Synthetic Strategies towards Therapeutically Relevant Tailored Macrocycles

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Authors’ contributions

This work was carried out in collaboration among all authors. Author AC designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors Subhash and Pinki managed the analyses of the study and also managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The normally used synthetic approaches toward macrocyclization join full scale lactonization, macro lactamization, transition metal catalysed cross coupling, ring-closing metathesis, and click reaction, among others. Picked continuous examples of macrocyclic synthesis of natural products and druglike macrocycles with noteworthy natural significance are highlighted in each class and outline the general engineered systems for the synthesis of macrocycles. The synthesis of macrocyclic compounds incorporating natural products with differing complexities by ring closing metathesis is depicted. Twelve to huge rings that have been orchestrated in moderate to great yields and the synthesis of larger rings as a part of bi-cyclic or poly-cyclic frameworks are likewise depicted in this review.
1. INTRODUCTION

The macrocyclization step is consistently weakened by low yields and regularly requires high weakening conditions to balance entropic loss. In other words, the reduction in entropy responsible for beneficial conformational restrictions to the final molecule comes at a price during synthesis. The examination of macrocyclic structural space requires strategies by which huge number of manufactured macrocycles can be acquired. Due to the auxiliary intricacy of normally happening macrocycles, they are both hard to synthesize or to modify to access close analogs. It is justifiable that such manufactured challenges have brought about the disregard of macrocycles for tranquilize revelation.

Synthetic polymer chemistry was developed before synthetic macrocyclic chemistry. Organic polymers cannot be synthesized without having macrocyclic compounds as side products and vice versa. The preferential formation of only one product often depends on the conditions of the reaction. During polymerization reactions, thousands of new bonds are formed while cyclization reactions result from only a few bonds are formed [1,2]. In the synthesis of macrocyclic ligands, different macrocyclic compounds can be formed at the same ratio of starting materials. For example, starting from diamine and dihalide (or ditosylate) at a 1:2 ratio, it is possible to obtain macrocyclic ligands or: 20 or more new bonds. Formation of a particular structure depends on reaction conditions such as template effects, temperature, concentration of starting materials, and other factors. Up to now, cryptands, bscrown ethers, supercryptands, cylindrical polycyclic compounds and cubic compounds have been prepared by direct one-step methods. However, nearly every day additional new and unique structures are added to this list [3,4].

We hope that this review will help in the search for new routes for "cyclo-oligomerization" to form new and unique macrocyclic compounds. Also, it provides information for non-synthetic chemists that will allow them to prepare desired macrocyclic compounds in order to study their physical and chemical properties. The main purpose of this review is to give examples of some of the most important syntheses of macrocyclic compounds and to show the fastest approach to these complicated molecules. A special place in the synthesis of macrocyclic compounds belongs to the synthesis of torands, especially one that is formed from an aromatic ketoaminoaldehyde during a triple cycopolymerization reaction. As of late, metathesis [5,6] has gotten one of the most significant reactions in synthetic organic chemistry. Among others, the ring closing metathesis (RCM) [7,8] has been
successfully applied. The ring closing metathesis reaction has developed as a significant tool for the development of different carbocyclic and heterocyclic ring frameworks of fluctuating size and multifaceted nature. RCM reactions have had an enormous impact in synthetic organic chemistry. Some of the most impressive examples of RCM reactions include the formation of poly functional, large heterocyclic rings that are often challenging or impossible to prepare efficiently by any other synthetic methods. A vast amount of work has been done on the macrocyclization via RCM reaction. Different researchers concerned on various aspects of RCM reactions, optimized reaction conditions and modified the troublesome RCM pathways by alternative RCM reaction mode. They have synthesized a large number of macrocyclic compounds including various naturally occurring compounds and their derivatives.

The word metathesis is derived from Greek for transposition and was coined by Calderon in 1967 [9]. The first observation of a metathesis was reported in 1931 and its mechanism was proposed in 1971 by Chauvin, who described the formation of a metallocyclobutane unit. By 1980, Schrock had isolated the first unimolecular catalyst, but Grubbs’ discovery of air stable Ru-catalysts (1992 and 1995) proved the watershed event in changing the way chemists think about metathesis and helped pave the way for Grubbs, Schrock and Chauvin being jointly awarded the 2005 Nobel prize in chemistry.

In recent years, metathesis [10-14] has become one of the most important tools in synthetic organic chemistry. Among its most successful applications has been the ring closing metathesis reaction (RCM) [15-25] which afford cyclic compounds from diolefinic precursors and the ring closing metathesis reaction has emerged as a valuable tool for the construction of various carbocyclic and heterocyclic ring systems of varying size and complexity.

