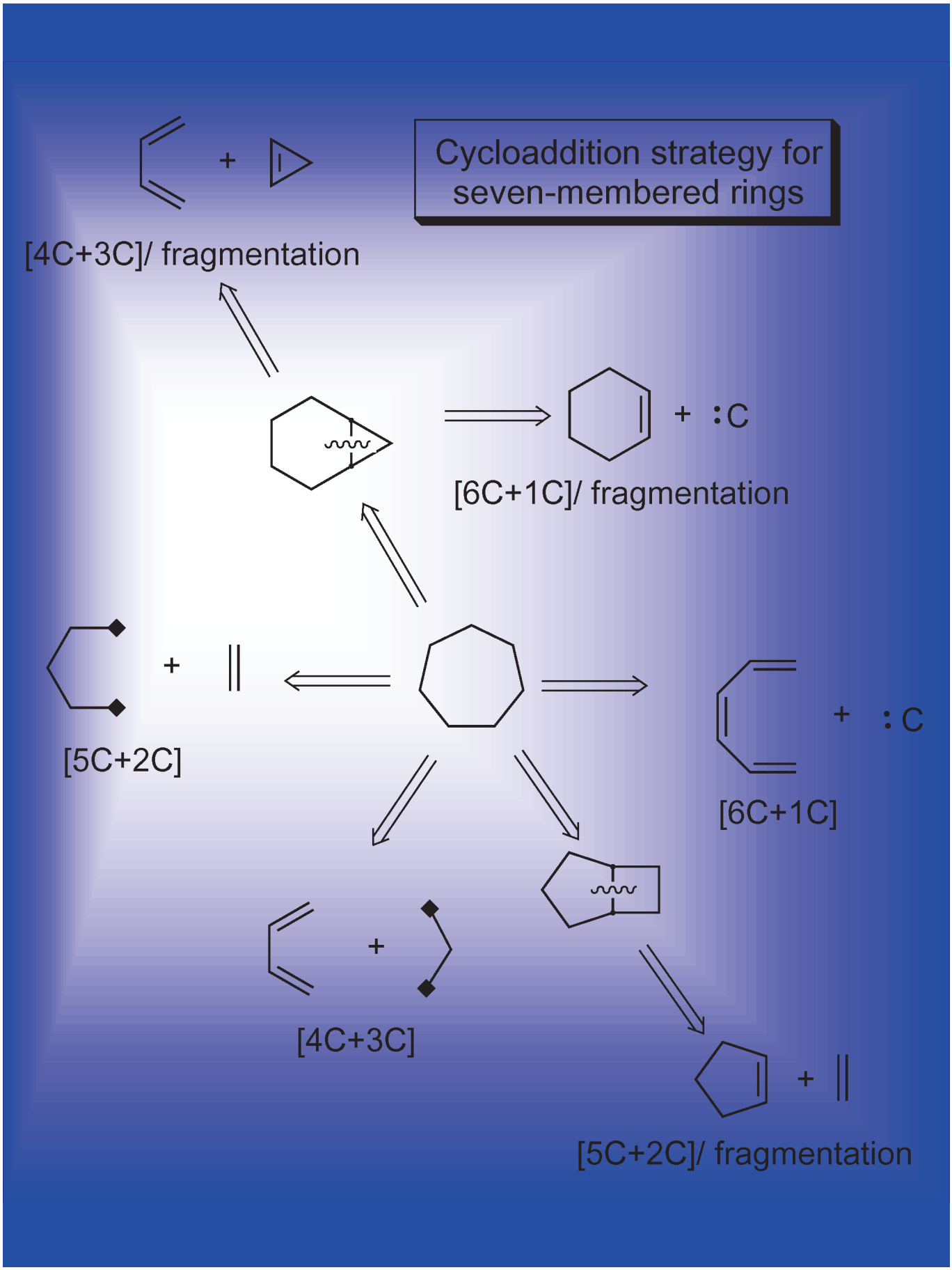

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The Cycloaddition Strategy for the Synthesis of Natural Products Containing Carbocyclic Seven-Membered Rings**

Merle A. Battiste,[a] Phillip M. Pelphrey,[b] and Dennis L. Wright*[b]

Abstract: Highly substituted carbocyclic seven-membered rings are frequently found in natural products and their synthesis represents a significant challenge to the synthetic chemist. Direct intramolecular cyclization of these systems often proves difficult and this fact has catalyzed the development of a variety of strategies based on a convergent intermolecular cycloaddition strategy. This concept article discusses the major cycloaddition approaches utilized to access these types of structures and primarily focuses on examples employed in the synthesis of natural products.

Keywords: cycloaddition · cyclopropene · natural products · oxyallyl cations · seven-membered rings

Introduction

Carbocyclic seven-membered rings appear as integral subunits of a variety of natural products, such as colchicine, guanacastepene, and the phorbol esters, and accordingly offer a significant challenge for the development of new synthetic methodology.[1] Unlike the other common ring sizes (five and six), seven-membered rings are difficult to access by direct cyclization reactions due to a combination of entropic factors and the development of nonbonded interactions in the transition state. These difficulties can be overcome if a cycloaddition rather than a cyclization approach is followed, whereby two of the bonds in the cyclic framework are formed simultaneously or almost simultaneously. However, this strategic disconnection also presents evident problems as the dissection of an odd-numbered ring yields one odd-numbered fragment, thus necessitating the use of zwitterionic or diradicaloid intermediates. In principle there are three possible constructions along a cycloaddition approach (Figure 1).

