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Concept

Cyclic Compounds

9-Membered Carbocycles: Strategies and Tactics for their Synthesis

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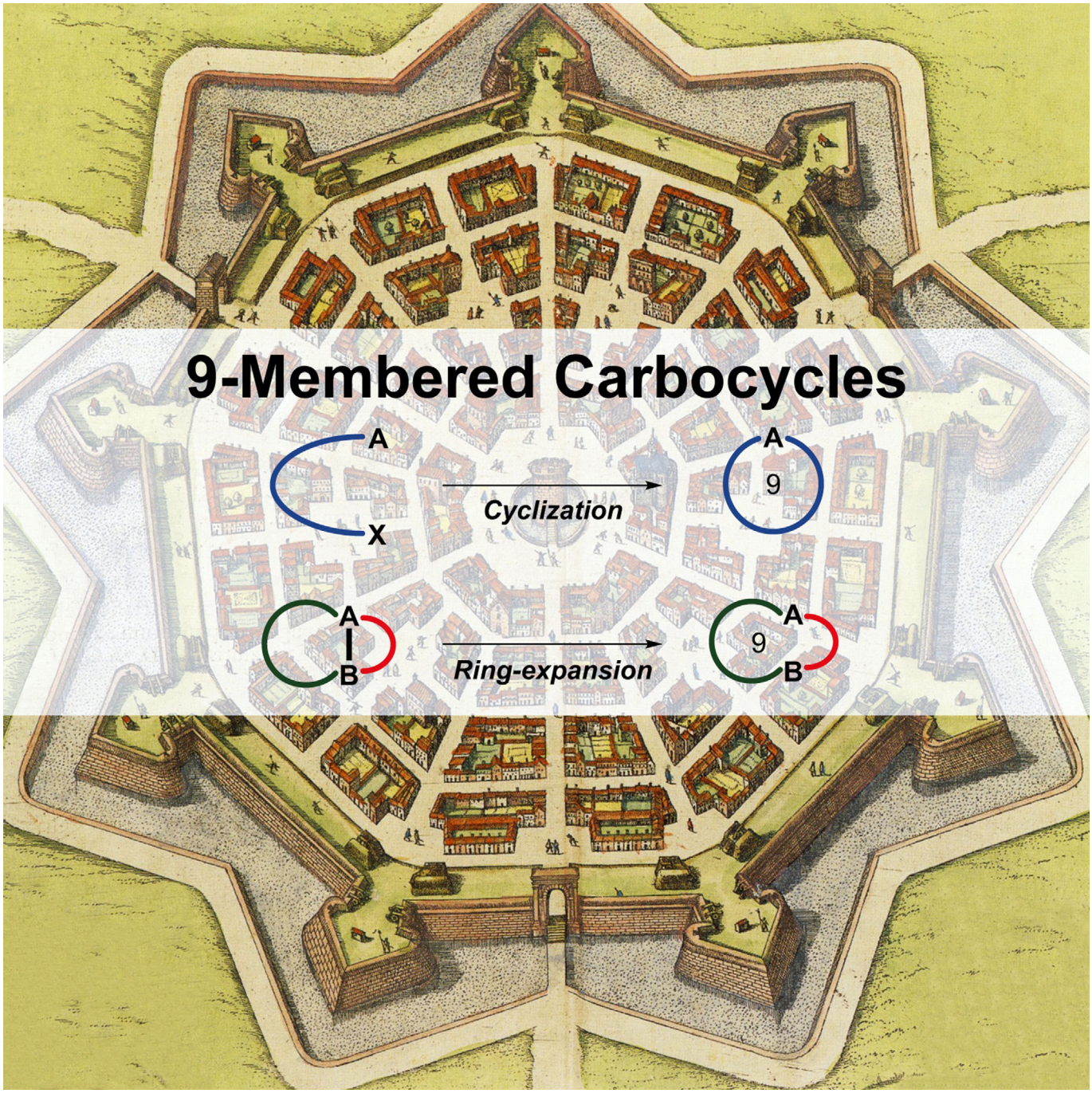

Abstract: Many natural products comprising a nine-membered carbocyclic core structure exhibit interesting biological effects. However, only a minority have succumbed to their synthesis in the past. The synthesis of functionalized nine-membered carbocycles still remains a challenging goal for synthetic 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 rubratoxin 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]

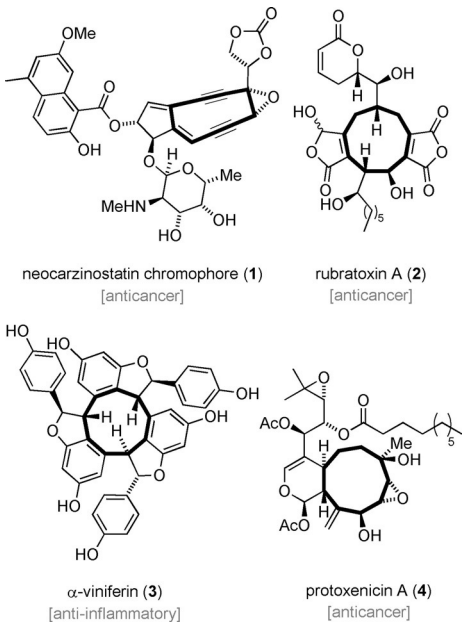

Figure 1. Selected nine-membered carbocyclic ring-containing bioactive natural products. The nine-membered rings are highlighted with bold bonds.

