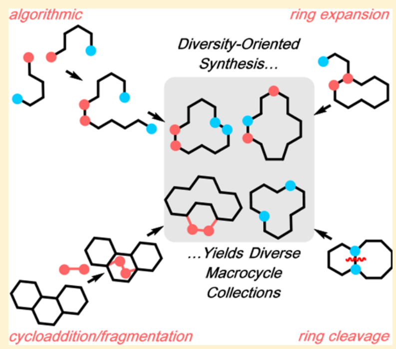
CHEMICAL REVIEWS
Review
Cite This: *Chem. Rev.* 2019, 119, 10288−10317
pubs.acs.org/CR

Strategies for the Diversity-Oriented Synthesis of Macrocycles

Kim T. Mortensen, Thomas J. Osberger, Thomas A. King, Hannah F. Sore, and David R. Spring*

Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, U.K.

ABSTRACT: Macrocycles have long been recognized as useful chemical entities for medicine, with naturally occurring and synthetic macrocycles clinically approved for use as prescription drugs. Despite this promise, the synthesis of collections of macrocycles has been historically challenging due to difficulties in the formation of large rings. Diversity-Oriented Synthesis (DOS) emerged in the early 2000s as a powerful strategic solution to the construction of diverse molecular libraries. This review details the various strategies developed within the field of DOS for the synthesis of macrocycle libraries, utilizing modern synthetic methodology to deliver structurally diverse collections of macrocyclic molecules, and the exploration of their therapeutic potential. Section 1 of this work details the use of algorithmic strategies and is divided into Build/Couple/Pair, Advanced Build/Couple/Pair, Initiate/Propagate/Terminate, Fragment-Based Domain Shuffling, Two-Directional Synthesis, and Successive Ring Expansion. Section 2 covers strategies based on ring distortion reactions, including Sequential Cycloaddition/Fragmentation, Ring Expansions, and Miscellaneous.



CONTENTS

1. INTRODUCTION

Nature has been an important source of bioactive macrocycles (cyclic molecules containing more than 12 covalent connected atoms),[1−4] compounds which have had a tremendous effect on human lives over the recent decades. Currently, there are more than 100 drugs approved or in clinical development which involve macrocyclic scaffolds as the bioactive component.[4−7] These molecules often display high-affinity binding, and they are able to occupy areas of chemical space that are not normally covered by smaller molecules. Macrocyclic compounds are conformationally preorganized, due to the restricted rotation within the molecules, but are not completely rigid and therefore offer lower entropic costs of binding[1,4,5] without compromising on the flexibility required to form optimal attachments with the site of interest.[8] This feature has been utilized by nature; a considerable number of natural products, for example vancomycin (isolated from *Amycolatopsis orientalis*[9]) and erythromycin (isolated from *Saccharopolyspora erythraea*[10]), contain a macrocyclic core (Figure 1).[1−4]

Upon binding to a biological target, the molecule is shaped into its bioactive conformer, and due to the restricted rotation imparted by the macrocycle, fewer possible conformers exist. Lower entropic costs and desirable flexibility are not the only benefits of macrocycles in the biomedical field; macrocyclization of linear molecules has also been proven to improve the stability of those compounds in physiological conditions.[1,4,11] Macrocyclic compounds have been shown to be a consistently useful source of hits for inhibitor and probe discovery as protein targets become increasingly more challenging.[12−15] For example, this family of compounds is attractive as it offers opportunities to modulate macromolecular processes by inhibition of protein−protein interactions (PPIs).[16−20] Protein−protein binding interfaces are often relatively "flat" and large compared to small molecule binding pockets, and thus the majority of small molecules consists of poor inhibitors of PPIs.[21] Macrocyclic "stapled" peptides have also proven efficient PPI inhibitors,[21−23] but this field is beyond the scope of this review.

Despite their proven utility, the development of synthetic macrocyclic compounds has been hampered by cumbersome synthetic approaches and nondruglike properties.[4] Consequently, there is an urgent need to develop more cost-efficient

Special Issue: Macrocycles

Received: February 4, 2019
Published: June 20, 2019

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

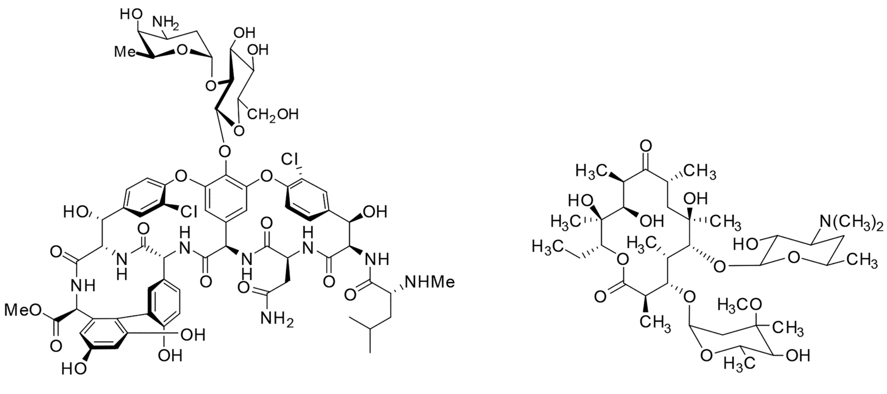


Figure 1. Structure of macrocyclic compounds found in nature.

and effective synthetic strategies which produce libraries of macrocyclic candidates for discovery. The research community has responded by utilizing established techniques to synthesize macrocyclic libraries, as well as developing new methods, including DNA-encoded macrocycle libraries,[24−28] cyclic peptide libraries via SICLOPPS[29] or enzymatic macrocyclization,[30] and multicomponent macrocyclization,[31−35] which have been extensively discussed elsewhere. One technique developed and applied extensively for nearly two decades is diversity-oriented synthesis (DOS). DOS, conceptualized in the early 2000s by the Schreiber lab,[36,37] is a strategy driven by the deliberate, simultaneous, and efficient synthesis of a library of small molecules with a high degree of diversity across their molecular scaffolds and with a high degree of complexity, for example presence of chiral centers, which lead to a better coverage of chemical space.

DOS differs from traditional target-oriented synthesis in that the goal of the synthesis is to generate structurally diverse and complex molecules. Structural diversity is generally assessed by four principal components:[38] 1) Appendage diversity (or building-block diversity) - variation in structural moieties around a common skeleton; (2) Functional group diversity - variation in the functional groups present; (3) Stereochemical diversity - variation in the orientation of potential macromolecule-interacting elements; and (4) Skeletal (scaffold) diversity - presence of many distinct molecular skeletons. Of these, skeletal diversity is the subject of the most focus, because the bioactivity of a compound arises primarily from the molecular scaffold and the positioning of any side groups. A smaller collection with high molecular diversity is regarded as superior to a larger, single-scaffold library in terms of diversity of biological function due to a broader coverage of chemical space.[39,40] Consequently, instead of being focused on achieving activity toward a single biological target, DOS procedures produce broadly diverse libraries which result in the possibility of screening a single library against any number of biological targets.

The purpose of this review is to offer a comprehensive overview of the different library design strategies that have been utilized to generate libraries of highly diverse macrocyclic compounds. This review is limited to DOS approaches to macrocycle synthesis published between 2001 and 2017. In many of the studies discussed, traditional and modern macrocyclization reaction methodologies were utilized and have been discussed in detail in recent reviews.[3,41] Peptide macrocyclizations, including "stapled" peptide technologies, were not covered in this work as reviews can be found elsewhere.[42,43] This review is organized into the following topics: Build/Couple/Pair, Advanced Build/Couple/Pair, Initiate/Propagate/Terminate, Fragment-Based Domain Shuffling, Two-Directional Synthesis, Successive Ring Expansion, Sequential Cycloaddition/Ring Cleavage, Ring Expansion, and Miscellaneous.

2. ALGORITHMIC STRATEGIES

2.1. Build/Couple/Pair

One popular systematic synthetic approach to generating diverse molecular libraries is the three-phase build/couple/pair (B/C/P) strategy (Figure 2).[44] In the "build" phase,

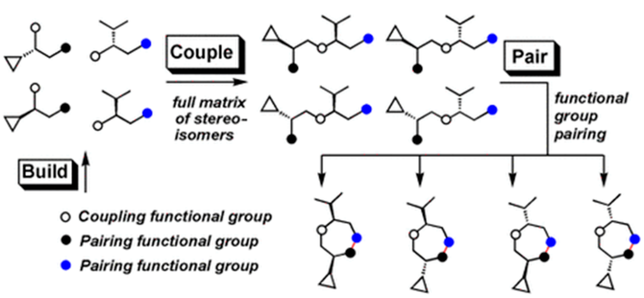


Figure 2. Illustration of the general build/couple/pair strategy for diversity-oriented synthesis. Adapted with permission from Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48. Copyright 2008 Wiley-VCH.[44]

building blocks are synthesized which are then connected together intermolecularly in the "couple" phase. The final "pair" phase involves an intramolecular functional group pairing[45] designed to introduce high molecular diversity. This approach is attractive for its modular nature and takes advantage of building blocks containing orthogonal chemical handles. To further expand the number and complexity of generated scaffolds, variation of building blocks and emphasis on diversity-generating reactions in each phase is crucial. The B/C/P algorithm has been a pioneering strategy for the generation of biologically-relevant small molecule libraries, which have afforded several bioactive compounds and probes for elucidating biological phenomena.[46−56] Furthermore, this systematic approach was applied to the synthesis of a collection of biaryl and bis(aryl)metal-containing medium rings.[57,58]

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

In the context of macrocycle synthesis, the pair phase is the macrocyclization of a linear precursor. Due to their versatility and robustness, azide−alkyne cycloaddition (AAC) and ring-closing metathesis (RCM) have become popular macrocylization methodologies for use in macrocycle library synthesis (Figure 3).

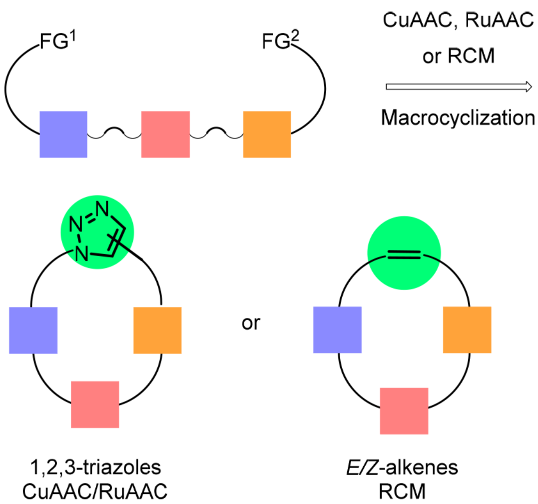


Figure 3. A general illustration of the two (AAC and RCM) most commonly applied macrocyclization strategies. FG = functional group.

