sized rings in past decades.[34] Previously employed [1,2]-sigmatropic rearrangements for the synthesis of nine-membered carboxycles are the pinacol rearrangement,[35] the semi-pinacol rearrangement,[36] the Tiffenau–Demjanow rearrangement[13] and related homologation reactions of cyclic ketones involving diazo compounds. The Tiffenau–Demjanow rearrangement has not found further application in the synthesis of nine-membered carboxycles in recent years, which can be mainly attributed to its harsh reaction conditions. The semi-pinacol rearrangement is a synthetically useful reaction and can be realized by using a variety of Lewis acids at low temperatures. The reaction therefore tolerates a variety of functional groups. A recent example for the utilization of the semi-pinacol rearrangement for the synthesis of medium-sized rings was reported by Liu and Yeung. They treated a variety of 1-vinylcycloalkan-1-ols with 1,3-dibromo-5,5-dimethylhydantoin (DBH) to activate the olefin by bromonium ion formation and isolated the corresponding one-carbon ho-
mologated β-bromo ketones 56 (Scheme 14). These substrates allowed further ring-expansion by the Dowd–Beckwith reaction to afford ketones 57.

Pertaining the use of [3,3]-sigmatropic rearrangements for the synthesis of nine-membered carbocycles, in particular, the oxy-Cope and the Claisen rearrangements are used. This can be mainly attributed to the broad applicability and irreversibility of these processes, which can be credited to the formation of a thermodynamically more stable C=O double bond. The oxy-Cope rearrangement can either be carried out thermally or by treatment with base to induce an anionic rearrangement. The latter has the advantages of an exceptional rate acceleration and of greater functional group tolerance due to decreased reaction temperatures. The utilization of the oxy-Cope rearrangement for the synthesis of nine-membered carbocycles was first described by Kato in 1980. The thermal activation (220 °C) of an 81:19 mixture of the isomers trans-58 and cis-58 led to the isolation of (E)-5-cyclononen-1-one (61) as a single isomer in good yield (Scheme 15). The stereochemical outcome of this reaction can be explained by the chair-like transition-state geometries as depicted in Scheme 15.

2.3.2. Cycloaddition and -reversion

The White group demonstrated the applicability of a [2+2]-photoaddition/cycloreversion strategy for the synthesis of nine-membered carbocycles in their asymmetric total synthesis of (+)-byssochlamic acid (30). Irradiation of a 1:1 mixture of diastereomers of dilactone 64 resulted in a [2+2]-cycloaddition and formation of the two stereoisomeric photoadducts 65 and 66 (1:1 mixture) (Scheme 17). Thermally induced cycloreversion led to cleavage of the four-membered rings and gave the nine-membered carbocycle 67 in good yield over two steps.

2.4. Miscellaneous

Recently, the synthesis of nine- and ten-membered carbocycles from phthalates via a dearmatization/cyclization/ring-opening cascade has been described. First, the phthalates were converted to fused 5,6-bicyclic systems 69 by reduction of 68 with sodium metal and alkylation with 1,3-dibromopropane (Scheme 18). A stereoselective ring-opening was then induced by treatment of the fused bicyclic system with lithium/naphthalene to give bis-enolate 71, presumably formed by bond cleavage of intermediate dianion diradical 70. Stereoselective protonation with acetic acid afforded the nine-membered carbocyclic dienes 72.
3. Transannular Ring-Contraction Reactions

Besides using ring-expansion reactions of fused bicyclic systems for the preparation of medium-sized rings, trans-annular ring contraction reactions can also be employed for the production of smaller, more strained rings. The applicability of this strategy for the synthesis of cyclononenes was demonstrated by the Oishi group in 1984, who developed a ring contraction strategy for the total synthesis of β-caryophyllene (18).[47] First, the 13-membered ring was prepared by conversion of alcohol 73 to the corresponding mesylate, followed by potassium tert-butoxide-mediated generation of a thiolate anion and subsequent cyclization to afford the 13-membered lactam 74 (Scheme 19). An intramolecular acyl transfer reaction was then employed to form the cyclononene ring. Sodium periodate oxidation of sulfide 74 to the corresponding sulfoxide and subsequent deprotonation with lithium diisopropylamide (LDA) led to the formation of cyclononene 75 in quantitative yield.