Table 1. Strain energy of cycloalkanes.

Ring size	6	7	8	9	10	11	12
Strain energy [kcal mol^{-1}]	1.4	7.6	11.9	15.5	16.4	15.3	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).

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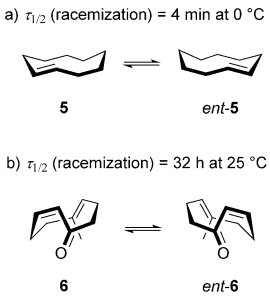
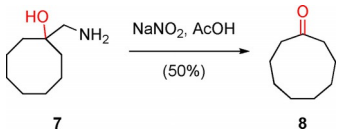


Scheme 1. Rate of racemization for two different *E*-cyclononenes.

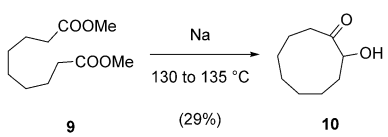
The synthesis of medium-sized rings is a long-standing challenge for synthetic chemists, mainly due to unfavorable enthalpic and entropic factors. About 100 years ago, it was commonly believed that carbocyclic rings containing more than eight carbon atoms were impossible to synthesize. In 1926, Ruzicka was the first to disregard this theory by elucidating the structures of the first macrocyclic natural products civetone, that exhibits a 17-membered ring,[9] and muscone, bearing a 15-membered ring.[10]

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.[11] 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 "polymethylenes and higher terpenes".[12] In 1943, he reported the first efficient three-step synthesis of cyclononanone (**8**) via a Tiffenau–Demjanow rearrangement[13] of 1-(aminomethyl)cyclooctan-1-ol (**7**), itself prepared from cyclooctanone in two steps, upon treatment with sodium nitrite and acetic acid (Scheme 2).[14]



Scheme 2. Synthesis of cyclononanone (**8**) by Ruzicka.

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).[15] Despite its harsh reaction conditions, this method has become a widely used transformation for the synthesis of medium-sized rings.[16]



Scheme 3. Synthesis of 2-hydroxycyclononan-1-one (**10**) by acyloin condensation.

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

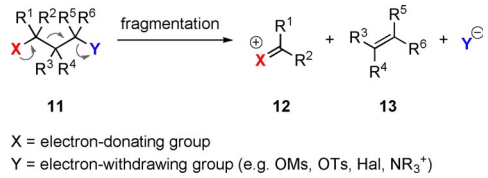
Many published methods for the preparation of nine-membered carbocycles rely on ring-expansion strategies and the reactions associated with them are (1) fragmentation reactions, (2) radical ring-expansion/-contraction reactions and (3) pericyclic reactions.

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,[17] which is still widely used today.[18] In this reaction, a molecule of the form **11** 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.

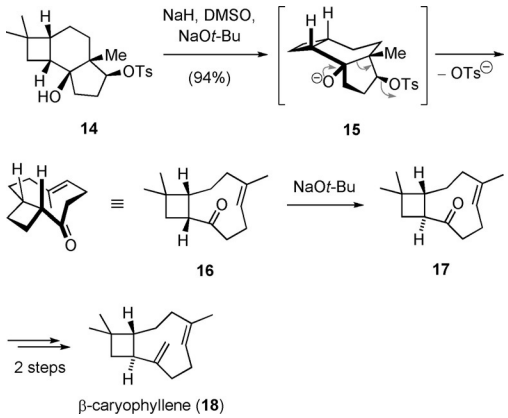
Thomas Magauer studied chemistry at the University of Vienna. In 2007, he joined the group of Prof. Johann Mulzer for his Ph.D., where he developed enantioselective syntheses of the complex polyketide kendomycin and echinopines A and B. In 2009, Tommy moved to Harvard University for postdoctoral studies with Prof. Andrew G. Myers. There, he worked on carbohydrates, chiral silicon protecting groups and a synthesis of antiproliferative trioxacarcins. In 2012, he started his independent research as a Liebig-junior research group leader at the LMU Munich. His group has been supported by the Emmy Noether Program of the German Research Foundation and a Starting Grant of the European Research Council. In 2017, Tommy was awarded the Goering Visiting Professorship at the University of Wisconsin, Madison and began a position as Full Professor of Synthesis and Synthetic Methods at the University of Innsbruck, Austria.



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

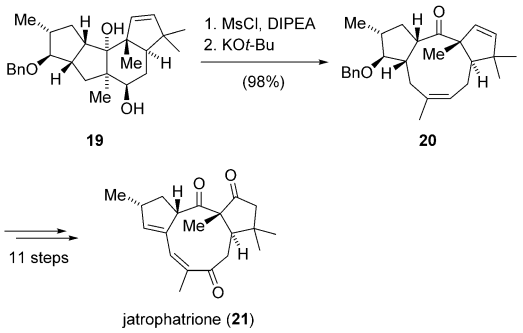
This strong thermodynamic driving force makes the Grob fragmentation a powerful synthetic tool in compensating the high ring strains associated with the formation of nine-membered carbocyclic rings. In the last 50 years, mainly 1,3-diols incorporated in fused 5,6-bicyclic ring systems were employed for 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.[19] 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]