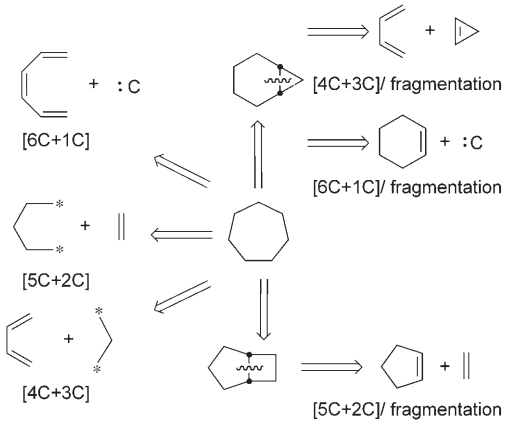

Figure 1. All possible cycloaddition strategies to prepare carbocyclic seven-membered rings. The * represents reactive centers.

For the purpose of this concept article, we will designate the different approaches only by the number of carbon atoms of the final ring present in each fragment. Thus the union of a four-carbon-atom fragment and a three-carbon-atom fragment will be designated as a [4C+3C] cycloaddition process. This formalism is only meant as a skeletal analysis and is not intended to imply electron counting or mechanistic detail. For example, the reaction of a 1,3-diene with an allyl cation equivalent such as an oxyallyl cation involves six π electrons distributed across seven carbon atoms (a 6π-$7C^+$ species), reacting through an aromatic tropylium-ion-like transition state. From a synthetic disconnection analysis, we will refer to this type of process as a [4C+3C] cycloaddi-

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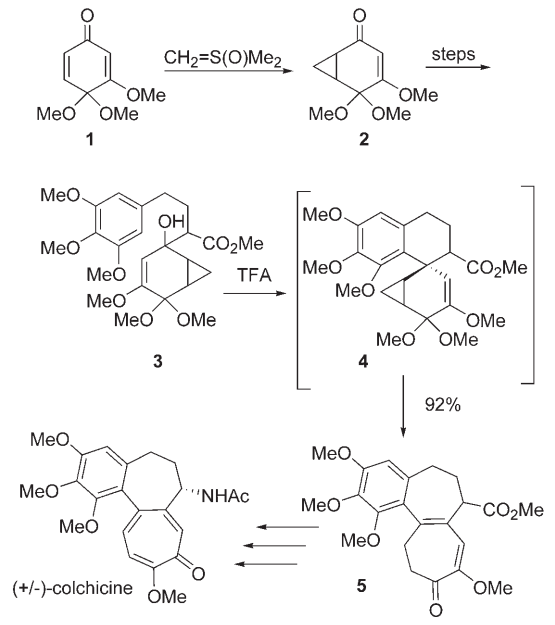
tion reaction to denote the convergent nature of a four- and three-carbon-atom unit being united to form a seven-membered ring. A simple analysis of the parent ring systems reveals the three possible disconnections as [6C+1C], [5C+2C], and [4C+3C]. Direct cycloadditions are typically formulated as shown on the left side of Figure 1. The cycloaddition of readily available 1,3-dienes with an allyl cation equivalent is typical for [4C+3C] reactions, while olefins can react with an allyl cation equivalent or 4π-$5C^+$ species in a net [5C+2C] approach. The [6C+1C] disconnection theoretically involves the addition of a carbene across a 1,3,5-hexatriene unit. Although known with sulfur dioxide,[2] the all carbon version of this process has not been developed in a synthetically useful manner, as carbenes typically attack the more electron-rich nonterminal olefin due to entropic factors.

In this article, we also include other cycloaddition reactions that initially produce fused bicyclic systems that are converted into the seven-membered system by fragmentation of the intracyclic carbon–carbon bond. Fragmentation of a bicyclo[4.1.0]heptane system can be used to effect a formal [4C+3C] reaction through an intermediate cyclopropene Diels–Alder [4+2] reaction or a carbene [2+1] cycloaddition to a cyclohexene. An intermediate bicyclo[3.2.0]heptane system reveals an alternative [5C+2C] cycloaddition based on an initial [2+2] cycloaddition. In this article, we will discuss the implementation of these different strategies in the context of the total synthesis of natural products. As this is not a comprehensive review, the examples have been chosen to illustrate the different methods and strategies.

[6C+1C] Approach

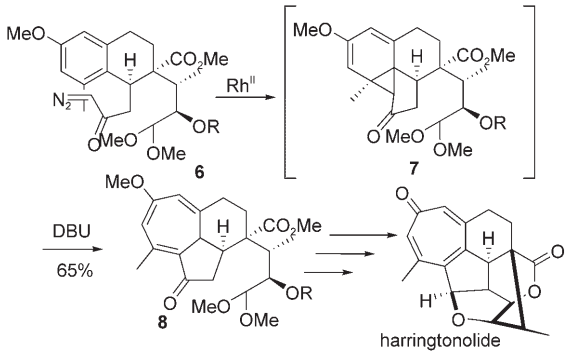
As detailed above, the [6C+1C] strategy has not been developed in a direct sense (carbene+hexatriene), but has been nicely utilized in the cycloaddition/fragmentation manifold en route to various cycloheptanoid natural products. Evans[3] has made elegant use of this two-stage protocol in a total synthesis of the tubulin polymerization inhibitor colchicine, a natural product containing two fused seven-membered ring systems (Scheme 1).

Cyclopropanation [2C+1C] of the quinone monoketal **1** is an overall [6C+1C] cycloaddition to prepare a key bicyclo[4.1.0]heptane intermediate **2**. This intermediate was converted to **3**, which underwent an initial cyclization to **4** upon treatment with a strong acid. Further exposure to acidic conditions effected rupture of the internal bond to a secondary carbonium ion which preceded aryl migration to give the dihydrotropolone system **5**. This example nicely illustrates how cleavage of the key bond can be coupled to further carbon–carbon bond formation. Overall one of the seven-membered rings of colchicine is made through a cycloaddition process, while the other is formed by a direct cyclization. Mander[4] has utilized the ability of highly electrophilic metallocarbenoids to effect cyclopropanation of a benzene



Scheme 1. Colchicine synthesis through a [6C+1C]/cleavage strategy (Evans).

ring. The initially formed norcaradiene intermediate undergoes a spontaneous electrocyclic ring-opening to the cycloheptatriene. A recent application of this method to the synthesis of harringtonolide involved decomposition of diazoketone **6** with rhodium (Scheme 2).