4. Cyclization Reactions of Acyclic Precursors

The construction of nine-membered carbocycles by ring-expansion reactions is a good strategy to compensate the high ring strain. However, it often requires the formation of complex, fused polycyclic substrates, themselves already challenging synthetic targets. In contrast, the formation of nine-membered carbocyclic rings from acyclic precursors enables a more conservative retrosynthetic C–C bond disconnection. In the following chapters, the strategies and reactions for the synthesis of nine-membered carbocycles from acyclic precursors by (1) ring-closing olefin metathesis, (2) cycloaddition, (3) intramolecular cross-coupling, (4) Conia-ene cyclization, (5) Friedel–Crafts cyclization, (6) Nozaki–Hiyama–Kishi reaction and (7) samarium(II)-promoted cyclizations will be discussed.

4.1. Ring-closing metathesis

Recently, the ring-closing metathesis (RCM) reaction has become one of the most powerful methods to construct medium-sized carbocycles from acyclic precursors.[48] To date, no example for the formation of E- or Z-cyclononene (77) from diene 76 by RCM has been reported (Scheme 20a). Functionalized nine-membered carbocycles could be successfully obtained from linear precursors containing some sort of conformational constraint. Substrates that are not conformationally predisposed for such cyclization reactions can be tuned by attaching an intramolecular tether (78). These substrates can then undergo low energy cyclization pathways via six- or seven-membered transition state structures (Scheme 20b). After cyclization, the temporary tether is degraded to provide the nine-membered carbocycle. In the following section, two examples for the formation of nine-membered carbocycles from non-bridged cyclization precursors and one example for bridged cyclization precursors are shown.

In 2008, the Altmann group described the total synthesis of the Xenia diterpenoid blumiolide C (83).[49] The Z-configured double bond of the nine-membered ring was formed by ring-closing metathesis of diene 80 (Scheme 21). Preliminary experiments showed that protection of the allylic alcohol as p-methoxy benzyl (PMB) ether was crucial for the success of this
transformation. After final optimizations, the best result was obtained by treatment of 80 with Hoveyda–Grubbs II catalyst (81) (50 mol %) in toluene at elevated temperature (90 °C) to give 82 in 66 % yield. This unprecedented construction of the [7.4.0]oxabicyclic ring system via RCM showed that the use of sterically congested alkenes required unusually high catalyst loadings to obtain Z-cyclononene 82 in sufficient yields.

The Clark group was confronted with a similar problem in their synthesis of the carbocyclic core structure of the cornexins by ring-closing metathesis. Initial attempts to form nine-membered carbocycle 88 by treatment of diene 87 with either Grubbs’ first (85) or Grubbs’ second generation catalyst (86) failed to give the desired product (Scheme 22a). To avoid the use of a trisubstituted, conjugated double bond in the RCM reaction, such as in 87, another C–C bond in the nine-membered ring was retrosynthetically disconnected which led to the revised cyclization precursor 89 (Scheme 22b). Treatment of a diastereomeric mixture of 89 with Grubbs’ second generation catalyst (86) (20 mol %) gave the desired nine-membered ring as a mixture of diastereomers 90 and 91. The desired, minor isomer 91 was further transformed into 5-epi-hydroxycornexitin (84) in eight steps.

The last two examples described the formation of nine-membered carbocycles by RCM of acyclic precursors bearing sufficient conformational constraint. The group of Mascareñas reported the synthesis of tethered eight- and nine-membered carbocycles through a ring-closing metathesis/ring-fragmentation reaction sequence. For the synthesis of nine-membered carbocycles, cyclization precursor 93 was readily prepared from ketone 92 in two steps and could be further transformed to alkene 94 upon treatment with Grubbs’ first generation catalyst (85) (5 mol %) (Scheme 23). The introduction of the keto-bridging tether was found to be crucial for the formation of the nine-membered ring under these relatively mild conditions. In the final step, oxidative cleavage of the carbonyl bridge with lead(IV) acetate afforded Z-configured cyclonononenone 95.