Synthesis of 1,2,3-triazoles was revolutionized by the discovery of the copper-catalyzed azide−alkyne cycloaddition (CuAAC) to selectively afford the 1,4-disubstituted triazoles under mild conditions in 2002, by Meldal and Sharpless independently.[59,60] Since its discovery, CuAAC has been used for an extensive range of applications in different fields of research.[61,62] Three years later, the first selective synthesis of 1,5-regioisomer was reported using ruthenium-based catalysts.[63,64] This transformation is therefore commonly known as ruthenium-catalyzed azide−alkyne cycloaddition (RuAAC) and also found to be extensively useful.[65] Finally, ring-closing metathesis has been utilized in countless applications but has been especially powerful in macrocycle synthesis due to the work of Grubbs and others on ruthenium catalysts.[66−68]

In their pursuit to generate bioactive macrolides, Schmidt et al.[69] devised a strategy by which they could selectively integrate multiple substituents with control over stereochemistry (Figure 4, **4-1**, **4-2**, and **4-3**). In the "build" phase, various hydroxy acids were synthesized with various substitution patterns and stereochemistry. A subset of these hydroxy acids was coupled to a solid-support via their free alcohol group. The library synthesis was initiated by coupling between pairs of the hydroxy acids via ester bond formation to provide the linear macrocyclic precursors. Terminal deprotection of the ester linkage product revealed both a carboxylic acid and a free hydroxyl group (**4-4**). These two functionalities were then paired together under Yamaguchi conditions to afford a library of 13- and 14-membered lactones (see, for example, **4-5** and **4-6**). It was found that the monomer used to connect to the macrobeads had a pronounced influence on the yield of the cyclization step. High diversity and broad substitution pattern were achieved by this strategy.

Marsault et al.[70] envisioned a B/C/P DOS strategy as a tool to exemplify the synthesis of and to introduce diversity to potent macrocyclic peptidomimetic antagonists against the human motilin receptor (*h*MOT-R).[71] The compounds were based upon a tripeptide that was linked together via a nonpeptidic tether group through a "head-to-tail" approach (Figure 5). The versatility, low cost, and commercial availability of both enantiomers of natural and non-natural amino acids quickly generated an extensive range of diverse macrocycles. Additional diversity was introduced by varying the ring size of the macrocycle by using different tether groups. Taking advantage of solid-phase synthesis and a semilabile thioester, the tripeptides were synthesized (**5-1**), and a tether (**5-2**) was attached to the *N*-terminal nitrogen (**5-3**). The authors employed Fukuyama-Mitsunobu alkylation or reductive alkylation to attach the tethers via either hydroxyl groups or aldehyde functionality, respectively. The tether group also contained a protected amine which was then revealed to allow macrolactamization, mediated by a silver salt. The generated compound library comprised 14- to 19-membered rings, exemplified by **5-4**, **5-5**, and **5-6**. It was found that linear precursors containing D- and L-amino acids afforded higher yield in the macrolactamization step compared to their homochiral counterparts, which was presumed to be due to a prefolded conformer. It was postulated that silver salts both activated the thioester and facilitated cyclization by interacting with the amino acid residues to encourage prefolding of the precursor.

Luo and Schreiber used a gold-mediated [3,3]-sigmatropic rearrangement of propargyl propiolate (Figure 6, **6-1**) to afford the lactone intermediates **6-2** followed by trapping with nucleophilic alkenols (**6-3**) to access building blocks of type **6-4**.[72] By incorporation of terminal alkenes in the appendages of the nucleophilic alcohol, the authors primed the linear ester for a RCM "pair" phase macrocyclization. Gold catalysts afford advantages of superior π-acidity, air and moisture stability, functional group compatibility, and often being able to operate under mild conditions.[73−78] Good to excellent yields were

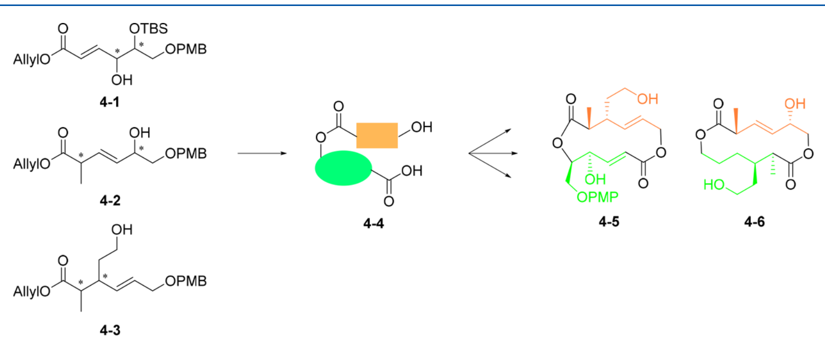


Figure 4. Schmidt et al.[69] utilized enantiopure hydroxy acids in an effort to generate macrolides. PMP = *p*-methoxyphenyl.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

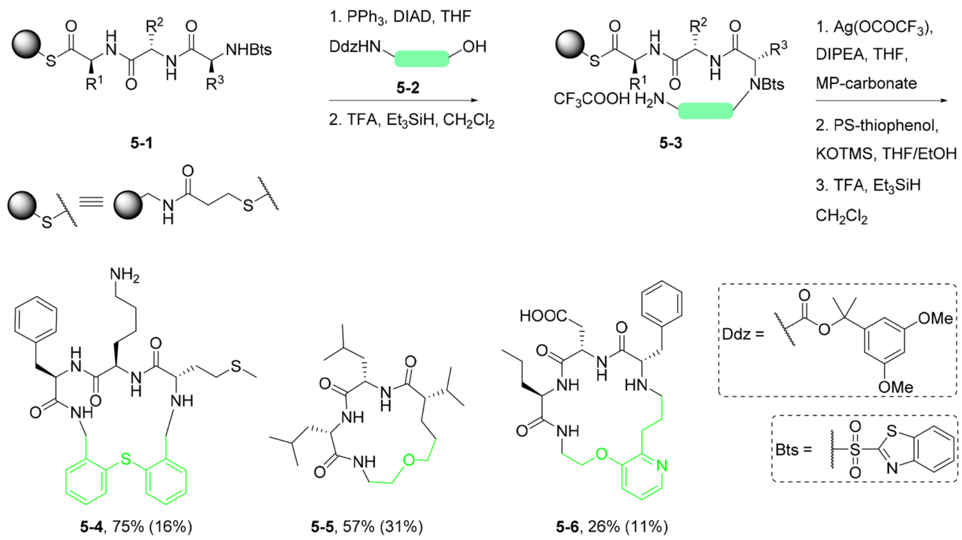


Figure 5. Generation of peptidomimetic antagonists against *h*MOT-R by Marsault et al.[70] Yields in parentheses indicate overall yield, MP-carbonate = supported resin, PS = polymer-supported.

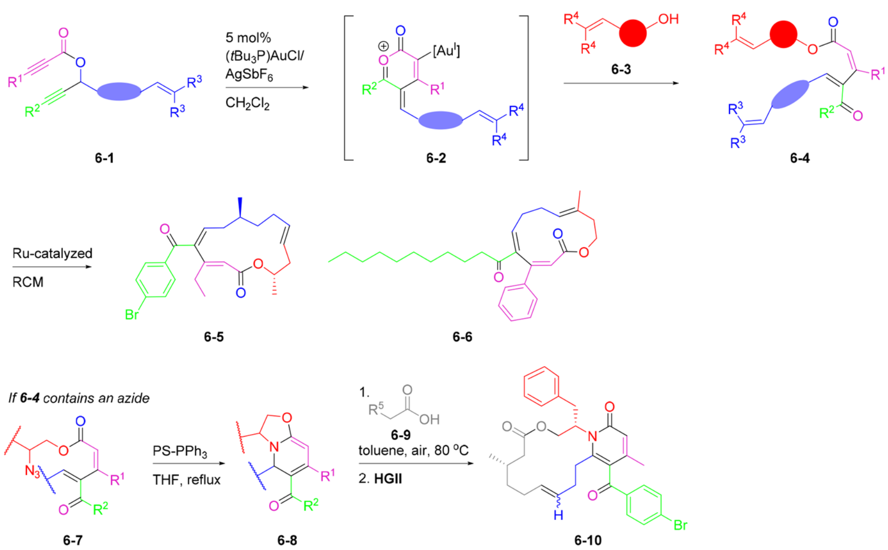


Figure 6. A gold-catalyzed [3+3]-sigmatropic rearrangement primed structures for macrocyclization by Luo and Schreiber.[72] PS = polymer-supported.

obtained by RCM conditions to generate 12-, 14-, and 15-membered rings with varying *E*/*Z* ratios (see examples in Figure 6, **6-5** and **6-6**). The authors envisioned that having an azide in **6-3** could undergo intramolecular functional group pairing. **6-7** was treated under thermal Staudinger conditions to afford the corresponding iminophosphorane that underwent an intramolecular aza-Wittig reaction and subsequently an aza-6π-electrocyclization cascade reaction to form cyclic ketene *N*,*O*-acetals (**6-8**). The *N*,*O*-acetals were ring-opened upon treatment with unsaturated carboxylic acids (**6-9**) to afford 2-pyridones. The primed precursors gave rise to 2-pyridone-containing 12- and 14-membered macrocyclic lactones (see example in Figure 6, **6-10**) by the treatment of Hoveyda-Grubbs' second generation catalyst, **HGII**. This strategy provides a high level of modularity and diversity with the incorporation of functionalities for further exploration.

Wingstrand et al. identified that macrocyclization could be achieved by bridging a pair of nucleophilic groups, such as in a diol, with a bis-electrophilic linker, such as carbonate, sulfite, or phosphate.[79] Starting from a monoprotected diol, **7-1** (Figure 7) was functionalized via an ester formation with **7-2** to afford **7-3**. The free diol could be extended through the use of a diverse set of bifunctional reagents which then allow for macrocyclization via the addition of a linking moiety (**7-4** and **7-5**). This linkage diversity strategy was further extended by transforming the diol functionality into the corresponding dialdehyde or diiodo compounds. This effectively reversed the polarity of the system, which could now be bridged via bis-nucleophilic linkers. Dialdehydes were treated with benzylamine in the first reported example of reductive alkylation macrocyclization with the example of **7-6**. This approach is particularly interesting as it offers the chance to introduce a synthetic handle for further elaboration. The diiodo compound was cyclized using radical chemistry to form a cyclic sulfide. 16- and 17-membered macrocycles were successfully synthesized in this work, which was further extended the following year to include a greater range of ring sizes and a new diol macrocyclization linker based upon malonates.[80]

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

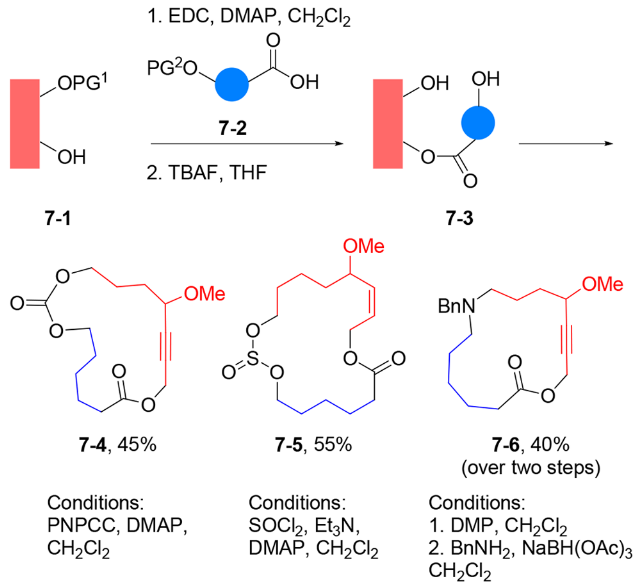


Figure 7. Wingstrand et al. integrated different linkages via a reagent-based approach.[79] PNPCC = *p*-nitrophenyl chlorocarbonate, PG = protecting group.

Grimwood et al. explored the powerful ring-closing enyne metathesis macrocyclization (RCEYM) reaction starting from an inexpensive and commercially available glucal building block (Figure 8).[81] Glucal was subjected to various reaction conditions to provide a primary and secondary alcohol, which was mono-alkylated to afford proparagyl ethers **8-1** and **8-2**. These building blocks were subsequently acylated with unsaturated carboxylic acid **8-3** with the outcome of the corresponding esters (**8-4** and **8-5**). By a calculated incorporation of alkyne and alkene functionalities during the "build" and "couple" phases, each linear macrocyclic precursor was poised for RCEYM macrocyclization. This was accomplished by Grubbs' second generation catalyst (**GII**) under an ethylene atmosphere to afford 12- to 18-membered rings, exemplified by **8-6** and **8-7**.