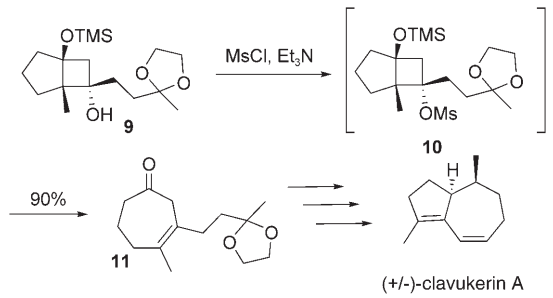


Scheme 2. Cyclopropanation/norcaradiene rearrangement (Mander).

Cyclopropanation of the electron-rich arene gave **7**, which was fragmented in the presence of an amine base to produce **8** in good overall yield. This intermediate could be converted into the natural product through several additional steps.

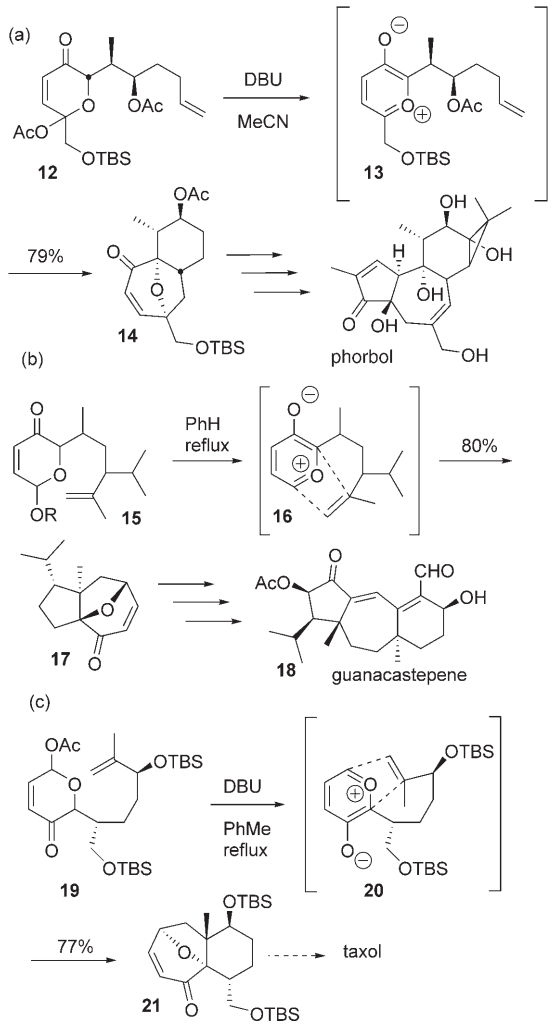
[5C+2C] Approach

The formation of seven-membered rings through a [5C+2C] strategy has been utilized both in a direct cycloaddition approach and through the fragmentation of bicyclic derivatives prepared through [2+2] cycloadditions of cyclopentenes and olefins. Pak[5] has utilized this overall strategy in a total synthesis of clavukerin A (Scheme 3).



Scheme 3. [2+2]/fragmentation approach to clavukerin (Pak).

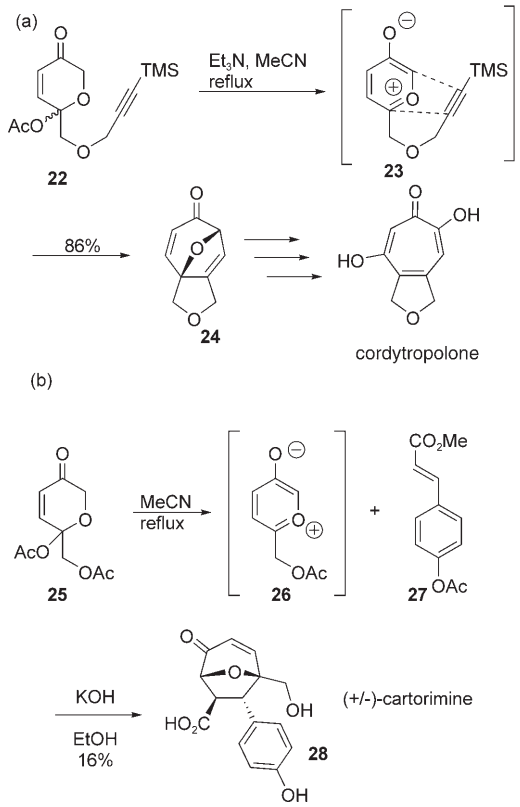
Bicyclic alcohol **9** was prepared through [2+2] cycloaddition of the silylenol ether of 2-methyl cyclopentenone and dichloroketene followed by reductive dechlorination and Grignard addition. Conversion of the tertiary alcohol into the corresponding mesylate **10** induced a spontaneous retro-aldol fragmentation to yield cycloheptenone **11**. This compound was converted into the natural product through several steps including an aldol condensation.



Scheme 4. Oxidopyrylium ions in [3+2] cycloaddition reactions to effect a net [5C+2C] cycloaddition reactions (Wender/Magnus).

A popular strategy for preparing seven-membered carbocyclic systems has involved the cyclcoaddition of an alkene or alkyne with a cyclic pentadienyl cation equivalent (a 4π-5C$^+$ species). The generation and stabilization of these mesoionic systems is greatly facilitated by the presence of both electron-donating and -withdrawing groups. Oxidopyrylium ions are one such stabilized 1,5-dipolar species that benefit from aromatic character in the zwitterionic state. These highly reactive intermediates are easily generated through the ionization of 3-pyrone acetal derivatives, which are in turn easily accessed through oxidation of hydroxymethyl furan derivatives (Scheme 4).