In summary, the ring-closing metathesis reaction displays a powerful method for the construction of nine-membered carbocycles. Dienes containing some sort of conformational constraint, introduced by either substituents on the linear cyclization precursor or by intramolecular tethering, undergo smooth nine-membered ring formation. However, substrates without conformational preorder or with sterically hindered double bonds (tri- or tetra substituted) exhibit low reactivity in RCM reactions and show either no reaction or require high catalyst loadings.

### 4.2. Cycloaddition

Transition-metal-catalyzed cycloaddition reactions are also powerful tools for the preparation of nine-membered carbocycles. For example, the Ito group described an interesting onestep procedure for the synthesis of C₉-symmetric nine-membered carbocycles via a [4+4+4+1]-cycloaddition by the palladium-catalyzed carbonylation of vinylallenene. Mechanistically, the authors proposed that the sequence commences with the formation of five-membered palladacycle 97, bound to another molecule of vinylallene 96 (Scheme 24). Subsequent C–C bond formation gives bis(η-allyl)-palladium intermediate 98, whose resonance structure, o-di(alkenyl)palladium intermediate 99, is
more stable. Migratory insertion of carbon monoxide into the Pd–C bond to give 100, followed by reductive elimination affords the corresponding nine-membered cyclic ketones 101.

The synthesis of medium-sized carbocycles via a tandem isomerization/intramolecular [3+2]-cross-cycloaddition (IMCC) was reported by the Wang group.[53] The E-configured enone moiety in substrate 102 was either installed by Horner–Wadsworth–Emmons olefination or by an aldol condensation. For the desired cycloaddition, the double bond had to be isomerized to the corresponding Z-enone. The carbonyl oxygen should thereby get closer to the reactive site of the cyclopropane to initiate the cycloaddition. This was realized by irradiation of enone 102 with ultraviolet (UV) light, giving a mixture of the E- and Z-isomer. The latter was directly consumed in the subsequent Lewis acid-catalyzed [3+2]-cycloaddition to afford oxygen bridged cyclononene 103 (Scheme 25a). Under constant irradiation, this process continues until 102 is fully consumed. In further studies, the scope was extended to propargylic alcohols (e.g. 104) that could be easily prepared by nucleophilic 1,2-addition of terminal alkynes to benzaldehydes.

As part of their studies, Wang also developed a one-pot protocol featuring a Meyer–Schuster rearrangement[54] and the previously developed isomerization/intramolecular [3+2]-cross-cycloaddition (Scheme 25b). In summary, these strategies constitute an efficient method for the construction of nine-membered rings and for the construction of carbocycle-based oxa-bicyclo[4.2.1] skeletons.

4.3. Intramolecular cross-coupling

Although no general procedure for the direct closure of nine-membered rings by cyclization of acyclic precursors via palladium-catalyzed cross coupling reactions has been described to date, scattered applications of this strategy have been demonstrated in natural product synthesis. In 2009, the Williams group reported the stereocontrolled total synthesis of 4-hydroxydictyolactone (108), a member of the xenicanediterpenoid family, featuring a rare nonconjugated E,Z-cyclononadiene motif (Scheme 26).[55] The formation of the E-cyclononene ring was accomplished by employing an intramolecular B-alkyl Suzuki cross-coupling reaction of 106. First, the hydroboration step was optimized to regioselectively target the monosubstituted double bond. Initial cyclization studies employing PdCl₂(dppf) as catalyst and thallium carbonate as base under optimized dilution conditions only afforded the desired product 107 in low yields. Eventually, the use of Pd(PPh₃)₄ as catalyst proved to be the key for achieving a high yielding cyclization and 4-hydroxydictyolactone (108) could be synthesized in four additional steps.