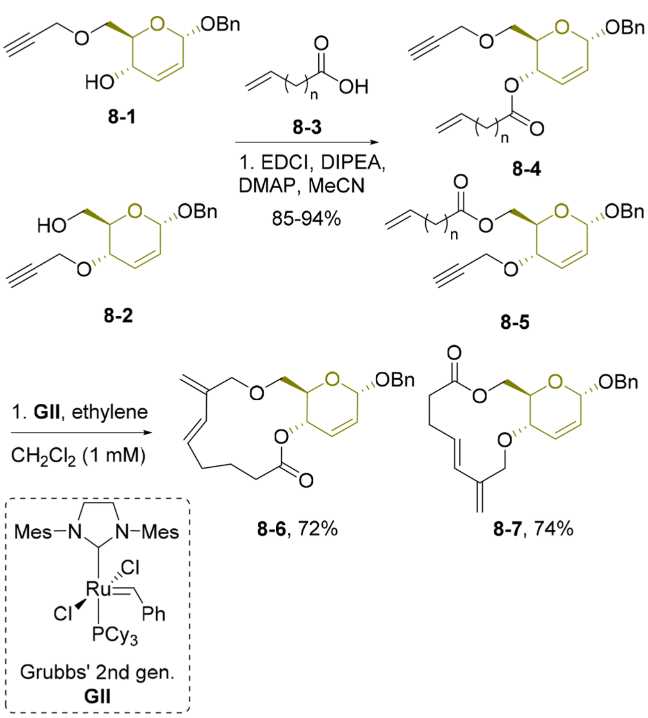


Figure 8. Modified glucals allowed Grimwood et al. to generate stereochemically rich compounds.[81]

Marcaurelle et al. devised a highly robust aldol strategy to increase skeletal diversity of macrocyclic compounds by introducing several stereocenters in the "build" phase.[82,83] These products were coupled to both L- and D-alaninol by amide coupling followed by amide reduction to provide the complete matrix of all eight stereoisomers (Figure 9, **9-1**). This quickly allowed for the incorporation of stereostructure/activity relationship (SSAR) in the compound collection. Various macrocyclization ("pair") strategies were employed, and by a deliberative incorporation of functionalities in the appendages. Nucleophilic aromatic substitution (S_NAr) macrocyclization strategy was used to generate 8- and 9-membered rings, CuAAC and RuAAC were used to generate a 12- or 13-membered ring, and finally RCM was used for the 14-membered ring. In the latter case, the produced *E*/*Z* macrocycles were hydrogenated to afford the fully saturated macrocyclic scaffolds. The generated scaffolds were later used to synthesize a combinatorial library by "post-pair" modifications as indicated in Figure 9. The scaffold synthesis commenced by diversification of the secondary amine and the internal secondary alcohol group (after a silyl-deprotection step) with functionalities to promote the macrocyclization (CuAAC/RuAAC and RCM). To explore the versatility and efficiency of azide−alkyne cycloadditions, the amine was acylated with an azido-containing acid, and the alcohol was alkylated with propargyl bromide to generate the 1,2,3-triazole macrocyclic precursor (**9-2**). The cycloadditions performed well with under CuAAC (PS-$CuPF_6$) and RuACC ($[Cp*RuCl]_4$) conditions to afford 13- and 12-membered rings, respectively, on a multigram scale. The authors observed that *syn*-aldol substrates provided higher yields than *anti*-aldol substrates in the RuAAC cyclization. The opposite was observed for the CuAAC cyclization. For the RCM macrocyclization approach, 14-membered rings were obtained by acylation of the amine with both enantiomers of 5-nitro-2-(pent-4-en-2-yloxy)-benzoic acid and allylation of the secondary alcohol with allyl bromide to afford **9-3**. The terminal alkenes were joined together under Hoveyda-Grubbs second catalyst conditions to provide *E*/*Z* macrocycles. A strong stereochemical dependency was observed to affect the efficiency of the macrocyclization, and modified conditions were necessary to cyclize the *syn*-aldol substrates. With the molecular scaffolds in hand, the combinatorial synthesis on solid support was conducted and thereby generated over 30,000 compounds including compounds **9-4** and **9-5**. Within the 30,000 generated combinatorial compounds are also the 8- and 9-membered ring scaffolds. The authors reported that they were able to generate 14,400 compounds from only 16 RCM scaffolds. The aforementioned hydrogenation of the RCM product revealed an aniline functionality as an extra handle for functionalization. Principal moment of inertia (PMI) analysis indicated that the RCM-derived compounds provide the most spherelike molecular shape out of the compounds reported. Furthermore, the authors went on to identify several low micromolar HDAC inhibitors (BRD-4805, **9-4**, Figure 9) from this library.

This aldol-based B/C/P strategy has laid the ground for an impressive body of work by both the Marcaurelle and Schreiber groups on the generation of diverse libraries. In 2011, the Marcaurelle group published a new RCM strategy to generate

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

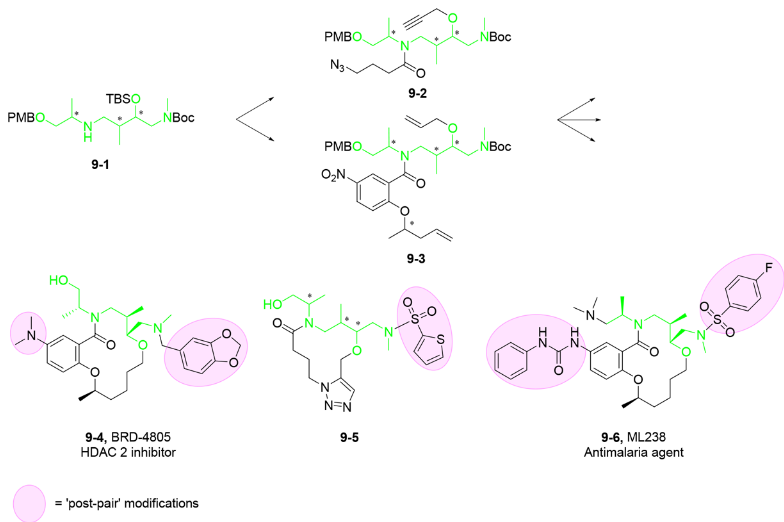


Figure 9. Marcaurelle et al. devised the use of stereochemically dense building blocks for a dual stereostructure/activity relationship (SSAR) study and elaborated with combinatorial library generation.[83]

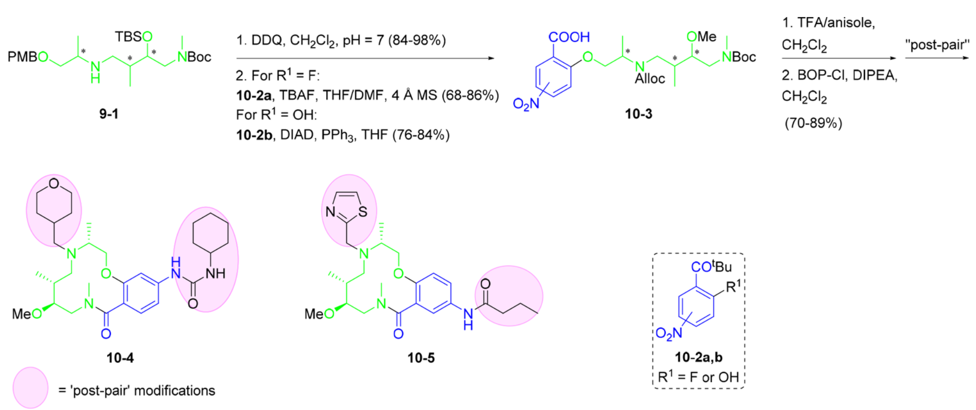


Figure 10. Fitzgerald et al. generated 12-membered rings by first using a S_NA "coupling" phase followed by a lactam macrocyclization "pair" step.[87]

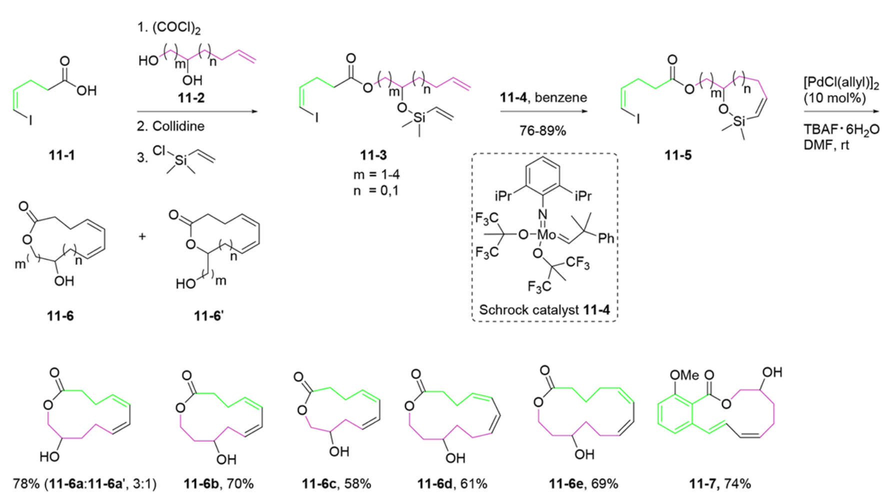


Figure 11. Synthesis of polyunsaturated macrolactones from siloxane **11-5**.

13- to 18-membered macrolactams. This was mediated by the key incorporation of 2-fluoro-4-nitrobenzoic acid which could be functionalized using commercially available alkenols via a S_NAr reaction.[84]

Marcaurelle and Schreiber later provided evidence that the saturated macrocycles showed activity against malaria, and further SAR studies were performed and found a potent hit compound ML238 (Figure 9, **9-6**).[85] Recently, the Schreiber group investigated analogues of ML238 to improve its activity and pharmacokinetic profile.[86]

The aldol-based starting point was further extended into a "head-to-tail" cyclization approach by the Marcaurelle group to

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

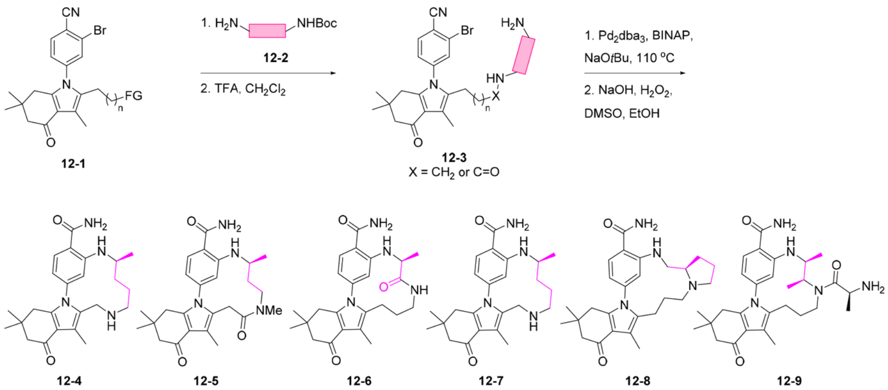


Figure 12. Pfizer scientists described the synthesis of tetrahydroindolone-containing macrocycles to target Hsp90 inhibitors.[89−92]