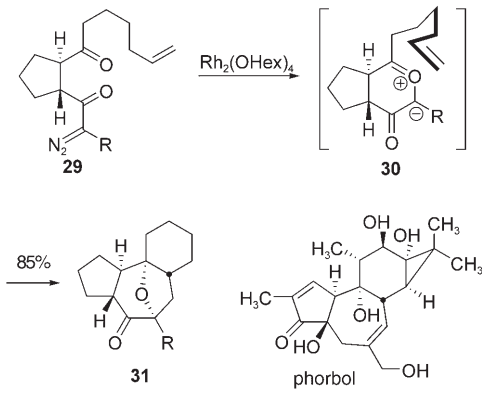
Wender[6] utilized this strategy for the first syntheses of the phorbol esters. This strategy was later adapted for the first asymmetric synthesis of the natural product, whereby treatment of **12** with base effected the net loss of acetic acid from the system to give the aromatic zwitterionic intermediate **13**, which was trapped in an intramolecular cycloadditon with an unactivated olefin to deliver tricyclic compound **14** (Scheme 4a). Magnus has also used this process extensively in an approach to guanacastepene[7] through the conversion of **15** to **17** as well as the synthesis of **21** an intermediate en route to the taxane[8] ring system (Scheme 4b). All of these cases nicely illustrate the high degree of relative stereocontrol possible in these cycloaddition reactions. Other variations on this reaction have been used to access related structural types (Scheme 5).



Scheme 5. Additional cycloaddition examples (Baldwin/Snider).

Baldwin has recently described an approach to the tropolone natural product cordytropolone involving the use of an alkyne trap in the [5C+2C] reaction.[9] Generation of pyrylium ion **23** by base-induced 1,5-elimination of **22** led to the synthesis of **24**, in which the seven-membered ring is in the same oxidation state as the natural product. It is also possible to trap these intermediates in an intermolecular reaction. Snider has recently used this variation in a short synthesis of cartorimine.[10] Intermolecular cycloaddition between the simple pyrylium ion **26** and cinnamate **27** generated the skeleton of the natural product. Simple basic removal of the protecting groups converted the primary adduct directly into the target natural product.

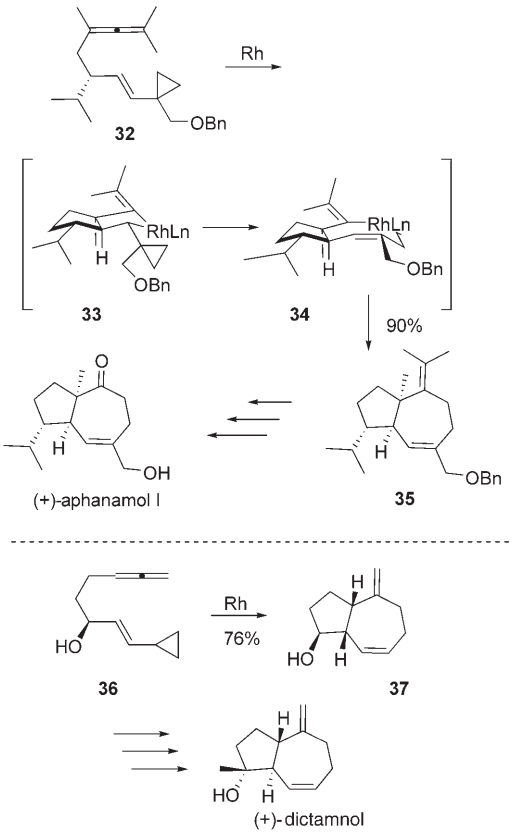
Another reliable and general way to prepare these types of 1,5-dipolar species is through the intramolecular addition of carbonyl groups to metallocarbenoid intermediates. The ensuing carbonyl ylide is also a stabilized 1,5-dipolar species and undergoes cycloaddition with unsaturated systems. An example of an application of this method was reported by McMills[11] and Dauben[12] in a synthesis of the tigliane skeleton (Scheme 6). Rhodium-catalyzed decomposition of α-diazoketone **29** produces an electrophilic metallocarbenoid that is captured by the proximal ketone carbonyl group to produce a stabilized 1,3-dipole **30**. An ensuing intramolecular [3+2] cycloaddition reaction yields the tigliane skeleton **31** through a net [5C+2C] reaction.



Scheme 6. Carbonyl ylide cycloaddition for the tigliane skeleton (McMills).

Over the past several years, Wender and co-workers have developed a new protocol to effect an overall [5C+2C] cycloaddition involving the reaction of vinyl cyclopropanes and olefins in a process that can be considered a formal homo Diels–Alder reaction (Scheme 7).

Wender has employed this strategy for the total synthesis of the natural products aphanamol[13] and dictamnol.[14] Treatment of vinyl cyclopropane **32** with a rhodium(I) catalyst leads to a metallocyclopentane intermediate **33**, followed by a strain-driven cyclopropane cleavage to produce the metallocyclooctane intermediate **34**. A final reductive elimination forms the second carbon–carbon bond of the cycloheptane system and produces **35** in an excellent 90% yield. A related strategy was used to convert **36** into **37**, an intermediate for the synthesis of dictamnol.

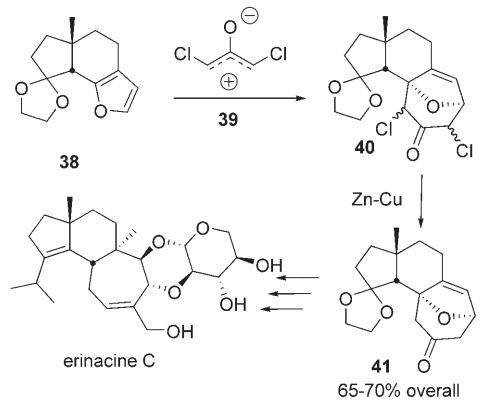


Scheme 7. Vinyl cyclopropanes in [5C+2C] annulation reactions (Wender).