Another palladium-catalyzed method for the construction of nine-membered rings was reported by the group of Corey in the synthesis of antheliolide A (111) (Scheme 27).[56] This marine natural product features a unique 6,5,6,4,9-pentacyclic framework and due to the embedded functionalities, the range of methods for the formation of the E-cyclononene was limited. The construction of the challenging 5,4,9-tricycle 110 from allylic methoxy carbonyl derivative 109 was finally realized by intramolecular Tsuji–Trost reaction of 109 by treatment with catalytic amounts of Pd₂(dba)₃·CHCl₃. For the conversion of 110 to antheliolide A (111) eight additional steps were required.

Scheme 24. Proposed mechanism for the (4+4+1)-cycloaddition to form cyclic ketones.

Scheme 25. Formation of nine-membered carbocycles via a) Lewis acid catalyzed isomerization/intramolecular [3+2]-cross-cycloaddition (IMCC) or b) one-pot tandem Meyer–Schuster rearrangement/isomerization/IMCC.

Scheme 26. Formation of the E,Z-cyclononadiene motif 107 by a B-alkyl Suzuki macrocyclization.
4.4. Conia-ene cyclization

The Conia-ene reaction is a useful reaction for the formation of five- to seven-membered rings. In 2007, the group of Naka-
mura reported the first example of an indium(III)-catalyzed
cycloisomerization of ω-alkynyl-β-keto esters to access five- to
fifteen-membered carbocycles. Mechanistically, the indium
catalyst activates the β-keto ester by formation of an indium(III)enolate that then activates the terminal alkyne unit
by coordination. Due to this double activation by the catalyst,
tropic and enthalpic factors normally restraining the forma-
tion of medium-sized rings could be circumvented. Neverthe-
less, the transannular steric repulsion from generic cyclono-
nane 113 impeded the cyclization of 112 and gave the nine-
membered ring product in only 7% yield (Scheme 28 a). How-
ever, substrates containing sp² carbon atoms led to efficient
nine-membered ring formation. Consequently, β-keto ester
114, featuring a phenylene motif, smoothly afforded the iso-
meric nine-membered carbocycles 115 and 116 (Scheme 28 b).

With this methodology, a broad range of nine-membered
carbocycles could be synthesized in good yields. To date, no example of nine-membered ring formation with a non-terminal
alkyne has been reported.

4.5. Friedel–Crafts cyclization

For the total synthesis of caraphenol A (117), the Snyder group
investigated different approaches for the formation of the nine-membered carbocycle. The envisioned late-stage forma-
tion of the nine-membered ring depends on a method com-
patible with highly functionalized substrates. In this context,
the first reported gold(III) promoted 9-exo-dig ring closure of
118 to 119 has been reported (Scheme 29 a). The success and
the efficiency (yield > 90%) of this cyclization reaction origi-
nates from the high conformational control of substrate 118.
Since 119 proved to be a dead end for the total synthesis of
caraphenol A (117), a second-generation approach based on a
Brønsted acid-mediated Friedel–Crafts cyclization of 120 was
pursued (Scheme 29 b). Exposure of 120 to an excess of methanesulfonic acid resulted in clean formation of nine-mem-
bered ring 121 in excellent yields (73%). Eventually, the Snyder
group was able to synthesize more than 600 mg of the final
product caraphenol A (117).

Scheme 27. Palladium-catalyzed formation of E-cyclononene 110 applied in
the total synthesis of anthelioide A (111).

Scheme 28. In³-mediated Conia-ene cyclization of a) the non-substituted
precursor 112 and b) the substituted substrate 114.

Scheme 29. Nine-membered carbocycle formation via a) gold(III) promoted
9-exo-dig ring closure and b) Friedel–Crafts cyclization applied in the total
synthesis of caraphenol A (117).
4.6. Nozaki–Hiyama–Kishi reaction

Recently, the Nozaki–Hiyama–Kishi (NHK) reaction has become a viable method for the formation of nine-membered rings and has been applied in studies towards the total synthesis of pestalotiopsin A (122) and in the total synthesis of cristaxenicin A (123). In 2008, the group of Tadano published the first total synthesis of the sesquiterpenoid pestalotiopsin A (122) bearing an unprecedented oxatricyclic structure with a cyclobutane ring fused to a γ-lactol and an E-cyclononene ring. The latter was constructed by a highly efficient (92%), intramolecular NHK reaction giving 125 as a single diastereomer (Scheme 30 a). In 2016, the intramolecular NHK reaction was applied in Hosokawa’s synthesis of the core structure of cristaxenicin A (123) (Scheme 30 b). Treatment of vinyl iodide (126) with CrCl$_2$ in the presence of NiCl$_2$ gave nine-membered carbocycle 127 in high yield (87%), but as an inconsequential mixture of diastereomers.