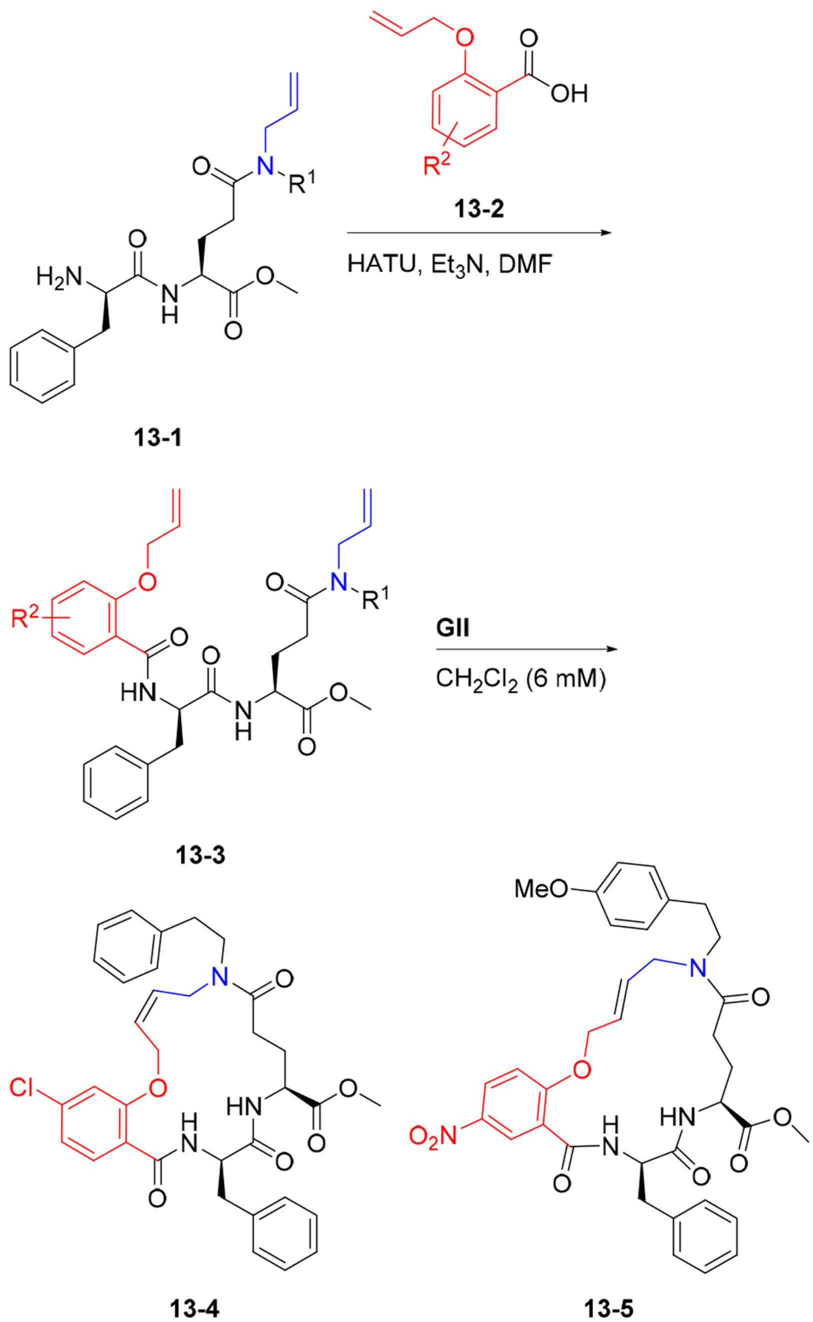


Figure 13. Heckrodt et al. devised a B/C/P DOS strategy to provide 17-membered rings by a RCM step.[99]

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

generate 12-membered rings given by examples **10-4** and **10-5** (Figure 10).[87] Changing to a "head-to-tail" cyclization protocol allowed the authors to include all of the stereocenters inside of the generated macrocycle and lower the number of rotational bonds present. Initially, a S_NAr macrocyclization strategy was attempted but was unfortunately proven to be low yielding. Therefore, the authors reversed the strategy. Thus, first they attached **10-2** in a "couple" phase to **9-1** with the aim of producing compounds with the overall structure of **10-3** and then applied a successful lactam macrocyclization approach. These compounds were found to occupy a distinct region in three-dimensional space. Despite the promising PMI results, the "head-to-tail" products were found to be much more rodlike compared to the previous[83] RCM-derived macrolactams. In analogy to the previous approach, the installed nitro groups were hydrogenated to the corresponding amine and used as an anchor group for solid-phase synthesis. A combinatorial library comprised 7,936 12-membered macrocycles was generated by "post-pair" functionalization (library examples include **10-4** and **10-5**).

Despite being well represented among natural products and biologically significant molecules, polyunsaturated macrolactones represent a significant synthetic challenge due to the high strain imparted on the macrocycle by the alkene units. Denmark and co-workers reported an elegant and general solution to the synthesis of polyunsaturated lactones based on the intramolecular cross-coupling of a vinyl iodide to a siloxane-based alkene partner as the key macrocyclization step (Figure 11).[88] The substrates for cross-coupling development were constructed in a build-couple sequence to form linear compounds **11-3**, which were then subjected to RCM with Schrock catalyst **11-4** to afford siloxane cross-coupling precursors **11-5**. The "pair" phase involved Pd-catalyzed intramolecular cross coupling to form macrocycles **11-6** and required extensive optimization. Careful control of the solvent and fluoride hydration level was required to avoid translactonization to **11-6′** under the basic conditions, and syringe pump addition of substrate was used to maintain low effective molarity and avoid high solvent volume conditions. Under these optimal conditions, a series of 11- to 14-membered, diene-containing macrocycles (**11-6a** to **11-6e**) could be formed. A similar scheme was also applied to the synthesis of benzo-fused macrocycle **11-7**.

In a series of publications, Zapf et al. at Pfizer described their work toward targeting the chaperone heat shock protein 90 (Hsp90) through macrocyclic *o*-aminobenzamides (Figure 12).[89−92] Inhibition of this protein results in inhibition of cell growth and apoptosis[93,94] and has been exploited in cancer therapy.[93,95] Zapf et al. explored the incorporation of a tetrahydroindolone moiety earlier reported to afford low-nanomolar Hsp90 inhibitors.[96] The authors took advantage of the versatile and modular Buchwald-Hartwig amination to synthesize a range (11- to 14-membered) of macrocyclic Hsp90 inhibitors. The alkene-functionality of the tetrahydroindolone-based starting materials was modified to the corresponding alcohols, aldehydes, ketones, or carboxylic acids (**12-1**) by a collection of functional group interconversions. In the "couple" phase these functionalities were either used directly or further modified to afford linear precursors primed for cross-coupling macrocyclization. Alcohols were transformed into the corresponding mesylates followed by displacement. Aldehydes and ketones were reacted with mono-Boc protected aliphatic diamines (**12-2**) under reductive amination conditions, whereas carboxylic acids were coupled with diamines to afford the corresponding amides. Unfortunately, the tertiary amine originating from reductive amination was found to contribute negatively to the hERG activity of the compounds, a general trend.[97,98] As a result of this observation, the tertiary amines were acylated or an alternative reductive alkylation strategy was used, whereby an amine was first introduced and then coupled with terminal-*N*-Boc-protected amino carboxylic acids. After deprotection of the Boc group (**12-3**), the free amino group and the 2-bromobenzonitrile were paired under Buchwald-Hartwig amination conditions. Following this, bioactive *o*-aminobenzamides were synthesized by "post-pair" hydrolysis of the aryl nitrile (**12-4** to **12-9**). The rigidity of the tether was found to be crucial for the activity of these compounds, as evidenced by the most potent compound in this series, **12-9**, containing two, rotationally restrictive, methyl substituents and acylated with alanine.

In an effort to synthesize analogues of biologically active macrocycles, Heckrodt et al. developed a synthetic strategy to efficiently generate 17-membered rings (see Figure 13).[99] In the "build" phase, peptidic building blocks containing an allyl glutamine derivative (**13-1**) were synthesized with the aim of a RCM macrocyclization strategy. The linear peptides were subsequently coupled with *O*-allyl salicylic acids (**13-2**) to afford molecules primed for RCM (**13-3**). Grubbs' second generation catalyst afforded a mixture of *E*/*Z* isomers ($E/Z \approx 3/1$), separable by HPLC (for examples see **13-4** and **13-5**). To extend the molecular diversity of the process, the fully saturated macrocycle was obtained by hydrogenation. Alternatively, the alkenes could also be further diversified via dihydroxylation. Finally, the use of functional groups incorporated on the salicylic acid pair-partner was explored.

Bahulayan and Arun synthesized 12- and 14-membered peptidomimetics using first a multicomponent reaction (MCR) to construct the core scaffold followed by CuAAC macrocyclization chemistry.[100] The authors aimed to incorporate the *β*-ketoamide structure into the molecular scaffold as it is an important motif in medicinal chemistry. The authors generated 14-membered macrocyclic compounds (Figure 14) by stirring bromopropionitrile (**14-1**), acetyl chloride (**14-2**), benzaldehyde (**14-3**, R^1 = H), and propargylated acetophenone (**14-4**, R^2 = $OCH_2C{\equiv}CH$) in the presence of copper sulfate. The bromine (**14-5**) was then substituted for an azide and finally paired with the incorporated alkyne, mediated by copper sulfate catalyst, to generate macrocyclic compounds in overall moderate to good yields (example **14-6**). The highly adaptive MCR allowed for the generation of multiple ring sizes by incorporating the alkyne functionality into the aldehyde component (**14-3**, R^1 = $OCH_2C{\equiv}CH$) or by changing the length of the nitrile source. Modified yne-aldehyde **14-3** afforded 12-membered rings, whereas changing the carbon count of the nitrile provided a broad selection of ring sizes. The authors assessed the druglikeness of the macrocyles by their logP values and found similar values to these seen for antineoplastics, hypnotic, antihypertensive, and anti-infective drug classes. The authors highlighted the modularity of this strategy, by synthesizing various ring sizes and demonstrated the ability of the method to incorporate several peptide bond bioisosteres.[101]

In an exploration of inverse-electron-demand hetero-Diels−Alder reactions, Dong et al. first coupled a series of 2-oxo-4-aryl-but-3-enoate building blocks to enol ether dienophiles via Steglich esterification, followed by intramolecular cycloaddition, to provide a collection of dihydropyran-bridged macrocyclic

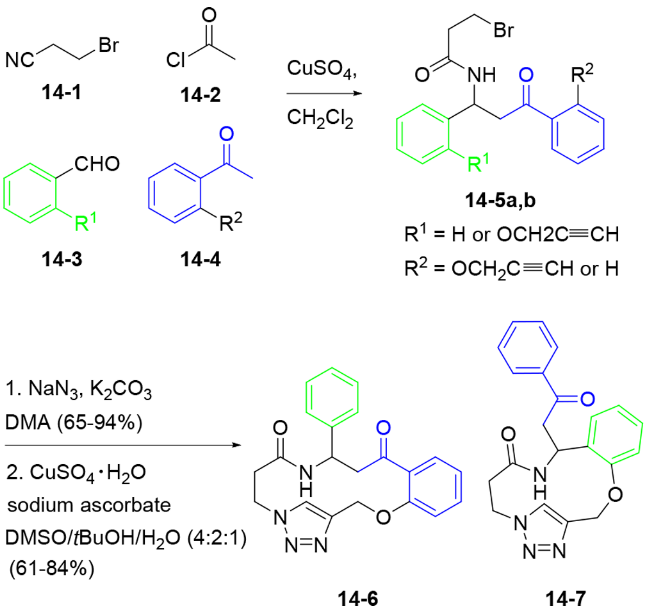


Figure 14. Bahulayan and Arun innovatively applied two successive MCRs to increase structural diversity across peptidomimetic macrocycles.[100]

molecules (Figure 15).[102] The authors explored the effects of varied tether length, aryl substitution, and position of enol ether substitution on macrocyclization via the $SnCl_4$-catalyzed hetero-Diels−Alder reaction using a substrate-based approach. Unfortunately, many reaction conditions evaluated produced mixtures due to poorly selective cyclooligomerization reactions. However, when conducted at low temperature (−78 °C to −20 °C) with 1 mol % $SnCl_4$, Dong et al. were able to isolate single products in moderate yields. In general, the regioselectivity of the Diels−Alder reaction followed known trends based on the placement of the enol ether. In the case of terminally substituted enol ether substrates **15-1**, cyclotrimerization to form macrocycle **15-2** occurred with a short tether (Figure 15A, $n = 1$), between the heterodiene and enol ether dienophile. With tethers of intermediate length ($n = 2$−5, 10) the major isolated products were found to be macrocycles **15-3** possessing two dihydropyran units resulting from cyclodimerization. Extending the tether further ($n = 13$) led to the major isolated product being that of intramolecular reaction (**15-4**).