[4C+3C] Approach

One of the most convenient approaches for the synthesis of carbocyclic seven-membered rings is the [4C+3C] strategy that uses readily accessible 1,3-dienes as the four-carbon-atom component. Cyclic dienes, such as cyclopentadiene and furan, are particularly useful for many of these reactions. The direct cycloaddition route requires a 1,3-dipolar species. Oxyallyl cations are generated from α-halo carbonyl derivatives through a 1,3-elimination process and yield stabilized allyl cation equivalents with sufficient lifetimes to engage in both intra- and intermolecular reactions. Wright and co-workers[15] have utilized the addition of an oxyallyl cation to an annulated furan in an approach to the diterpene erinacine C (Scheme 8).

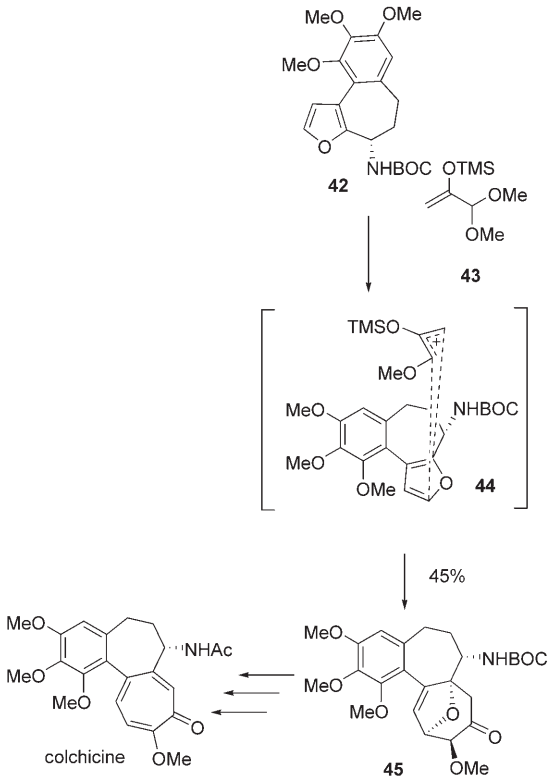
Addition of oxyallyl cation **39** (generated by a 1,3-elimination of trichloroacetone) to the annulated furan **38** led to a highly diastereoselective cycloaddition to produce the adduct **40**. Treatment of the crude cycloadduct with zinc–copper couple gives a key intermediate **41** for the synthesis of cyathane diterpenes in very good overall yield. Cha has made elegant use of oxyallyl cation additions to annulated



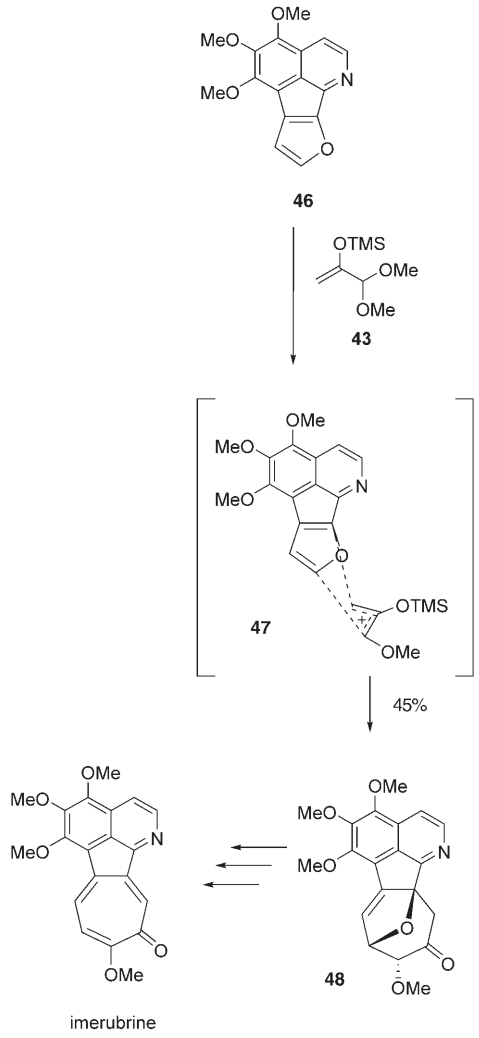
Scheme 8. An oxyallyl-cation-based approach to the cyathanes (Wright).

furans *en route* to several tropolone natural products (Scheme 9).

Colchicine has remained the most pursued troponoid natural product. One of the more difficult features of a colchicine synthesis is controlling the formation of the methyl tropolone C-ring. Methylation of the parent tropolone is not regioselective and produces both colchicine and isocolchicine. Cha's strategy[16] avoided this difficulty by placing the methyl group prior to formation of the tropolone. Cha constructed an annulated furan intermediate **42** and reacted it in a [4C+3C] cycloaddition reaction with silyl enolether **43**. The oxyallyl cation cycloaddition proceeded through an *endo* transition state **44** to produce **45** as a single regioisomeric adduct in 45% yield. Remarkably, altering the nitrogen protecting group could completely reverse this regioselectivity. Double elimination of the oxabridge from the cycloadduct served to form the tropolone and lead to a concise synthesis of the natural product. Although colchicine is the best known of the tropolone-containing natural products, other related targets have become of interest in recent years. Cha was able to utilize the methodology used for the colchicine synthesis in a total synthesis of imerubrine,[17] an unusual tropoloisoquinoline natural product (Scheme 10).



Scheme 9. Synthesis of colchicines through an oxyallyl cation cycloaddition (Cha).