4.7. Samarium(II)-promoted cyclizations

Samarium(II) iodide, first introduced and utilized as a reducing agent in 1980, has recently become a popular reagent for the formation of medium-sized carbocycles. In the following examples, both radical and anionic formations of bridged and non-bridged nine-membered carbocycles are discussed. The group of Miyashita demonstrated that treatment of aldehyde 128 with samarium(II) iodide in the presence of hexamethylphosphoramide (HMPA) led to the formation of cyclononanol 129 in excellent yields (82%) (Scheme 31). It is noteworthy that the reductive cyclization was completed within seconds after addition of the SmI$_2$/HMPA mixture to the substrate and did not require high dilution conditions.

In the last decades, the group of Molander has published several samarium(II) iodide-based annulative routes for the construction of oxygen bridged cyclononanes.$^{[63]}$ In their recent report, nine-membered carbocycles were accessed via a one-pot Reformatsky reaction followed by a nucleophilic acyl substitution (Scheme 32). Treatment of 130 with samarium(II) iodide gives β-hydroxy lactone 131 in a Reformatsky reaction.$^{[64]}$ Alkoxide 132 undergoes a nucleophilic acyl substitution reaction to form stereodefined nine-membered carbocycle 133. This method facilitates an efficient access to a variety of nine-membered carbocyclic derivatives under mild conditions.

The Reissig group demonstrated the use of a samarium(II) iodide-induced radical cyclization as a powerful tool for the formation of medium-sized benzannulated carbocycles.$^{[65]}$ Exposure of 134 to the developed cyclization conditions, promoted a 9-endo-trig cyclization to give tricyclic compound 135 in only moderate yields but with excellent stereoselectivity (Scheme 33 a). If alkynyl-substituted substrate 136 was subjected to these conditions, the nine-membered ring 137 was formed via a 9-endo-dig cyclization mode in moderate yield (Scheme 33 b). Although it exhibits moderate efficiency, this methodology rapidly provides access to highly substituted nine-membered carbocycle derivatives.

5. Conclusion

In the last century, the increasing interest in medium-sized carbocycles has led to the development of several powerful and practical protocols. Despite the advancement in recent years, the synthesis of highly-substituted nine-membered rings remains a great challenge. Several natural products have eluded their synthesis in recent years and in many cases, the available

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Scheme 30. The Nozaki–Hiyama–Kishi reaction applied in a) the total synthesis of pestalotiopsin A (122) and b) the formation of the core structure of cristaxenicin A (123).

Scheme 31. Reductive cyclization promoted by samarium(II) iodide.

Scheme 32. Proposed mechanism of the samarium(II) iodide promoted sequential Reformatsky/nucleophilic acyl substitution for the formation of oxygen bridged nine-membered carbocycles.

Scheme 33. The Reissig group demonstrated the use of a samarium(II) iodide-induced radical cyclization as a powerful tool for the formation of medium-sized benzannulated carbocycles.
methods were not compatible with their delicate molecular framework. In this Concept article, we have shown strategies and tactics for accessing nine-membered carbocycles classified into two main categories: ring-expansion/-contraction reactions and cyclization reactions of acyclic precursors. In summary, no general procedure for the synthesis of nine-membered rings has been reported to date, but the ongoing effort of synthetic chemists has created a variety of methods to form highly complex nine-membered carbocycles.