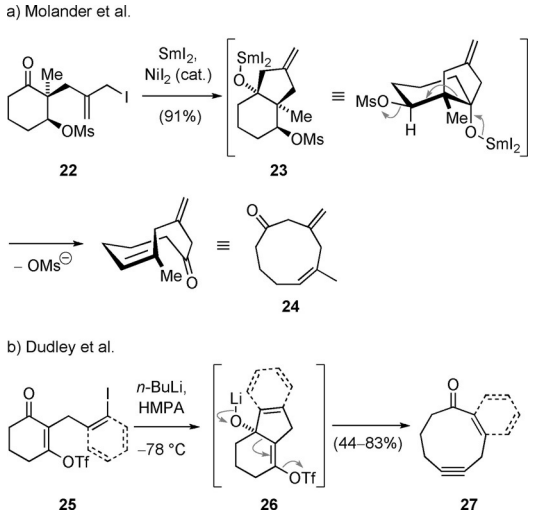
Scheme 5. Grob fragmentation approach to β-caryophyllene (**18**).

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 jatrophatrione (**21**) by Paquette (Scheme 6). First, mesylation of the sterically less congested secondary alcohol in tetracycle **19** resulted in the formation of a monomesylated 1,3-diol, which was readily fragmented upon treatment with potassium *tert*-butoxide (KO*t*Bu) to construct the *Z*-configured cyclononene fragment **20** of jatrophatrione (**21**).[21]



Scheme 6. Paquette's jatrophatrione (**21**) synthesis.

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 diioide-mediated intramolecular cyclization of δ-iodoketone **22**, which then fragmented to afford cyclononene **24** (Scheme 7 a). In a conceptually related approach, the Dudley

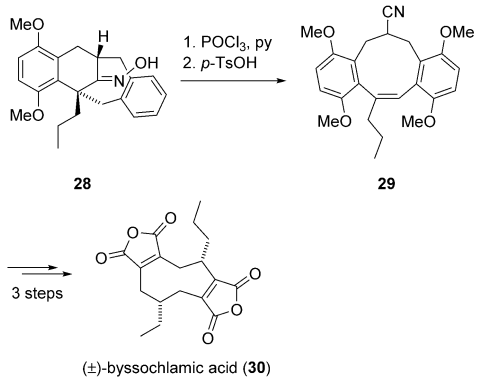


Scheme 7. Molander's and Dudley's cyclization/fragmentation cascades.

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 7 b). 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

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 (±)-byssochlamic acid (**30**) by Stork.[25] Treatment of tetracyclic oxime **28** with phosphoryl trichloride ($POCl_3$) 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).



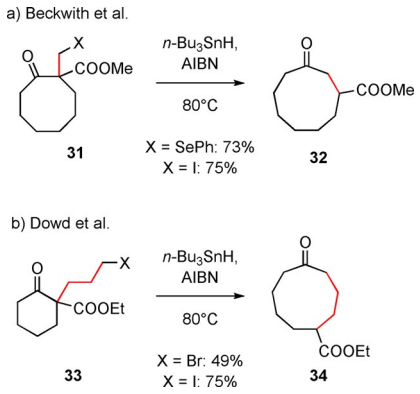
Scheme 8. Beckmann rearrangement approach to (±)-byssochlamic acid (**30**).

2.2. Radical ring-expansion reactions

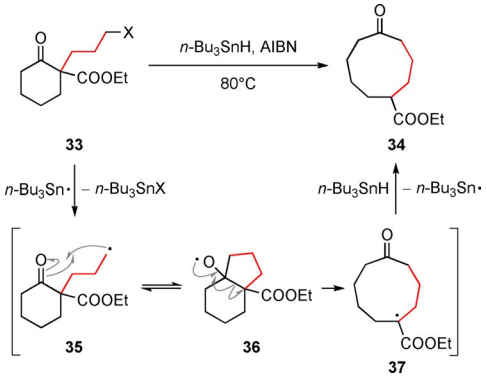
Free radical-mediated ring-expansion reactions have been frequently utilized in the synthesis of medium-sized rings in the past.[26] Radical fragmentations can usually be conducted under mild reaction conditions and are operationally simple. Furthermore, a variety of functional groups are tolerated. 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.[27] 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.[28] 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.[29] These β-keto esters could be easily alkylated with a variety of electrophiles to introduce the radical precursors.

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



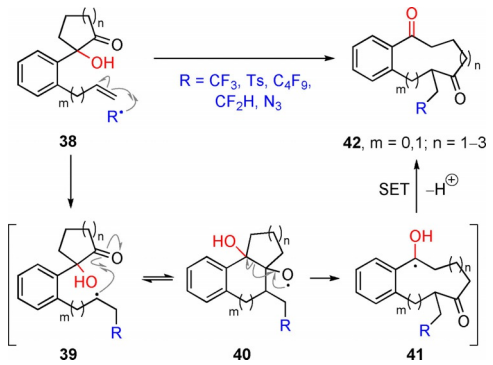
Scheme 9. Radical ring-expansion by Beckwith and Dowd.



Scheme 10. Mechanism for the Dowd–Beckwith reaction.