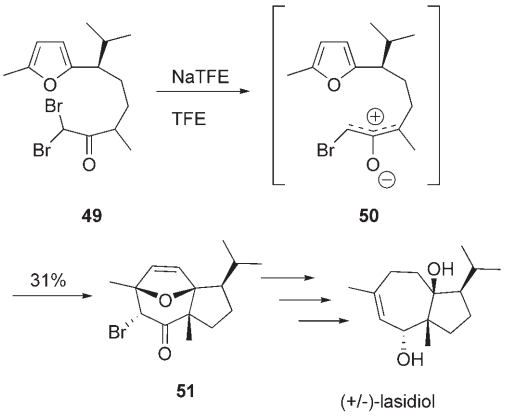


Scheme 10. Synthesis of imerubrine (Cha).

For the synthesis of the natural product, a tetracyclic furan intermediate **46** was prepared and subjected to an oxyallyl cation cycloaddition to produce the key seven-membered ring intermediate **48**. The oxabicyclic adduct could be easily taken on to the desired tropolone ring system.

In addition to intermolecular oxyallyl cation cycloaddition reactions, it has also proven possible to implement this strat-

egy for the construction of seven-membered rings in an intramolecular sense. This has the added advantage of forming two rings during the cycloaddition process. Föhlisch[18] has utilized this process in an elegant synthesis of the terpenoid natural product lasidiol (Scheme 11).



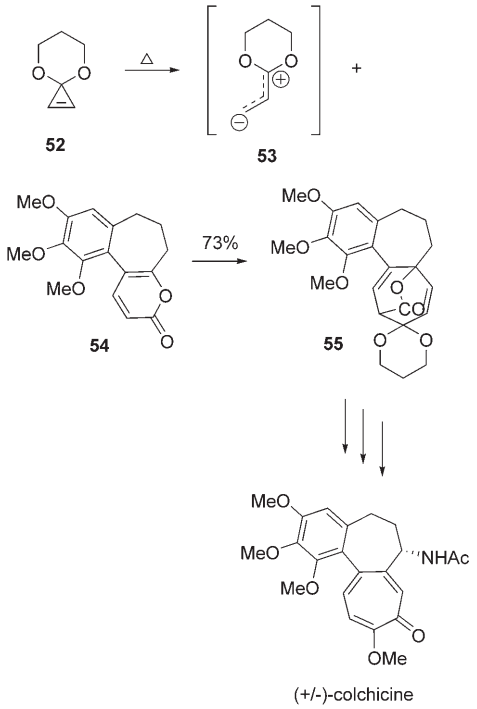
Scheme 11. Intramolecular [4C+3C] route to lasidiol (Föhlisch).

Treatment of the α,α-dibromoketone **49** with sodium trifluoroethoxide (a non-nucleophilic base) effects the 1,3-elimination of HBr from the molecule to yield the zwitterionic intermediate **50**. Again, furan serves well as an electron-rich 1,3-diene and undergoes an intramolecular cycloaddition to produce **51**, a late stage intermediate for the synthesis of lasidiol.

An alternative to generating the reactive oxyallyl cations for this type of [4C+3C] cycloaddition methodology is to utilize a cyclopropene in place of the oxyallyl cation. Cyclopropanes themselves can also be precursors and in fact are often observed as decomposition products of the oxyallyl cations described earlier. Boger has made elegant use of this strategy for the synthesis of several natural product targets, including colchicine,[19] through the ring-opening of cyclopropenone ketals (Scheme 12).

Thermolysis of ketal **52** induces ring-opening to a vinylcarbene **53**, which reacts as a 1,3-dipolar species with the annulated α-pyrone **54** in a [4C+3C] cycloaddition to produce adduct **55**. Thermal extrusion of carbon dioxide from this intermediate and ketal hydrolysis provide ready access to the tropolone ring system of colchicine.

In addition to the use of cyclopropenes as a precursor to 1,3-dipolar species for a [4C+3C] cycloaddition reaction, a cyclopropene can also be utilized as a 2π component in a Diels–Alder reaction. This process initially generates a bicyclo[4.1.0]heptane system that is a direct precursor of a carbocyclic seven-membered ring through cleavage of the intracyclic bond. Cyclopropenes are very reactive dienophiles owing to the large amount of ring strain (~55 kcal mol^{-1}) and undergo cycloaddition with a wide range of 1,3-dienes.[20] The first example of a direct synthesis of a cycloheptatriene by this approach, heptaphenylcycloheptatriene, was reported in 1961,[21] with subsequent examples following shortly thereafter.[22] This strategy could also



Scheme 12. Cyclopropenes as precursors to 1,3-dipoles: colchicine synthesis (Boger).

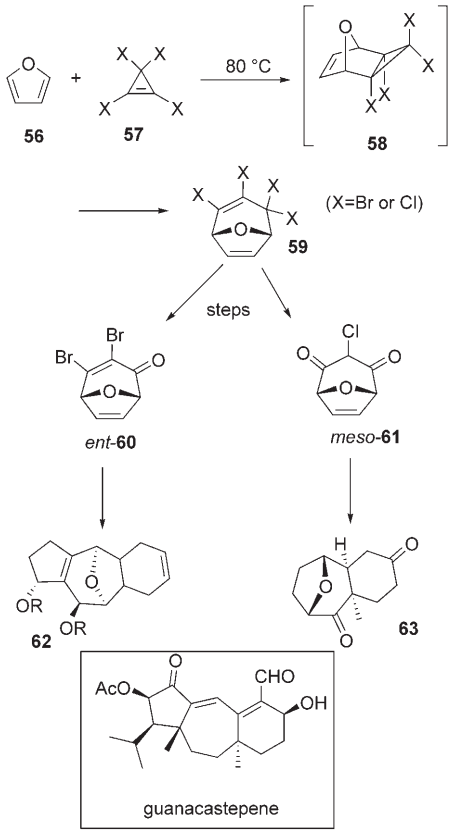
be used with **52** to lead to similar cycloadducts. Boger showed that **52** and **54** can be condensed at high pressure to give an intermediate that can be taken on to similar tropone systems.