In the case of internally substituted enol ether substrates **15-5** connected by polyethylglycol (PEG) tethers, the regioselectivity of the Diels−Alder reaction was reversed, as expected based on previous studies. The hetero-Diels−Alder reactions of shorter-chained substrates (PEG1-2, Figure 15B) favored formation of cyclodimerized macrocycles **15-6**. Longer tethers (PEG3-5) resulted in intramolecular cyclization, forming dihydropyran-containing macrocycles **15-7** as the major isolated products. This study demonstrated the subtle interplay between chain length and other parameters in the formation of a diverse family of dihydropyran-containing macrocycles.

Harran et al. have investigated the macrocyclization of native peptides with cinnamyl alcohol-containing templates in an effort to explore the properties such as stability, enhanced membrane solubility, and membrane permeability. Early reports described the formation of complex mixtures of products,[103,104] but further studies with a refined template highlighted the power of this concept for the construction of diverse macrocyclic products from simple peptide starting materials. Synthesis of a library of peptide macrocycles from native, unprotected, linear peptides (Figure 16, **16-1**) was accomplished with the use of template molecule **16-2**, containing an *N*-hydroxysuccinate (NHS) ester handle and a cinnamyl carbonate electrophile.[105] Initial *N*-terminal acylation using the NHS ester appended the template to the peptide (**16-3**). Subsequent treatment of the molecule with Pd^0 salt led to the formation of a π-allyl-Pd electrophile intermediate (**16-4**) which was intercepted in a macrocylization step to afford compounds of type **16-5**, by nucleophiles native to the peptide, including phenol, imidazole, aniline, and carboxylate functional groups. This method led to the generation of diverse macrocyclic compounds (for example **16-5a** to **16-5d**).

In line with the previous section, depending on the conditions, selectivity among these nucleophiles could be achieved (Figure 17). For example, in the cyclization of templated peptide Ala-Leu-Glu-Tyr (**17-1**), subjection to standard conditions of $Pd(PPh_3)_4$ in DMF resulted in preferential alkylation of the carboxylate side chain of glutamic acid to form **17-2**; when Cs_2CO_3 base was added to otherwise unchanged conditions, alkylation of tyrosine was observed, forming **17-3**. Similarly, when the peptide Leu-Gln-Tyr-His (**17-4**) was subjected to $[PdCl(allyl)]_2$ and xantphos with no added base, *N*-alkylation of the histidine imidazole occurred furnishing macrocycle **17-5**; with added Cs_2CO_3, tyrosine phenol alkylation occurred preferentially, affording **17-6**. Notably, for this substrate $Pd(PPh_3)_4$ was ineffective, presumably due to

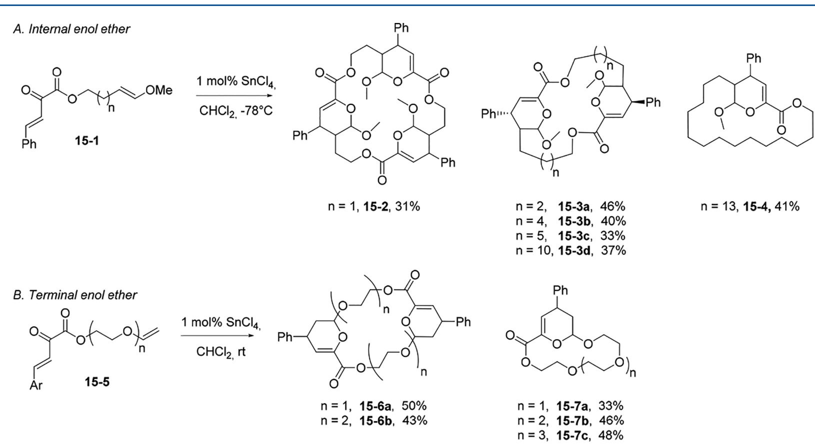


Figure 15. Synthesis of dihydropyran-containing macrocycles via inverse-electron-demand Diels−Alder reactions.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

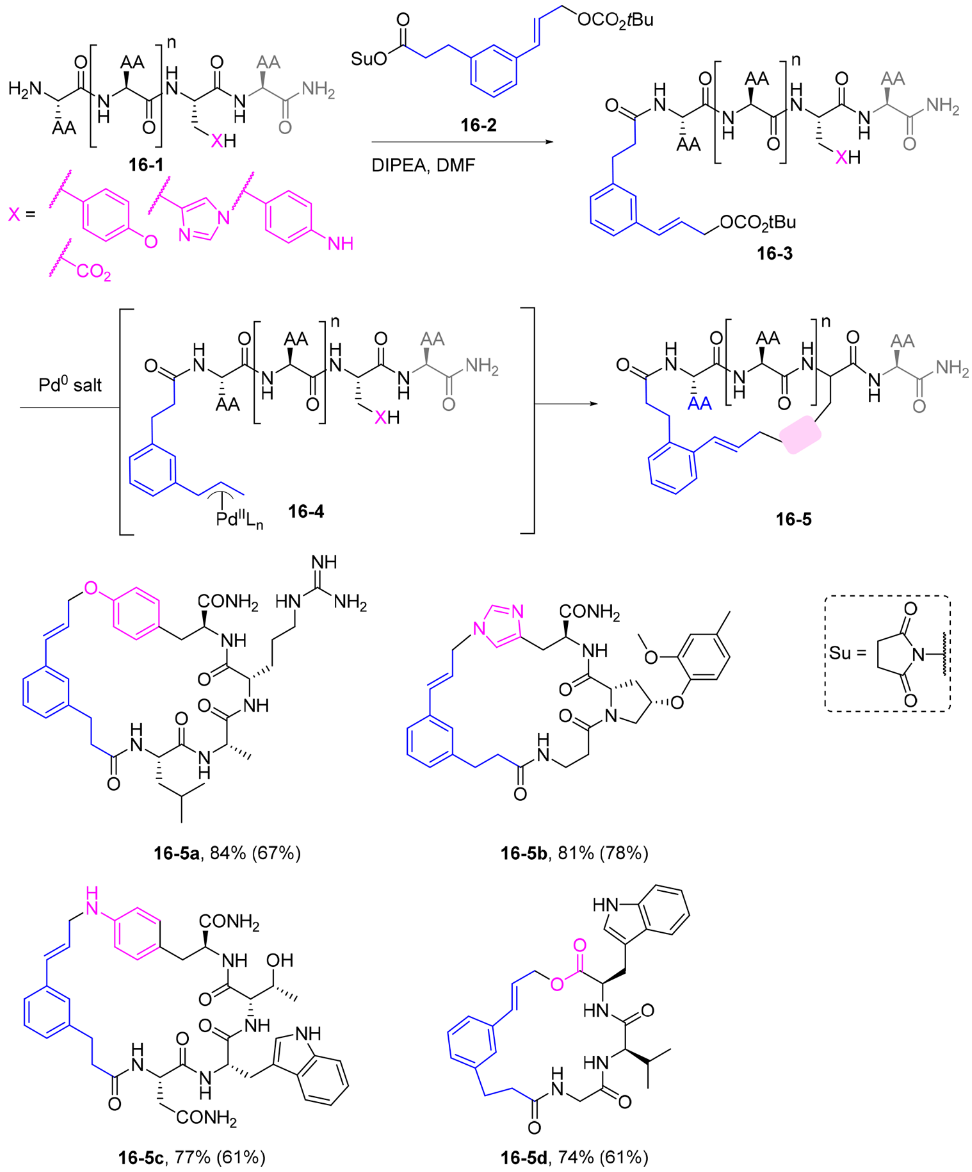


Figure 16. Peptide macrocyclization utilizing template **16-2**. Yields in parentheses refer to those of the initial acylation reaction to afford **16-3**.

catalyst poisoning. The macrocyclization proved remarkably effective even with longer peptide chains, resulting in 38- and 47-membered macrocycles. The resulting macrocycles constructed in this manner were demonstrated to be more stable to *in vivo* proteolysis, than their linear counterparts were.

Applying this same template strategy to peptides containing tyrosine and multiple tryptophan residues, the Harran group has also explored the macrocylization chemistry of both Pd-mediated cyclization and Friedel−Crafts alkylation, via Brønsted and Lewis-acid mediated cyclizations, on the allylic carbonate.[106] These reactions produced mixtures of macrocyclic products with different connectivities, multiple ring sizes, and newly formed C−C, C−O, and C−N linkages based on different nucleophilic sites in the parent peptides. Building on this work, the Friedel−Crafts alkylation of cinnamyl alcohol-containing peptides was further investigated. The authors examined the selectivity and electronic tunability of C−C bond formation over tyrosyl C−O bond formation, regioselectivity and selectivity between different arene nucleophiles (Figure 18).[107] For example, variants of a cis-aryloxy(thio)proline peptide containing a tyrosine moiety were constructed, and their acid-mediated reactivity was explored to demonstrate the tunability of the cyclization reaction. Electronic tuning was possible by changing the tethering functional group between the arene and the proline residue; in the case of ether or thioether tethers, tyrosine alkylation was favored over arene alkylation (for example **18-1a** vs **18-1b**). Similarly, electronic tuning by addition of substituents to the respective arenes was also possible (**18-1a** vs **18-1c**). These macrocyclization reactions afforded several macrocyclic scaffolds (**18-2** to **18-4**) and offered further proof-of-concept for the use of the Friedel−Crafts reaction as a key strategy for macrocycle construction. The authors illustrated that treatment of **18-5** with the Lewis acid $Sc(OTf)_3$ induced indole C5-alkylation of the adjacent tryptophan to form the macrocyclic product **18-6**.