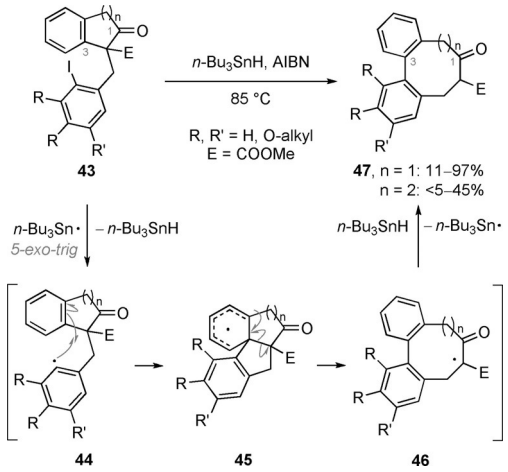
radical **36**. Radical ring-opening of bicycle **36** leads to **37** with the tertiary radical stabilized by the ester group,[30] providing the driving force for the fragmentation. Hydrogen abstraction from tributyltin hydride finally gives the nine-membered cyclic ketone **34** and generates a tributylstannyl 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.[31] Addition of azide, difluoromethyl, trifluoromethyl, tosyl or perfluoroalkyl radicals to the terminal alkene functionality 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 ($R = CF_3$, N_3) or single-electron reduction under photoredox catalysis ($R = Ts$, C_4F_9, CF_2H). 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**.



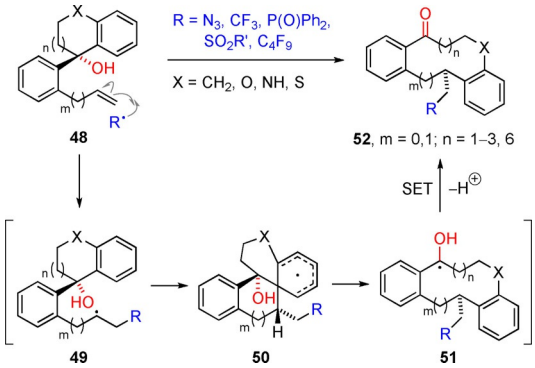
Scheme 11. Liu's method for the synthesis of medium-ring sized benzannulated ketones.

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 **44** and subsequent *5-exo-trig* cyclization via radical *ipso*-substitution at C3 position gives the delocalized radical **45**. Rearomatization of the acceptor ring by radical fragmentation affords tertiary radical **46**, which is stabilized by the ester functionality. The eight- and nine-membered β-keto esters **47** 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 **44** to the tetralone ring.



Scheme 12. Synthesis of eight- and nine-membered β-keto esters by radical *ipso*-substitution at C3 position.

Building upon their previous work on the construction of benzannulated medium-sized rings via ring-expansion, the Liu group reported on the synthesis of carbocycles of medium and large ring 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 (R = N_3, CF_3), alkyl or aryl sulfonyl chlorides (R = SO_2R', C_4F_9) and copper(I) iodide, or diphenylphosphine oxide and silver(I) nitrate (R = $P(O)Ph_2$). The first step of their procedure is the addition of the generated radicals to the terminal alkene of substrate **48** (Scheme 13). The secondary radical **49** undergoes a 1,4- or 1,5-aryl migration/ring-expansion sequence to afford neutral ketyl radical **51**. The migration presumably proceeds through spiro radical intermediate **50**.[34] Oxidation of the tertiary radical **51** to the ketone by the copper or silver catalyst and loss of a proton gives the ring-expanded medium-sized cyclic or macrocyclic ketones **52**. 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.

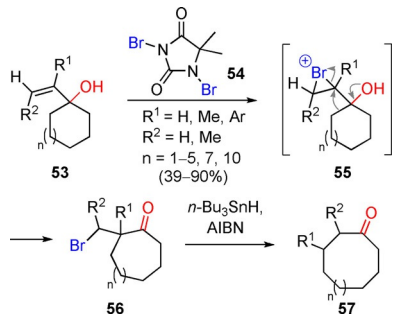


Scheme 13. Radical aryl migration/ring-expansion sequence for the synthesis of medium-sized cyclic or macrocyclic ketones.

2.3. Pericyclic ring-expansion reactions

2.3.1. Sigmatropic reactions

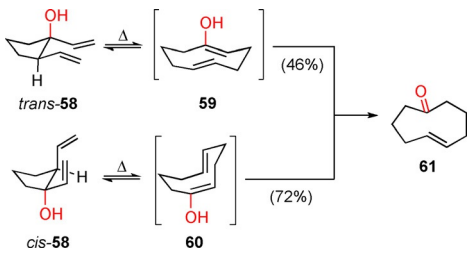
Sigmatropic rearrangements were well explored for the synthesis of medium-sized rings in past decades.[35] Previously employed [1,2]-sigmatropic rearrangements for the synthesis of nine-membered carbocycles are the pinacol rearrangement,[36] the semi-pinacol rearrangement,[37] the Tiffenau–Demjanow rearrangement[13] and related homologation reactions of cyclic ketones involving diazo compounds.[38] The Tiffenau–Demjanow rearrangement has not found further application in the synthesis of nine-membered carbocycles 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.[39] 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 **53** with 1,3-dibromo-5,5-dimethylhydantoin (DBH, **54**) to activate the olefin by bromonium ion formation and isolated the corresponding one-carbon ho-



Scheme 14. Semi-pinacol rearrangement and subsequent Dowd–Beckwith reaction for the synthesis of medium-sized carbocycles.