Wright and Battiste have utilized the reaction of perhalogenated cyclopropenes and furans to generate highly versatile seven-membered-ring building blocks for application to the synthesis of several natural products including guanacastepene (Scheme 13).

Furan **56** reacts with both tetrabromo and tetrachlorocyclopropene in a Diels–Alder reaction to presumably give the *exo*-adducts **58**.[23] These adducts are highly unstable and undergo a spontaneous rearrangement to the oxabicyclo-[3.2.1]octadienes **59**, likely through a carbonium ion intermediate.[24] The tetrabromoadduct can be converted into either isomer of the enantiomerically pure building blocks **60** through resolution of the corresponding tartrate ketals.[25] Elaboration of the unsubstituted olefin through a Diels–Alder reaction[26] and the annulation of the dibromoenone through a chromium-mediated closure[27] has been used to generate the core structure of guanacastepene A. The tetrachloroadduct has been converted into the *meso*-diketone **61**, which was elaborated to intermediate **63** through Robinson annulation chemistry.[28]

Alternative Cycloadditions

In the examples discussed above, cycloaddition approaches were defined as processes in which two of the carbon–



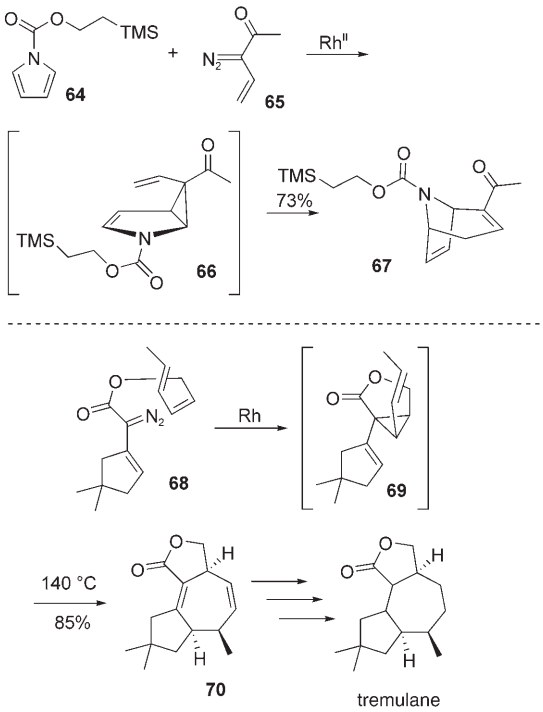
Scheme 13. Perhalocyclopropenes for [4C+3C] cycloaddition (Wright/Battiste).

carbon bonds of the seven-membered ring were formed in a synchronous manner. In addition to these main classifications outlined above, there are alternative cycloaddition/fragmentation strategies in which only one of the carbon–carbon bonds of the final ring is made through cycloaddition, the other being broken during a fragmentation or rearrangement. Included below are a few examples of this alternative cycloaddition/fragmentation strategy. Davies has developed a very efficient route to seven-membered carbocyclic rings relying on an initial [2C+1C] cycloaddition between a diene and a vinyl carbenoid species (Scheme 14).

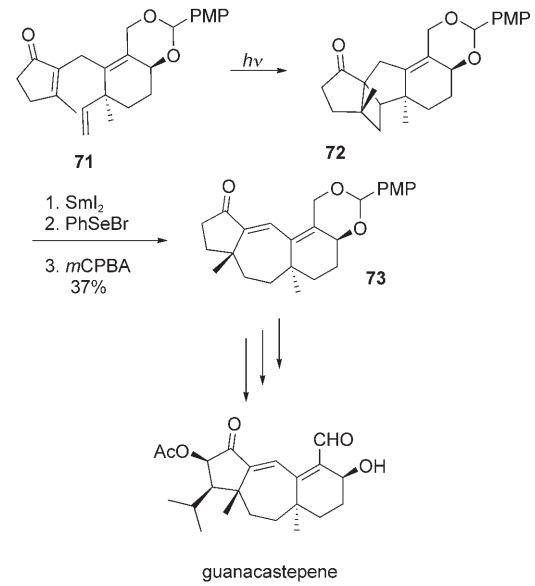
Intermolecular cyclopropanation of pyrrole **64** with a vinyl diazo derivative **65** produces the intermediate cyclopropane **66**. This compound suffers strain accelerated Cope rearrangement to produce **67**, which was converted into ferruginine[29] by deprotection and methylation of the bridging nitrogen atom. An intramolecular example **68** was also developed by Davies[30] for a synthesis of the tremulane class of natural products. This represents a formal overall [4C+3C] cycloaddition (diene+vinyl carbene).

Recently, Sorensen has made nice use of the [2C+2C]/fragmentation strategy in the preparation of the core structure of the antibiotic guanacastepenes[31] (Scheme 15).

A photochemically initiated [2+2] cycloaddition was utilized with **71** to give the highly substituted cyclobutane derivative **72**. A regioselective cleavage of the cyclobutane was



Scheme 14. Sequential cyclopropanation/[3,3] rearrangement to natural products (Davies).

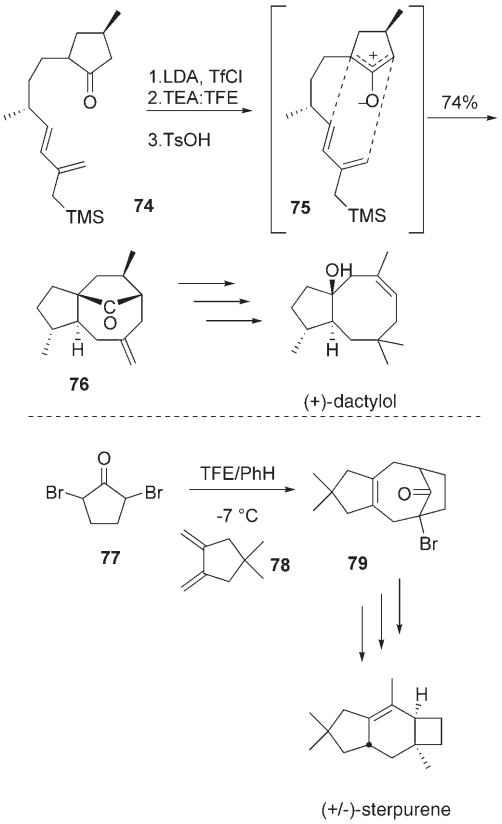


Scheme 15. Sequential [2+2]/fragmentation for the synthesis of guanacastepene (Sorensen).

accomplished in a reductive fashion with samarium iodide to unveil the central cycloheptane ring of the natural product. Notice that in these last examples only one of the two carbon–carbon bonds remains in the final carbocyclic seven-membered ring.