2. SYNTHETIC APPROACHES TO MACROCYCLES

2.1 Macrocyclization Reactions

One of the difficulties related with the investigation of the macrocyclic system for medicate revelation is the trouble in synthesizing such structures, especially as a sequence of molecules for SAR explanation or to construct screening libraries. As can be surmised from the variety of structures described in the first part, various reasonable engineered courses have in any case been effectively evolved. Certain techniques have demonstrated more flexible than others, including amide and ester coupling, nucleophilic displacement chemistries, ring closing metathesis (RCM), cycloadditions, as were shown for a considerable lot of the specific examples already presented.

Customary systems, for example lactonization and lactamization are among the most standard ways to deal with macrocycle formation [26,27]. The wide assortment of coupling agents accessible from peptide chemistry furnishes the chemists with a significant alternate for macro lactamization [28,29]. As anyone might expect, such strategy is especially Not surprisingly, such methodology is particularly advantageous in the assembly of macrocyclic peptidomimetics, including the range of protease inhibitors described earlier. In one imperative modification, macro lactamization can be effected on an activated solid support where cyclization happens concurrent with discharge from the resin, for example, with an oxime linker, which works basically as a leaving group right now. Such a cyclative discharge technique can demonstrate profitable, as will be additionally talked about later [30].

Various strategies have been created for macro lactonization. The lion’s share of them started from the significant efforts coordinated toward the total synthesis of macrolide characteristic products [31]. These two methodologies have various points of interest: (1) settled sciences and procedures; (2) an assortment of promptly accessible reagents; (3) utility for a wide scope of ring sizes; (4) direct antecedents effortlessly integrated with high decent variety; (5) clear execution in either solid or solution phase. However, not all desired targets lend themselves readily to these methods, which typically require high dilution conditions to prevent formation of dimeric and higher order oligomeric side-products.

An elective sort of "click chemistry," the thiolene reaction, which to date has seen more prominent application in the materials field, was as of late announced as a route to cyclic RGD peptide mimetics (Scheme 1) [32]. The secured straight forerunner 1 was collected either on resin or in
solution. At that point cyclization executed either photochemically (solid phase) or thermally (solution) gave 2. In spite of the fact that the potential for restorative chemistry applications shows up more restricted than the azidealkyne cycloaddition, the reactions occur quickly with comparable or better yields to other solid phase procedures.

In addition to the organometallic chemistry utilized for RCM and click cycloadditions, a number of other such approaches have been developed to successfully access the macrocyclic framework. For example, an interesting alternative chemistry with ruthenium was observed in the construction of macrocyclic toxoids designed to mimic the bioactive conformation of paclitaxel [33]. In this case, the expected RCM of 3 did not proceed, but rather a diene-coupling reaction occurred to give the highly bioactive compound 4 (SB-T-2054, Scheme 2). However, the scope of this reaction was not further explored.

Ruthenium complexes were likewise instrumental in another way to deal with macrocyclic structures, specifically those containing a biaryl ether, reciprocal to the S$_{Ar}$ technique previously examined. Ru π-arene chemistry was abused to efficiently shape biaryl ether macrocycles for the preparation of inhibitors of the HCV NS3/4A and the HIV proteases [34,35]. In the typical, though low yielding, arrangement introduced in Scheme 3, the direct forerunner was changed over to the Ru complex 5. At that point arylation was prompted through treatment with an overabundance of strong base to produce macrocycle 6. The ruthenium was thusly efficiently expelled through photolysis. Notwithstanding the formation of biaryl ethers, this reaction can give other biaryl frameworks and thioethers through help of the S$_{Ar}$ procedure [36] Despite the disadvantages of this system, including the utilization of stoichiometric Ru and high dilution to restrict oligomerization, it proceeds by and large in great to excellent yields for macrocyclization and gives simple access to a scope of pharmaceutically appealing structures.

Likewise, a copper-helped process was applied to the synthesis of biaryl ether containing macrocyclic metalloprotease inhibitors (Scheme 3) [37]. The objective molecules 8 were gotten to through the intramolecular reaction of a phenol with a subbed aryl boronic acid 7. Cyclization conditions were sufficiently gentle to endure extra functionalities, for example, amides and esters. In any case, the presence of an extra phenol demonstrated inconvenient and gave <5% of the normal item.

![Scheme 1](image_url)
Heck reactions have been utilized in the synthesis of HCV protease [38] and macrocyclic taxoids just as other natural products [39]. The last applications showed the high intricacy of substrates that this procedure can oblige. For taxoid structures, this course ends up being more effective than RCM, which was languid [40].

In a far superior outline of the intensity of Pd-intervened forms, one considers coordinated actions toward the complete synthesis of complestatin depended on the utilization of an intramolecular Larock indole synthesis to effect macrocyclization (Scheme 4). Precise examinations prompted upgraded conditions for this reaction, opening up another road for the development of complex ring frameworks using palladium chemistry [41].