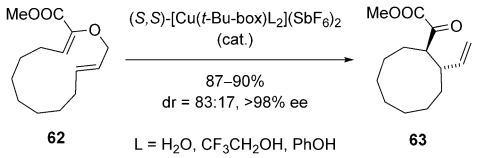
mologated β-bromo ketones **56** (Scheme 14).[37b] These substrates allowed further ring-expansion by the Dowd–Beckwith reaction to afford ketones **57**.

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.[40] 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.[41] 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.



Scheme 15. Thermal oxy-Cope rearrangement.

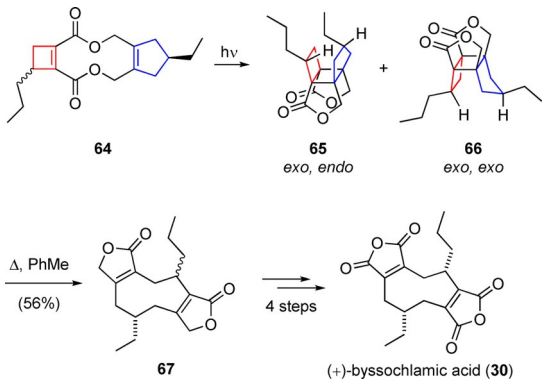
The reaction was later performed as an anionic oxy-Cope rearrangement by treatment of *trans*-**58** with potassium hydride at 0 °C and afforded the ring expanded product **61** in 86% yield.[42] In 2012, the Hiersemann group utilized a catalytic asymmetric Gosteli–Claisen rearrangement for the synthesis of nine-membered carbocycles.[43] In their work, 13-membered cyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers, such as **62**, were transformed to nine-membered carbocycles in the presence of different chiral bis(oxazoline) copper(II) catalysts. The good diastereoselectivity of this reaction results from the preference of the substrate to adopt a chair-like transition state. The reaction could also be performed in an uncatalyzed fashion by heating **62** to 140 °C, resulting in the formation of racemic **63** in 92% yield (d.r. = 94:6) (Scheme 16).



Scheme 16. Synthesis of nine-membered carbocycles by asymmetric Gosteli–Claisen rearrangement.

2.3.2. Cycloaddition and -reversion

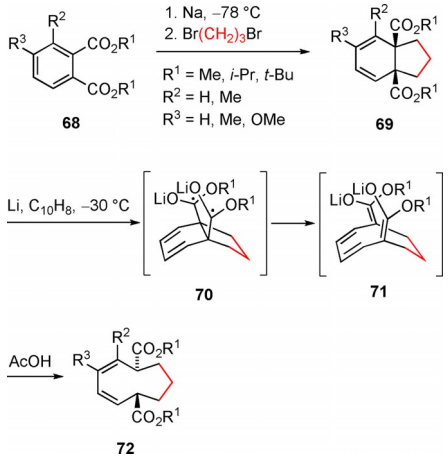
The White group demonstrated the applicability of a [2+2]-photoaddition/cycloreversion strategy[44] for the synthesis of nine-membered carbocycles in their asymmetric total synthesis of (+)-byssochlamic acid (**30**).[45] Irradiation of a 1:1 mixture of diastereomers of dilactone **64** resulted in a [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.



Scheme 17. [2+2]-Photoaddition/cycloreversion strategy for the asymmetric total synthesis of byssochlamic acid (**30**).

2.4. Miscellaneous

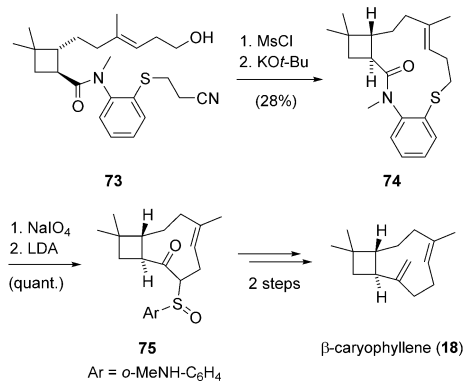
Recently, the synthesis of nine- and ten-membered carbocycles from phthalates via a dearomatization/cyclization/ring-opening cascade has been described.[46] First, the phthalates were converted to fused 5,6-bicyclic systems **69** by reduction of **68** with sodium metal and alkylation with 1,3-dibromopropane (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**.



Scheme 18. Synthesis of nine-membered carbocycles **72** via stereoselective reductive ring-opening.

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.



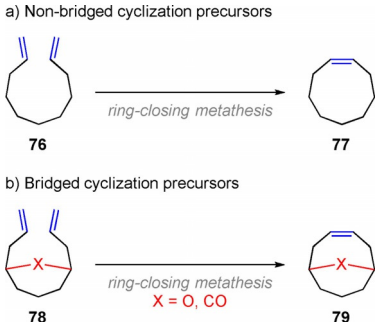
Scheme 19. Ring-contraction strategy by Oishi for the total synthesis of β-caryophyllene (**18**).

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.