Seven-Membered Rings as Precursors to Other Structures

Although the majority of synthetic applications of these types of cycloaddition reactions are aimed toward natural products that contain seven-membered rings, there are several examples in which the ring is ultimately used as a precursor to other structural types. In this section a few illustrative examples of this strategy are shown. Ring-contraction or expansion of a seven-membered ring can be used to gain access to other common ring sizes (Scheme 16).

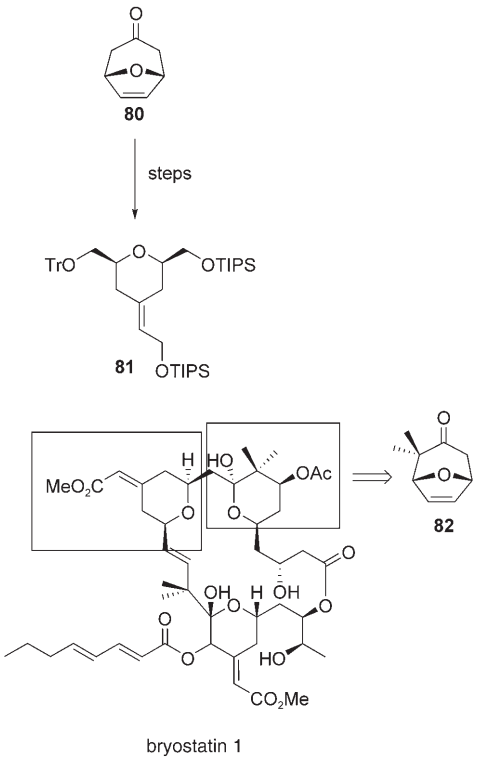


Scheme 16. Other carbocyclic sizes from a [4C+3C] adduct (Harmata).

Harmata utilized an intramolecular oxyallyl cation cycloaddition of **74** to provide access to the tricyclic intermediate **76**. Cleavage of the keto bridge of this adduct provides access to the carbocyclic eight-membered ring of dactylol.[32] In a related strategy, an intermolecular addition between the oxyallyl cation derived from **77** and the constrained diene **78** gave the primary adduct **79**. Skeletal rearrangement of this intermediate provided for a synthesis of sterpurene.[33]

Another tactic that has found application in natural product synthesis is the use of these seven-membered ring intermediates in the synthesis of acyclic or heterocyclic systems, particularly the polyketides. Hoffmann has utilized the oxabicyclic adducts arising from the cycloaddition of furan and oxyallyl cations to gain access to highly substituted pyrans (Scheme 17).

The well-known ether-bridged seven-membered ring **80** (prepared by oxyallyl cation addition to furan) was converted into the pyran **81** through a key cleavage of the olefinic bond. This pyran is a key structural component of the anticancer agent bryostatin.[34] Likewise, the structurally related **82** serves to construct another unit of the bryopyran framework.[34a] In addition to heterocyclic intermediates, acyclic polyols have also been accessed from seven-membered ring intermediates (Scheme 18).

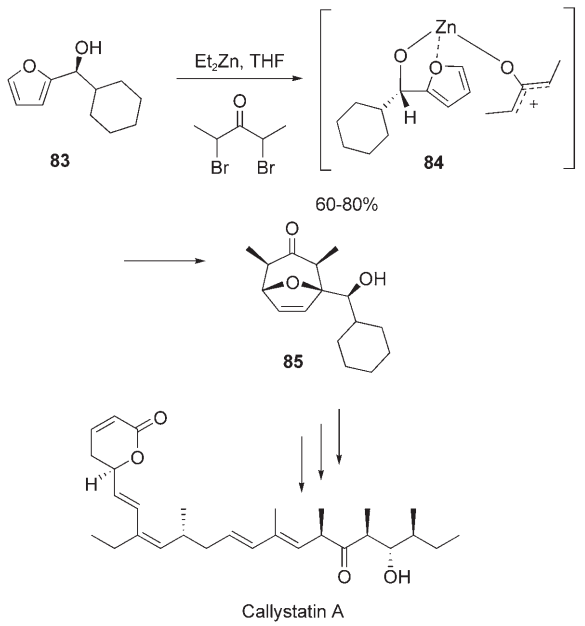


Scheme 17. Bridged seven-membered ring intermediates for pyran natural products (Hoffmann).

Lautens employed a highly diastereoselective addition of an oxyallyl cation to furan carbinol **83** to give **85**; a series of cleavage reactions converted this seven-membered ring into an acyclic portion of callystatin A.[35]

Conclusion

Seven-membered carbocycles continue to present a significant synthetic challenge that is often driven by their presence in complex natural products. These important natural products have catalyzed the development of several new synthetic methods and strategies. Cycloaddition reactions have proven to be extremely effective for the construction of these intermediates and many variations in the cycloaddition theme have been realized. The ready access to some of



Scheme 18. Bridged seven-membered ring intermediates for polyketide synthesis (Lautens).

these seven-membered ring derivatives even makes them suitable intermediates for the preparation of other cyclic and acyclic moieties. The importance of these ring systems will ensure a continued development of new methods and upscaling for their synthesis.

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