2.2. Advanced Build/Couple/Pair

B/C/P has proven to be a vital approach to generate diverse and complex macrocyclic compounds. As a means to increase this further, the original B/C/P strategy has over time evolved to incorporate multiple/iterative coupling steps to achieve a higher

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

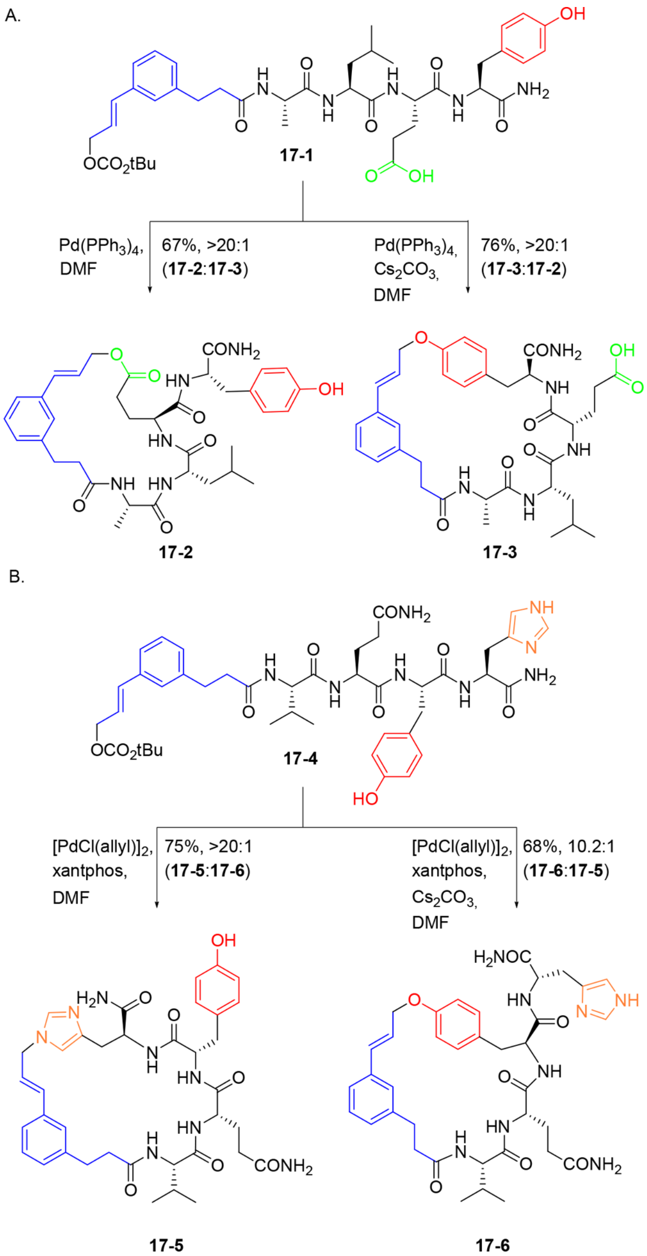


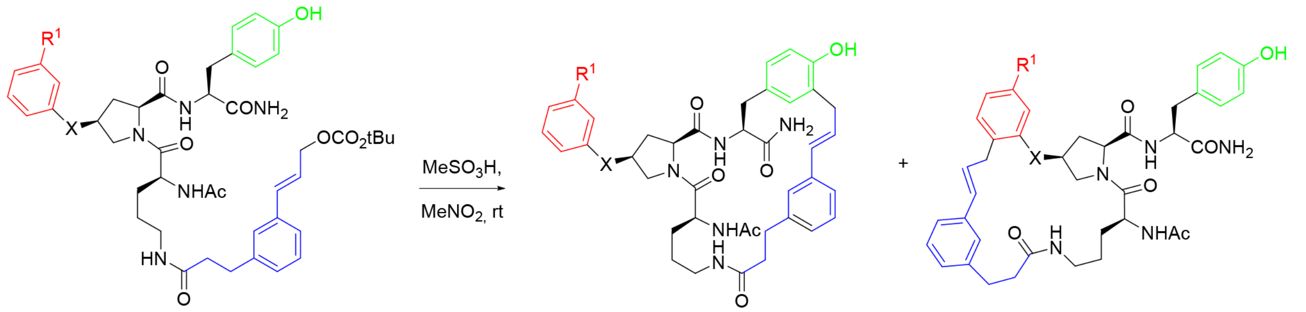
Figure 17. Selectivity switching in the macrocyclization of templated peptides **17-1** and **17-4**.

degree of structural diversity. We have classified this strategy as advanced B/C/P. In 2016, inspired by their previous progress in the field of diversity-oriented macrocycle synthesis, Ciardiello et al. further developed iterative coupling steps (B/C/C/P, B/C/C/C/P, etc.) to generate a library with a high level of skeletal diversity in a low step count (Figure 19).[108] The authors investigated the application of readily available phenolic starting materials containing an electrophilic carbonyl group and a nucleophilic hydroxyl group to the expedient production of novel macrocycles. To successfully generate highly diverse macrocycles, four different coupling substrates were employed: two hydroxyl (not shown) and two carbonyl coupling partners (**19-2** and **19-3**). The phenol was alkylated with azide- or alkene-containing reagents to form compounds of type **19-1** followed by reductive alkylation or amidation using **19-2** and **19-3** provided macrocyclic precursors of type **19-4**, **19-5**, and **19-6**. Incorporation of complementary functional groups primed the structure for CuAAC and RCM macrocyclization to generate B/C/C/P products **19-7** and **19-8**. For the **19-6** compound class, a spacer was introduced to facilitate the generation of B/C/C/C/P products and thereby expand the range of available ring sizes (not shown). The authors introduced an alkene in the appendages to obtain macrocycles via a RCEYM-macrocyclization (example **19-7**). To verify the diversity and modularity of this strategy, the authors performed a proof-of-concept run-through to generate a small series of four macrocycles containing 13-, 18-, and 19-membered rings. RuAAC-conditions had originally been proposed as a fourth macrocyclization process but unfortunately did not provide the desired 1,5-triazole products in this case. The generated molecules contained various vectors, which could be utilized for further functionalization.

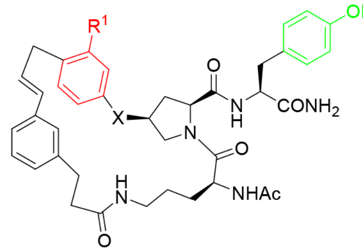
Maurya et al. investigated the use of carbohydrate building blocks as an embedded moiety in macrocycles and developed a more eco-friendly cyclization strategy, illustrated in Figure 20.[109] The authors established eco-friendly versions of the CuAAC and RCM macrocyclization strategies by investigating the use of alternative, "green" solvents. Two sets of starting materials were synthesized: enyne- and azido-alkene-functionalized carbohydrates, **20-1** and **20-2**, respectively. First, the two carbohydrate substrates were linked together using CuAAC conditions to afford compounds of type **20-3**. The macrocycles were then synthesized under RCM conditions (examples **20-4**, **20-5**, and **20-6**). The optimized CuAAC cycloaddition was mediated by CuI in H_2O at 70 °C and provided the triazole-linked linear precursors, which were set up for macrocyclization. A sustainable RCM reaction was performed with Grubbs' second generation catalyst in EtOAc at 75 °C to provide exclusively the *trans*-product. This strategy afforded 13- and 17- to 19-membered macrocycles with high stereogenic center content.

In a recent example of introducing scaffold diversity, Estrada-Ortiz from the Dömling group explored the use of the four component Ugi reaction in the "couple" phase to generate a diverse set of macrocyclic compounds which displayed potential as novel p53-MDM2 inhibitors.[110] A key indole-3-carboxaldehyde derivative was used as the aldehyde component due to the "anchoring" behavior of the tryptophan residue.[111] The appendages were primed for RCM macrocylization with terminal alkene-functionalities incorporated in both the isocyanide and the carboxylic acid components. An equimolar mixture of benzylamine (**21-1**), isocyanide (**21-2**), indole-3-carboxyladehyde (**21-3**), and carboxylic acid (**21-4**) in 2,2,2-trifluoroethanol (TFE) heated at 120 °C (microwave, MW) for 1 h afforded the Ugi products (**21-5**) in low to good yield, Figure 21. In the "pair" phase, macrocylization was achieved by Grubbs' second generation catalyst in low to excellent yield. "Post-pair" hydrogenation and ester hydrolysis were introduced (**21-6** and **21-7**), producing compounds which showed a greater activity than their precursors. Varying the length of the carbon chains of the isocyanide and the carboxylic acid afforded a range of 12- to 24-membered macrocycles. The formation of a saturated carbon linker was thought to allow for strong binding to a large hydrophobic surface area. Initial SAR studies identified an optimal ring size of 18, with one of the macrocyclic compounds showing an activity of 100 nM as a diastereomeric mixture, product-type **21-6**. In the case of product-type **21-7**, a racemic mixture was obtained, for which enantiomers could be separated by chiral supercritical fluid chromatography (SFC). This proved

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

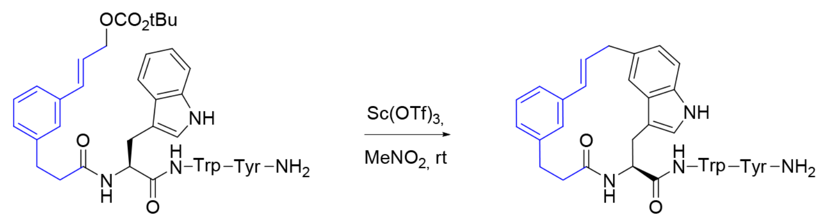


18-1 18-2 18-3



18-4

Starting material	X	R1	18-2	18-3 + 18-4
18-1a	X = O	R^1 = H	42%	54%
18-1b	X = S	R^1 = H	64%	0%
18-1c	X = O	R^1 = OMe	20%	59%



18-5 **18-6**, 68%

Figure 18. Selectivity in the Friedel−Crafts macrocyclization of templated peptide **17-1**.

that the (+)-enantiomer was more active than the racemic mixture and the (−)-enantiomer.

Carbohydrates are interesting building blocks in organic chemistry due to their high sp^3-content and multiple stereogenic elements as well as their commercial and synthetic accessibility. Kim et al. recognized carbohydrates as ideal starting points for the generation of a DOS library.[112] The authors realized that bisacylation of vicinal diols (Figure 22, **22-1** and **22-2**) with unsaturated carboxylic acids (**22-3**) afforded macrocyclic precursors of the form **22-4.** These were subsequently treated with Grubbs' second generation catalyst to afford bicyclic products. *trans*-Vicinal diols afforded planar structures (**22-5**), whereas *cis*-diols provided conformationally constrained bicyclic products (**22-6**). These differences added an extra dimension to the structural diversity of the library. By coupling the carbohydrates to macrobeads, the authors were able to generate a library of 19,952 compounds using solid-phase synthesis, consisting of macrocycles and their respective linear precursors. The compounds were screened intensively across 40 parallel cell-based assays to reveal 36 macrocycles showing positive activity, with more than half of them active in more than one assay.

In an extension of previous work,[113] Peng et al. utilized solid-phase synthesis in an extended B/C/P strategy to generate a series of macrocyclic compounds from **23-1** (Figure 23) which ultimately led to the discovery of Robotnikinin (**23-6**).[114,115] The authors employed 1,2-aminoalcohols (**23-2**) and unsaturated carboxylic acids (**23-4**) to obtain **23-5** which by exposure to RCM conditions generated a library of 12-, 13-, and 14-membered macrocycles classified as B/C/C/P products (**23-7**). Using macrobeads as a solid support for the substrates allowed the expedient generation of 2,070 compounds. Upon screening of the library, a number of macrocyclic compounds were found to bind to the Sonic Hedgehog (Shh) protein. Regulation of this protein has been shown to be valuable in the treatment of cancer. The authors extended their approach by developing a solution-phase strategy to provide analogues of the hit compounds, which ultimately led to the discovery of the highly active compound Robotnikinin (**23-6**).