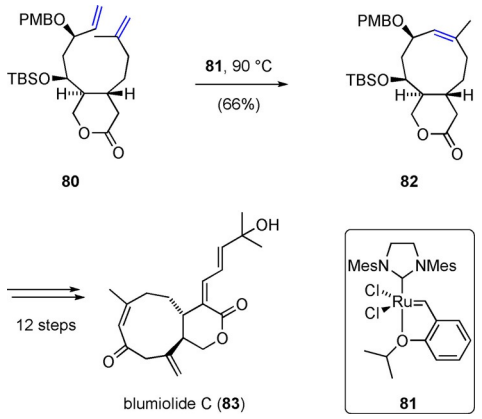
4.1. Ring-closing metathesis

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.



Scheme 20. Ring-closing metathesis as a powerful method to form nine-membered carbocycles.

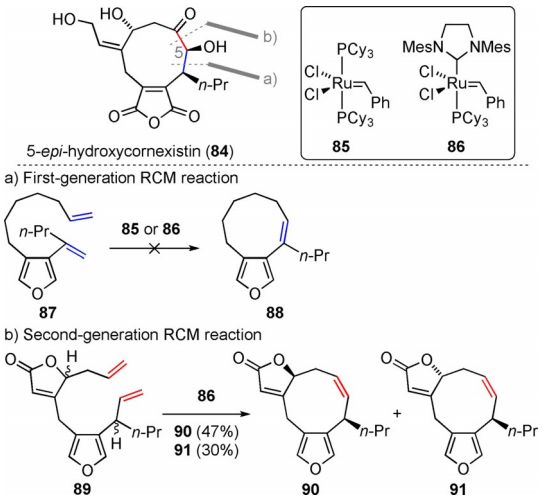
In 2008, the Altmann group described the total synthesis of the *Xenia* diterpenoid blumiolide C (**83**).[49] The, *Z*-configured double bond of the nine-membered ring was formed by ring-closing metathesis of diene **80** (Scheme 21). Preliminary experiments showed that protection of the allylic alcohol as *p*-methoxy benzyl (PMB) ether was crucial for the success of this



Scheme 21. Application of the RCM reaction in Altmann's total synthesis of blumiolide C (**83**).

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.

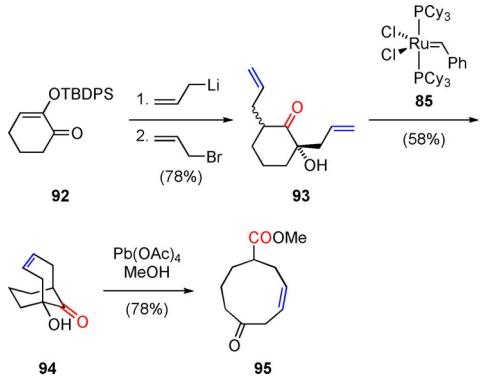
The Clark group was confronted with a similar problem in their synthesis of the carbocyclic core structure of the cornexistins by ring-closing metathesis.[50] Initial attempts to form nine-membered carbocycle **88** by treatment of diene **87** with either Grubbs' first (**85**) or Grubbs' second generation 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



Scheme 22. Synthesis of an intermediate in route to 5-*epi*-hydroxycornexistin (**84**).

isomer **91** was further transformed into 5-*epi*-hydroxycornexistin (**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.[51] 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-



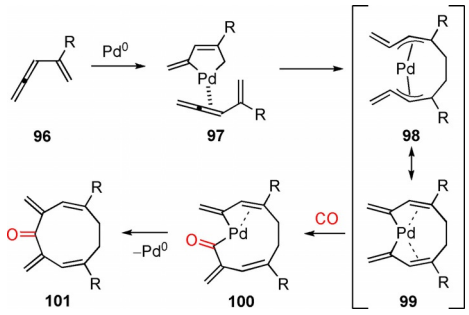
Scheme 23. Formation of the nine-membered carbocycle via RCM reaction facilitated by a carbonyl tether.

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 cyclononenone **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

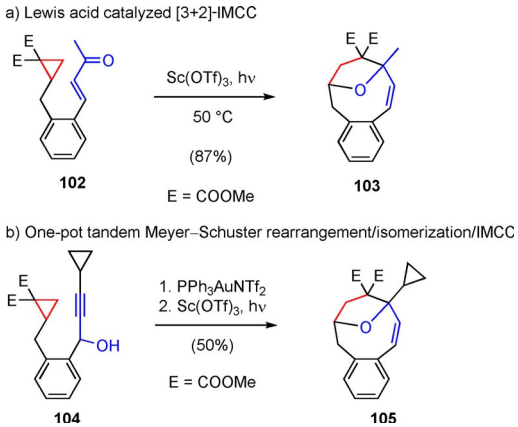
Transition-metal-catalyzed cycloaddition reactions are also powerful tools for the preparation of nine-membered carbocycles. For example, the Ito group described an interesting one-step procedure for the synthesis of C_{2v}-symmetric nine-membered carbocycles via a [4+4+1]-cycloaddition by the palladium-catalyzed carbonylation of vinylallenes.[52] 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(π-allyl)-palladium intermediate **98**, whose resonance structure, σ-di(alkenyl)palladium intermediate **99**, is



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

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 25 a). 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.