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) K. C. Nicolaou, W.-M. Dai, Angew. Chem. Int. Ed. Engl. 1991, 30, 1387–1416; Angew. Chem. 1991, 103, 1453–1481; b) N.-I. Hiroshi Maeda, Kyoto Edo, Neocarzinostatin, Springer Japan, Tokyo, 1997.
[2] S. Wada, I. Usami, Y. Umezawa, H. Inoue, S. Ohba, T. Someno, M. Kawada, D. Ikeda, Cancer Sci. 2010, 101, 743–750.
[3] a) E. Y. Chung, E. Roh, J.-A. Kwak, H.-S. Lee, S.-B. Han, K. Y. Lee, M. J. Park, J. H. Kim, J. H. Park, Y. C. Kim, J. Kim, Y.-F. Cheng, N. Wang, X.-W. Dong, C. Kawada, D. Ikeda, Kiyoto Edo, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011, pp. 1–420.
[4] G. Stork, J. M. Tabak, J. F. Blount, J. Am. Chem. Soc. 1972, 94, 4735–4737.
[5] P. Dowd, W. Zhang, Chem. Rev. 1993, 93, 2091–2115.
[6] D. Ardura, T. L. Sordo, J. Org. Chem. 2005, 70, 9417–9423.
[7] a) P. Dowd, S. chang Chai, J. Am. Chem. Soc. 1987, 109, 6548–6549; b) A. L. J. Beckwith, D. M. O’Shea, S. W. Westwood, J. Am. Chem. Soc. 1988, 110, 2565–2575.
[8] J. P. Schaefer, J. J. Bloomfield, in Org. React., John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011, pp. 1–203.
[9] M. L. Coote, C. Y. Lin, H. Zipie, in Carbon-Based Free Radicals Radic. Cations (Ed.: M. Forbes), John Wiley & Sons, Inc., Hoboken, NJ, USA, 2010, pp. 83–104.
[10] Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang, X.-Y. Liu, Angew. Chem. Int. Ed. 2016, 55, 15100–15104; Angew. Chem. 2016, 128, 15324–15328.
[11] D. C. Harrowven, N. L’Helias, J. D. Moseley, N. J. Blumine, S. R. Flanagan, Chem. Commun. 2003, 2658.
[12] Z.-L. Li, X.-H. Li, N. Wang, X.-W. Dong, C. Fang, J. Liu, C. Hou, Nat. Commun. 2016, 7, 13852.
[13] Z.-M. Chen, X.-M. Zhang, Y.-Q. Tu, Chem. Soc. Rev. 2015, 44, 5220–5245.
[14] J. R. Donald, W. P. Unsworth, Chem. Eur. J. 2017, 23, 8780–8799.
[15] J. H. Rigby, K. F. Fales, Tetrahedron Lett. 1998, 39, 1525–1528.
[16] a) C. M. Marson, A. Khan, R. A. Porter, A. J. A. Cobb, Tetrahedron Lett. 2002, 43, 6637–6640; b) Y. Liu, Y.-Y. Yeung, Org. Lett. 2017, 19, 1422–1425.
[17] V. L. Rendina, D. C. Moebius, J. S. Kingsbury, Org. Lett. 2011, 13, 2004–2007.
[18] T. J. Snape, Chem. Soc. Rev. 2007, 36, 1823.
[19] a) A. L. Paquette, Angew. Chem. Int. Ed. Engl. 1990, 29, 609–626; Angew. Chem. 1990, 102, 642–660; b) A. M. Martin Castro, Chem. Rev. 2004, 104, 2939–3002.
[20] T. Kato, H. Kondo, M. Nishino, M. Tanaka, G. Hata, A. Miyake, Bull. Chem. Soc. Jpn. 1990, 53, 2958–2961.
[21] K. Tomooka, T. Ezawa, H. Inoue, K. Uehara, K. Iwagawa, J. Am. Chem. Soc. 2011, 133, 1754–1756.
[22] T. Jaschinski, H. Strich, Org. Lett. 2012, 14, 4114–4117.
[23] E. Schaumann, R. Ketcham, Angew. Chem. Int. Ed. Engl. 1982, 21, 225–247; Angew. Chem. 1982, 21, 225–247.