Balraju and Iqbal utilized the Buchwald-Hartwig C-N coupling reaction for macrocyclization in the
development of peptidomimetics 12 compelled with a diphenylamine linker (Scheme 4) [42]. A similar research group portrayed the utilization of Trost's palladium-catalyzed enyne cycloisomerization as another course to macrocyclic structures of this general kind (Scheme 5) [43]. Use of this chemistry to the diene tripeptidomimetic structure 13 continued to give 14. As opposed to the standard item with two exocyclic double bonds, a conjugated diene with one endocyclic and one exocyclic double bond was acquired. The E-stereochemistry and s-transoid type of the macrocyclic diene was only framed paying small heed to the length of the linker on the alkyne bit of the substrate. Besides, modifications to the position of the reactive functionalities gave the equivalent stereochemical result for 15, regardless of the expanded rigidity nature of the arylalkyne starting material. A comparative response was executed with a dipetidic starting particle, yet in lower yield (28%). The product dienes 14 were exposed to a Diels-Alder response for additional structure elaboration.

Denmark et al. as of late announced an efficient report on a mix RCM/Pd cross-coupling reaction as another course to unsaturated macrolactones (Scheme 5). A pair succession comprising of RCM to form siloxane 17, trailed by a Pd-catalyzed, Si-helped cross-coupling cyclization, if great yields of product 18 as a single stereoisomer. A definite investigation of the second step of this procedure decided the ideal catalyst and solvent while additionally finding that hydrated fluoride ion was required as an activator for best outcomes. Under the upgraded conditions, great yields for the typically very difficult medium ring sizes of 11-14 atoms were gotten and high dilution conditions were a bit greater (Scheme 5). This convention was effectively stretched out to the all the more testing synthesis of the benzo-fused macrocyclic lactones 19 too.

![Scheme 4](image-url)
Another possibly amazing procedure that has seen just constrained application to the macrocyclic system is the Wittig reaction and its variants. The development of VCAM-VLA-4 antagonists, in which a carbon chain was filled in for a disulfide linkage in a previous generation of compounds, was empowered through ring conclusion between an aldehyde and a phosphonoglycine moiety (Scheme 6) [44]. Forerunner phosphonate 20 was oxidized with osmium tetroxide/sodium periodate, which gave cleaner conversion than ozone. At that point the
unrefined moderate aldehyde was treated with DBU or another hindered base in methylene chloride to give macrocycle 21. Reduction of the double bond alongside with an appropriate deprotection sequence yielded the target structures. The Wittig reaction was also the cornerstone for a diversity-oriented approach to macrocyclic molecules.

Multicomponent responses (MCR, for example, the Ugi, Biginelli, Staudinger, and Passerini reaction, have experienced a renaissance as scientists keep on looking for methods for quickly assembling complex structures of potential pharmaceutical interest [45,46] Applications to macrocyclic structures are, nonetheless, to some degree restricted, in spite of the fact that the MiB approach depicted is a special case. Domling and change have announced the combination of the Ugi and Passerini type MCR with RCM and portrayed the potential pertinence of this succession for producing libraries of different macrocycles. The methodology for a representative compound is illustrated in Scheme 7, wherein 22-membered macrocycle 26 was delivered after the couple succession starting from acid 22, isocyanide 23, and paraformaldehyde. Along these lines, the 17-membered macrocycle was gotten to 25. In view of the restricted accessibility of the acid and isocyanide compounds for this methodology, strategies for their synthesis from all the more promptly accessible beginning materials were likewise evolved.

2.2 SYNTHESIS OF OXYGEN HETEROCYCLES

Furstner et al. [47] synthesized the 16-membered lactone, precursor of exaltolide, via RCM reaction and they demonstrated that macrocycles can be produced from dienes devoid of any conformational constraint with variable $E/Z$-selectivity's. During their synthesis they treated diene with catalyst. Similarly, they also synthesized a good number of macrocycles (ranging from 12- to 21-membered) with varying $E/Z$-stereoselectivities. But, interesting enough that during the synthesis of 14-membered lactone ($R = $Me) attempts to effect RCM with catalyst to generate double bond at a position gave only 10% yield while double bond at b position gave 72% yield ($E/Z = 96:4$). Later on, Weller group made a systematic investigation on forming 14-membered lactones and lactams with catalyst. Their result showed that RCM to generate double bond at a position ($R = $H) gave highest yield (70%) with $E/Z$ selectivity 87:13, double bond at b position gave a good yield (62%) ($E/Z = 99:1$), whereas the double bond at c position gave a poor yield with no stereoselectivity (50:50) [48]. So, their inference was that the difference in stereoselectivity might be due to the steric effect exerted by the methyl group. These studies also indicated that functional group