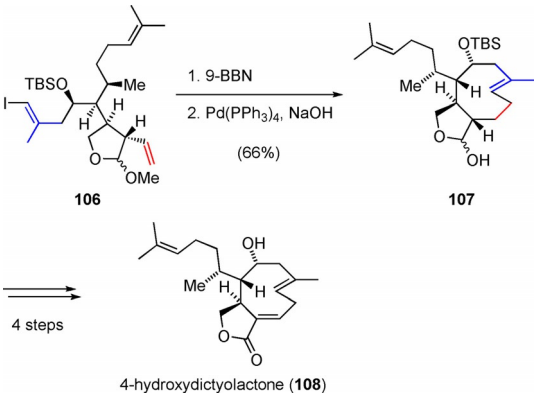


Scheme 25. Formation of nine-membered carbocycles via a) Lewis acid catalyzed isomerization/intramolecular [3+2]-cross-cycloaddition (IMCC) or b) one-pot tandem Meyer–Schuster rearrangement/isomerization/IMCC.

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 25 b). In summary, these strategies constitute an efficient method for the construction of nine-membered rings and for the construction of carbocycle-based oxabicyclo[4.2.1] skeletons.

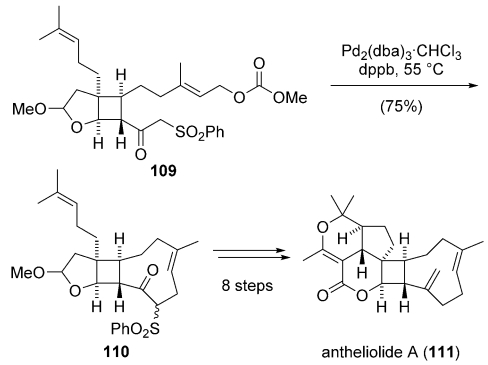
4.3. Intramolecular cross-coupling

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 xenicane diterpenoid 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 $PdCl_2$(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 $Pd(PPh_3)_4$ as catalyst proved to be the key for achieving a high yielding cyclization and 4-hydroxydictyolactone (**108**) could be synthesized in four additional steps.



Scheme 26. Formation of the *E*,*Z*-cyclononadiene motif **107** by a *B*-alkyl Suzuki macrocyclization.

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 $Pd_2(dba)_3{\cdot}CHCl_3$. For the conversion of **110** to antheliolide A (**111**) eight additional steps were required.

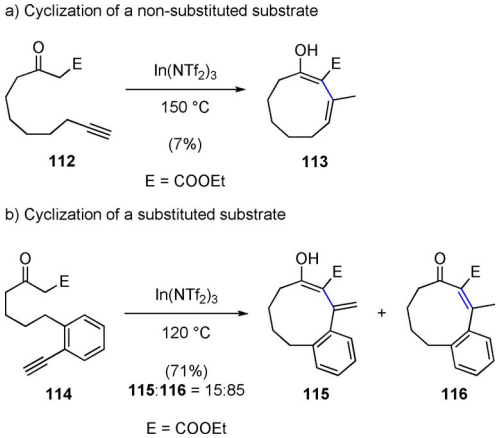


Scheme 27. Palladium-catalyzed formation of *E*-cyclononene **110** applied in the total synthesis of antheliolide A (**111**).

4.4. Conia-ene cyclization

The Conia-ene reaction is a useful reaction for the formation of five- to seven-membered rings.[57] In 2007, the group of Nakamura reported the first example of an indium(III)-catalyzed cycloisomerization of ω-alkynyl-β-keto esters to access five- to fifteen-membered carbocycles.[58] 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, entropic and enthalpic factors normally restraining the formation of medium-sized rings could be circumvented. Nevertheless, the transannular steric repulsion from generic cyclononane **113** impeded the cyclization of **112** and gave the nine-membered ring product in only 7% yield (Scheme 28a). However, substrates containing sp^2 carbon atoms led to efficient nine-membered ring formation. Consequently, β-keto ester **114**, featuring a phenylene motif, smoothly afforded the isomeric nine-membered carbocycles **115** and **116** (Scheme 28b).

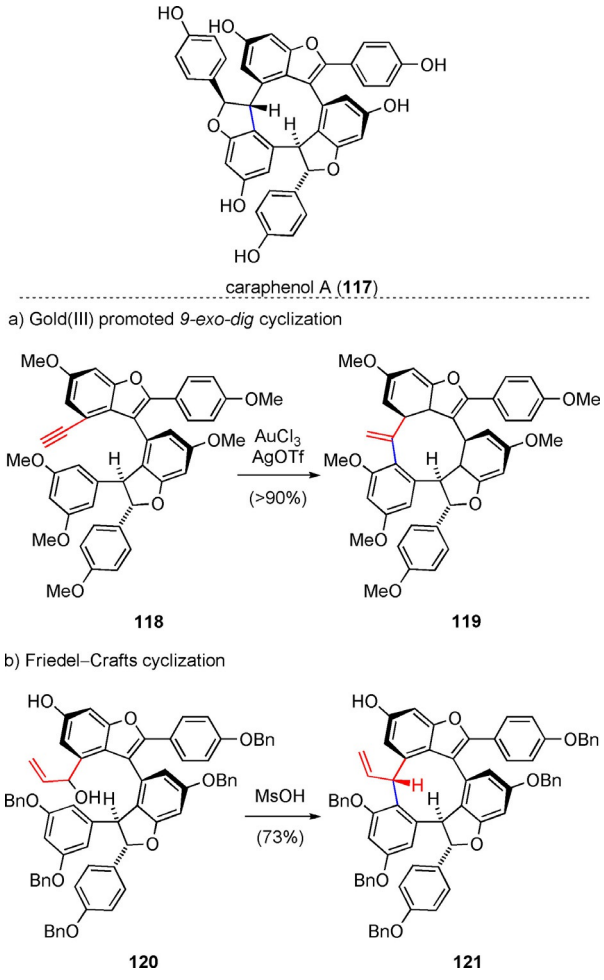
With this methodology, a broad range of nine-membered carbocycles could be synthesized in good yields. To date, no example of nine-membered ring formation with a non-terminal alkyne has been reported.