Diketopiperazine (DKP) represents a privileged scaffold observed in cyclic peptides and peptidomimetics and as such was the subject of a proof-of-concept effort by Isidro-Llobet et al., who set out to incorporate this moiety into a compound library.[116] By 2011, only a few examples of cycloaddition with α-azido amino acids had been reported, of what the main contributions were from van Maarseveen[117−119] and Ghadiri.[120] Initially, an alkyne-acid (**24-1**) was coupled with an azido-amine (**24-2**) via amide bond formation. This primed the cyclic precursor (**24-3**) for the versatile CuAAC and RuAAC "pair" reaction to afford compounds such as **24-4** (Figure 24). The use of CuAAC and RuAAC was a mean to increase the structural complexity among the products by incorporating both 1,4- and 1,5-triazoles, respectively, in the compound library. In some cases, the free amine and the methyl ester could be further

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

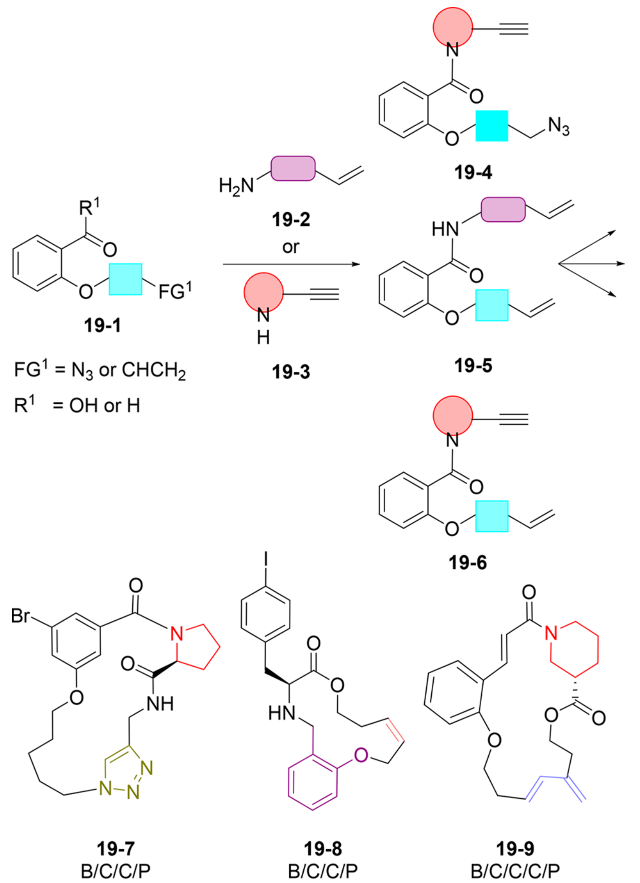


Figure 19. Ciardiello et al. explored iterative coupling steps to generate B/C/C/P, B/C/C/C/P, etc. products in their effort to provide high level of skeletal diversity.[108]

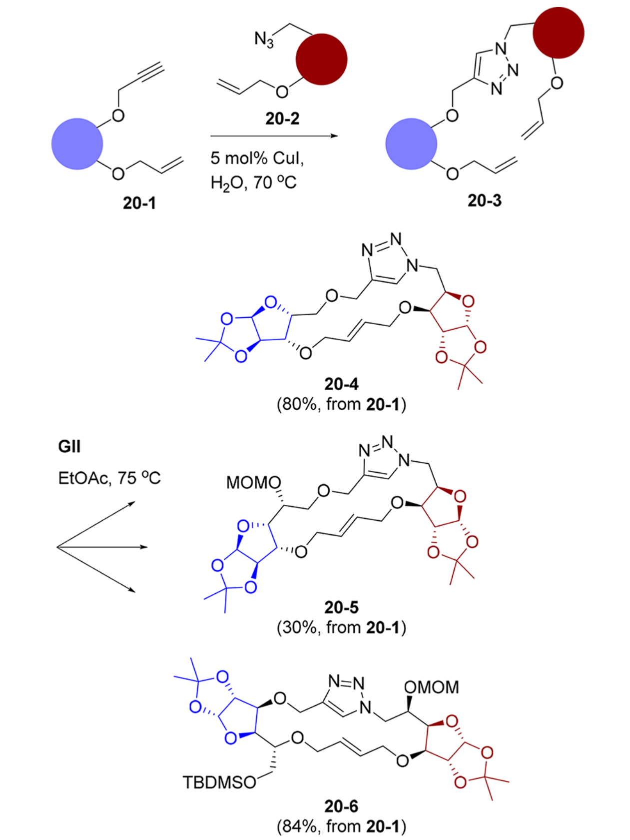


Figure 20. Maurya et al. established more eco-friendly versions of CuAAC and RCM macrocyclization conditions.[109]

utilized to form the DKP moiety in a "post-pair" step (for example **24-5**). Fortunately, no loss of stereochemical information was observed under AAC conditions. Fourteen structurally diverse compounds, composed of various biologically important moieties, were generated. This strategy was successful in generating a series of macrocycles which occupy previously underrepresented chemical space, as shown through principle component analysis (PCA), in a relatively small number of steps. Screening of this library also led to the identification of a hit compound against *Staphylococcus aureus*.

Niu et al. executed a highly innovative synthesis of 14- and 15-membered peptidomimetics (Figure 25) by using MCRs in two "couple" phases to generate scaffolds with diverse molecular backbones.[121] MCR are highly efficient as they are able to incorporate a diverse range of structural diversity without the need for protecting groups. The authors decided to incorporate a propargyl group and a halide into the appendages to explore a Sonogashira macrocylization strategy. Extensive optimization of the reaction conditions was needed to successfully perform the two MCRs and the Sonogashira macrocylization. In the first "couple" step (first MCR), an Ugi reaction was performed by the addition of amine (**25-1**), isonitrile (**25-2**), *o*-azido-benzoic acid (**25-3**), and 2-bromobenzaldehyde (**25-4**). The crude Ugi-product (**25-5**) was carried through as crude substrate for an additional MCR[122] by the treatment of 2-propynylamine, a diketene (**25-6**), and DBU to afford a triazole-containing macrocylization precursor (**25-7** and **25-8**). Intramolecular Sonogashira macrocylization was achieved by treatment with $PdCl_2(PPh_3)_2$ and CuI without the need of high dilution conditions, which is generally needed for macrocyclization conditions. Diversity was increased by changing the position of the azide and the bromine to afford **25-9** and **25-10**. Skeletal diversity was further enhanced by swapping around on the substitution pattern of the amine and the isonitrile components to afford compounds like **25-11**. A total of 14 macrocylic compounds were generated based upon three distinct molecular scaffolds. This is a highly simple strategy with a strong emphasis on diversity by utilizing two MCRs.

Beckmann et al. explored the use of aza-ylides (Figure 26, **26-2**) as a pluripotent functional group to provide handles for the multidimensional coupling of a broad array of coupling reagents.[123] This approach efficiently integrates molecular diversity, via both appendages' versatilities and linkage diversity, in a highly step efficient manner. The concomitant installation of alkynes in the building blocks (**26-1**) and "pair"-matching functionalities, such as azide or alkene, in the appendages (**26-3**) sets up these linear precursors (**26-4** to **26-7**) for functional group pairing via CuAAC and RuAAC or RCEYM macrocyclization steps to generate macrocyclic compounds with respect to the incorporated functionalities. Metathesis also provides an additional handle for a "post-pair" Diels−Alder reaction to further increase the diversity generated using this approach (not shown). The authors neatly displayed the flexibility and multidimensional coupling of the aza-ylides (**26-2**) to generate urea (**26-4** and **26-5**), amide (**26-6**), guanidine (**26-7**), and imine (**26-9**) functionalities by varying the applied electrophile. To extend the level of linkage diversity further, the ureas could be cyclized to the corresponding oxalylurea, using oxalyl chloride, or to the hydantoin and dihydrouracil, using

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

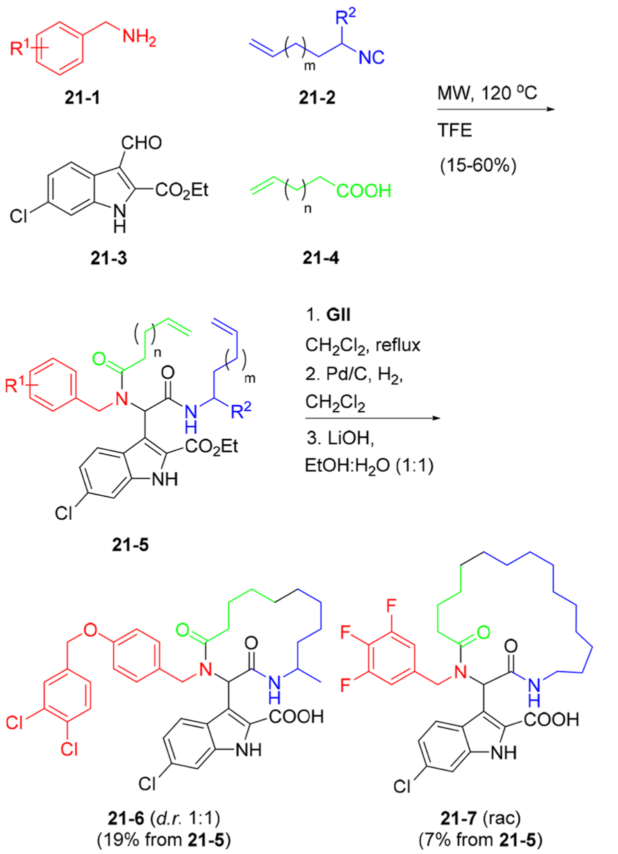


Figure 21. Estrada-Ortiz et al. applied the versatile Ugi reaction for a B/C/P strategy to produce novel p53-MDM2 inhibitors.[110]

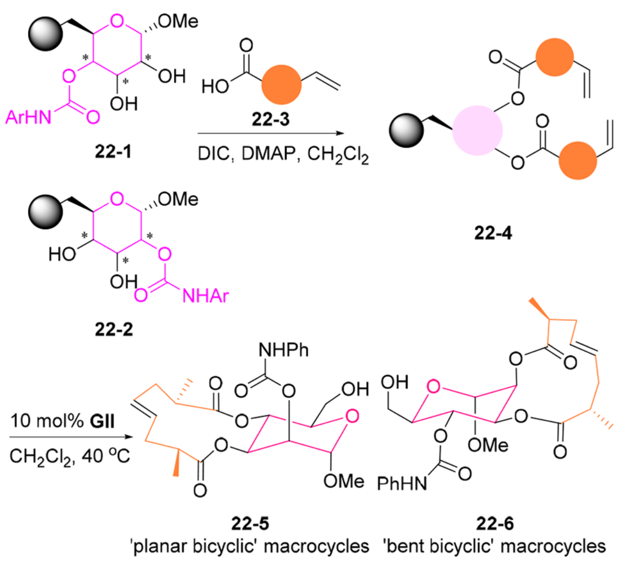


Figure 22. Kim et al. utilized vicinal diols as their starting point for producing a DOS-derived library.[112]

CDI (not shown). The authors further explored this multidimensional strategy by the generated imines (**26-9**) from aldehyde species (**26-8**), as they were reduced to the amine **26-10** or reacted with Danishefsky's diene to form aza-Diels−Alder product **26-11**. The authors took advantage of an ester moiety on the azido building blocks (**26-1**) to introduce a fluorous tag, which both aided purification and provided a further site for "post-pair" functionalization. An impressive total of 73 macro-