Scheme 7
away from the double bond can have significant effect on E/Z stereoselectivity. Furstner envisioned that the formation of stable 5-membered chelate 27 between the ester carbonyl and the Lewis acidic metal of the intermediate alkylidene carbene (Scheme 8) was responsible for low yield to form c double bond as proposed by Grubbs in their problematic cyclization’s of unsaturated amides via RCM reaction [49]. Similarly, the 6-membered chelate 28 formation also lowers the yield. To overcome this problem, Furstner et al. gave a solution by the discovery of binary catalyst system. Diene 29 reacted with for 3-days to afford only 22% of the desired product 30 and starting material was recovered. However, the reaction under identical conditions with 2 eqv. of Ti (O\text{Pr})_4 afforded 40% of 30. Reaction at 40°C with Ti (O\text{Pr})_4 gave 55% yield [50]. This indicated the influence of added titanium tetraisopropoxide, though the nature of the effect to the mixture was not clear. It may be thought that added isopropoxide interferes the formation of very less reactive chelate or destabilizes the chelate.

They applied this methodology [50] also to the total synthesis of the macrolide (-)-gloeosporone (33). The intermediate 31 did not react with catalyst, (Scheme 9). However, in the presence of titanium tetraisopropoxide it afforded desired cyclic product 32 (E/Z = 2.7:1).

Use of catalyst in RCM reactions provide mixtures of E and Z isomers and the E/Z selectivity depends on ring size, position of the double bond and nature of the substrate. Again, functional groups [47] far from the double bond can have significant effect on E/Z stereoselectivity. So, it becomes difficult to predict and control the double bond geometry. Therefore, investigations have been made to control the E/Z selectivity. Grubbs et al. [51] investigated by positioning an auxiliary group to one of the double bonds (during the course of the RCM reaction this group will be removed). Their investigation indicated that the use of catalyst gave thermodynamically more stable compound as the major product (Scheme 10) whereas the catalyst gives the kinetically controlled product. It should be noted that for those syntheses where RCM is followed by hydrogenation reaction the E/Z stereoselectivity is not important.

2.3 SYNTHESIS OF NITROGEN, PHOSPHORUS AND SULPHUR HETEROCYCLES

The presence of heteroatoms in the RCM substrates leads to a variety of results [52]. Nitrogen is generally not tolerated unless nonbasic functional groups such as tosylamides or the corresponding ammonium salts are used. Furstner et al. synthesized [53] the azalactone alkaloids where they utilized

**Synthesis of macrocyclic compound by Ring Closing Metathesis**

![Scheme 8](image-url)
the RCM reaction in presence of catalyst. Substrate 36 (R= H) or its ammonium salt failed to cyclize with catalyst, but the corresponding N-Fmoc derivative (R = Fmoc) cyclized smoothly affording the 13-membered ring alkene 37 with Z configuration (Scheme 11).

Encouraged by this result, they attempted [53] the synthesis of epilachnene (39, R=H) containing a Z-alkene moiety. A series of suitable diene substrates bearing different N-protecting groups were treated with catalyst to afford the cyclic product. This time even the ammonium salt reacted, but in all the cases a mixture of E/Z isomers was obtained. Due to this variation in stereoselectivity of the aforesaid RCM they concluded that they were neither in control of the configuration of the newly formed double bond nor they were able to predict it properly Frustner group prepared [54] pyridinophanes by the use of RCM reaction with catalyst. During their synthesis of muscopyridine they noticed the greater ease of formation of the 13-membered ring 41 as compared to the kinetically and thermodynamically handicapped 11-membered analogues from substrates 40 and 42 (Scheme 12).
The cyclic lactam 44 has been synthesized [55] from the acyclic precursor 43 with catalyst (Scheme 13).

3. CONCLUSION

Engineered macrocycles speak to the latest subclass, yet as exemplified in the previous areas, their substance decent variety will be constrained distinctly by our creative mind. Synthetic macrocycles have just made contributions to drug discovery. On proteases, macrocyclization is a worthwhile method to redesign a peptidomimetic ligand in the β-turn conformation reasonable for binding to the
dynamic site of serine, aspartyl, cysteine, and metalloproteases. Thus, macrocyclization is an excellent way to lock out alternative conformations that may lead to liabilities such as side effects or poor bioavailability.

Topologically, macrocycles can cover an expansive surface area in a conformationally confined manner, rather than acyclic small molecules of comparable molecular weight. At an equivalent number of heavy atoms, this is an immediate outcome of their lower number of rotatable bonds. We accept that this special property of macrocycles makes for a rotatable bonds. We accept that this special property of macrocycles makes for a conduct that is nearer to small molecules than their molecular weight would really anticipate. As a result, it seems that macrocyclization extends the acceptable range of molecular weight and polarity toward higher values.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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