Scheme 28. In^{III}-mediated Conia-ene cyclization of a) the non-substituted precursor **112** and b) the substituted substrate **114**.

4.5. Friedel–Crafts cyclization

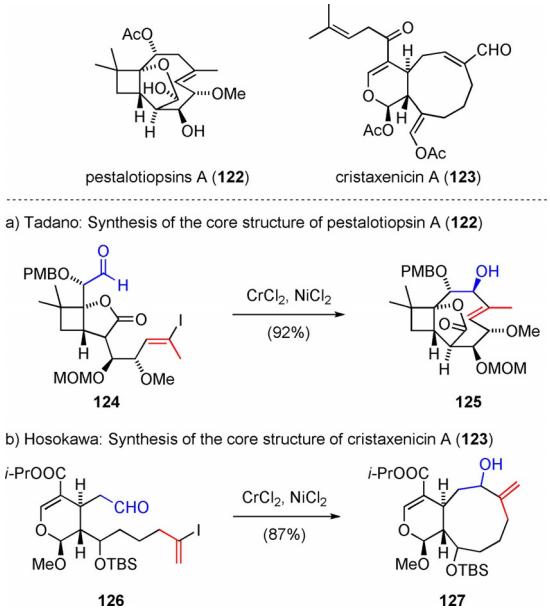
For the total synthesis of caraphenol A (**117**), the Snyder group investigated different approaches for the formation of the nine-membered carbocycle.[59] The envisioned late-stage formation of the nine-membered ring depends on a method compatible with highly functionalized substrates. In this context, the first reported gold(III) promoted *9-exo-dig* ring closure of **118** to **119** has been reported (Scheme 29a). The success and the efficiency (yield >90%) of this cyclization reaction originates 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 29b). Exposure of **120** to an excess of methanesulfonic acid resulted in clean formation of nine-membered 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 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

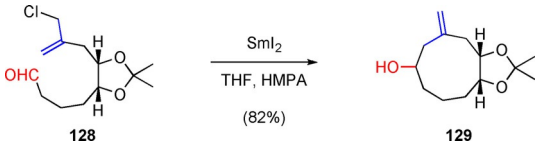
Recently, the Nozaki–Hiyama–Kishi (NHK) reaction has become a viable method for the formation of nine-membered rings and has been applied in studies towards the total synthesis of pestalotiopsin A (**122**) and in the total synthesis of cristaxenicin A (**123**).[60] In 2008, the group of Tadano published 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 30a). In 2016, the intramolecular NHK reaction was applied in Hosokawa's synthesis of the core structure of cristaxenicin A (**123**) (Scheme 30b). 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.



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**).

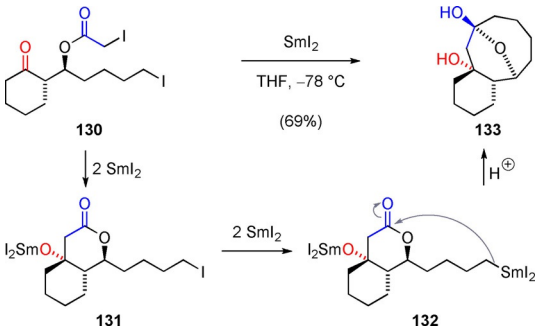
4.7. Samarium(II)-promoted cyclizations

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.[61] 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).[62] 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.



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

In the last decades, the group of Molander has published several samarium(II) iodide-based annulative routes for the construction of oxygen bridged cyclononenes.[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.

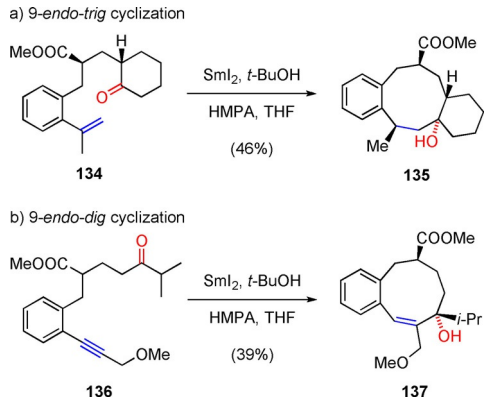


Scheme 32. Proposed mechanism of the samarium(II) iodide promoted sequential Reformatsky/nucleophilic acyl substitution for the formation of oxygen bridged nine-membered carbocycles.

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 33a). 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 33b). 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



Scheme 33. Samarium(II) promoted intramolecular a) carbonyl-alkene or b) carbonyl-alkyne coupling to construct nine-membered 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.

Keywords: carbocycles · cyclization · fragmentation · nine-membered ring · ring-expansion

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