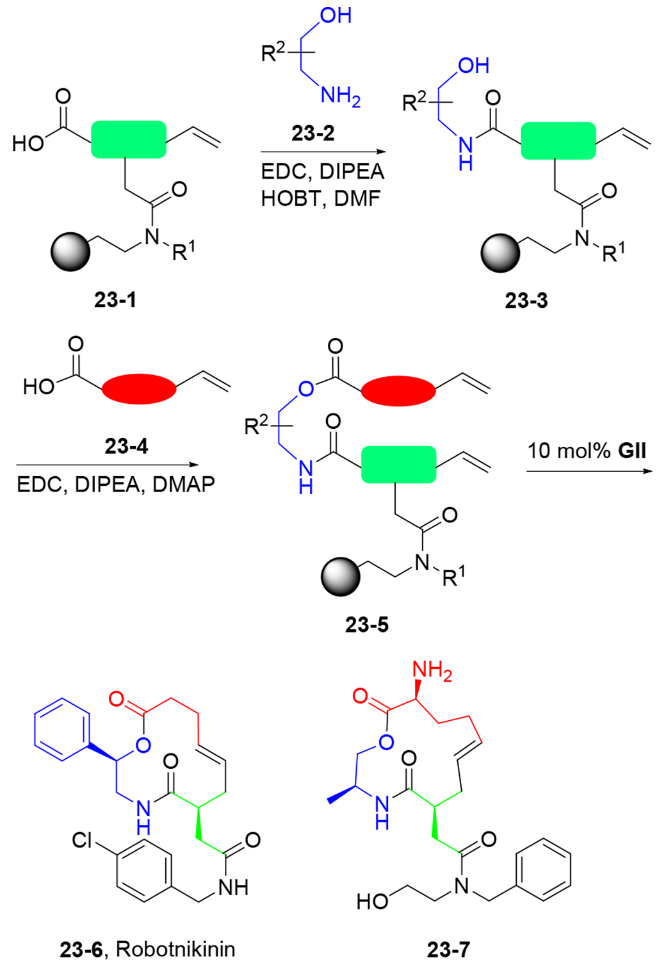


Figure 23. Peng et al. disclosed the synthesis of a macrocyclic compound library which led to the discovery of Robotnikinin.[114,115]

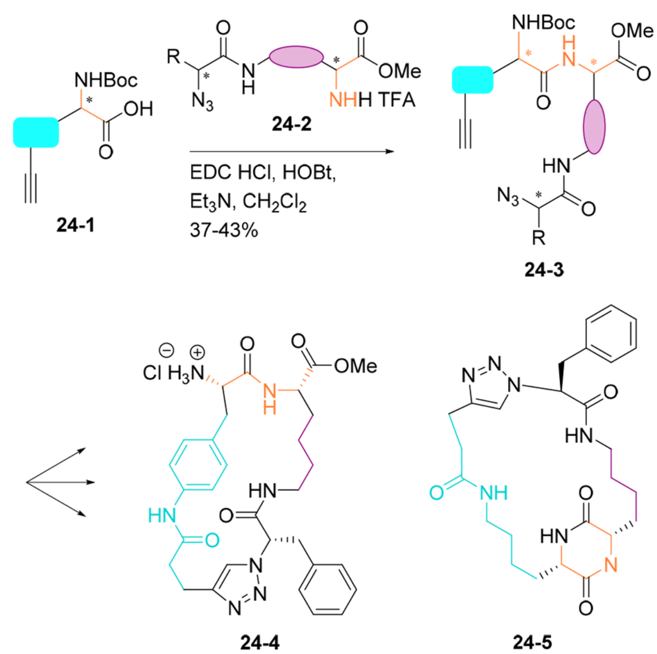


Figure 24. Isidro-Llobet et al. designed macrocycles with the incorporation of the DKP moiety to generate a compound with *Staphylococcus aureus* activity.[116]

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

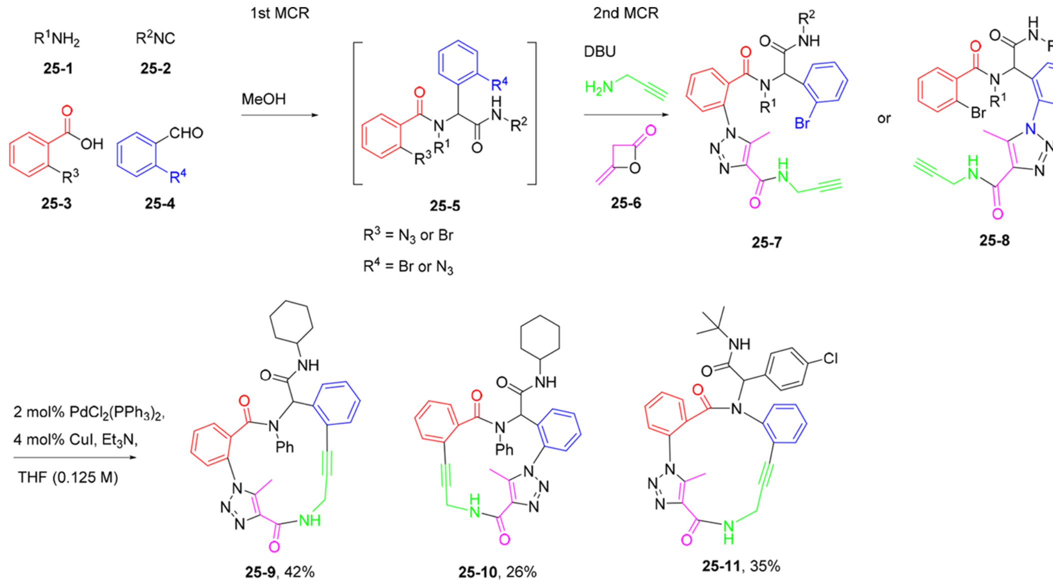


Figure 25. Niu et al. conducted iterative "coupling" phases by the use of a MCR strategy and finalized their effort to generate macrocycles with a Sonogashira macrocyclization without the use of protecting groups.[121]

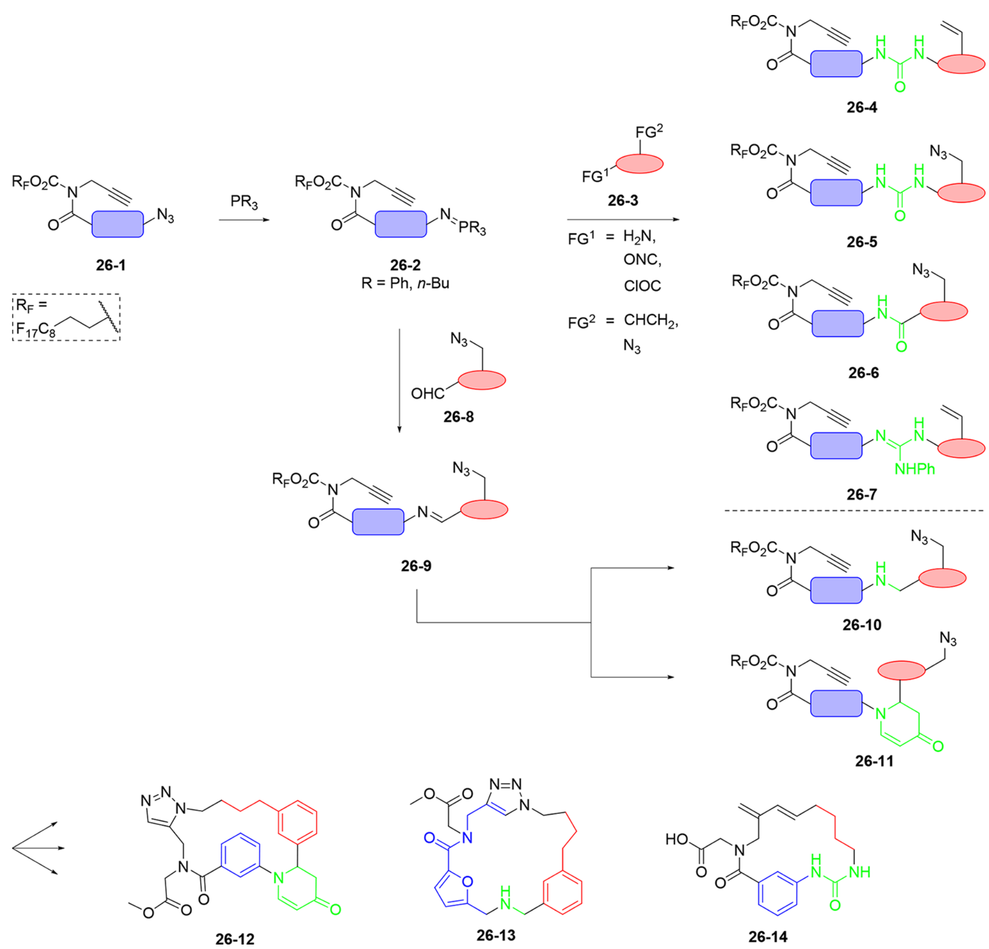


Figure 26. Beckmann et al. probed the use of aza-ylides (26-2) as a pluripotent functional group in their multidimensional coupling application to integrate not only substrate diversity but also linkage diversity.[123]

cycles, based upon 59 discrete scaffolds, were synthesized to prove the viability of this strategy (exemplified by **26-12**, **26-13**, and **26-14**). The group used a PMI plot to assess the diversity of the generated library and found that the compounds occupy a large area of chemical space as is desirable for screening campaigns.

Grossmann et al. produced a natural-product-like macrolactone compound collection, by an organocatalyzed B/C/P

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

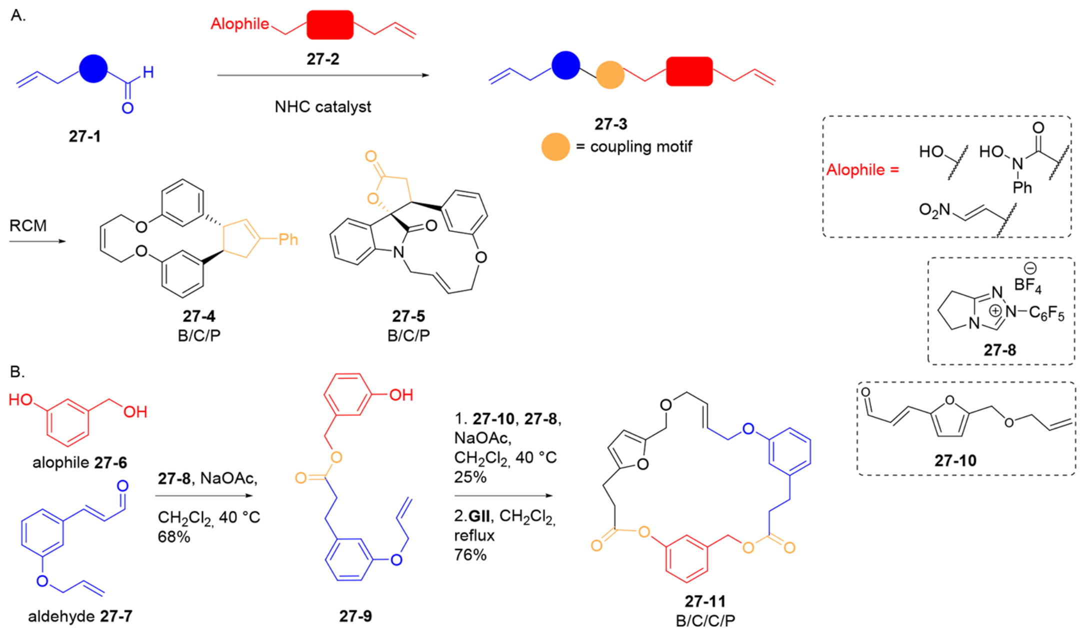


Figure 27. Grossmann et al. synthesized 51 macrocycles with 48 unique scaffolds by the use of organocatalysts their superior "umpolung" application.[124]

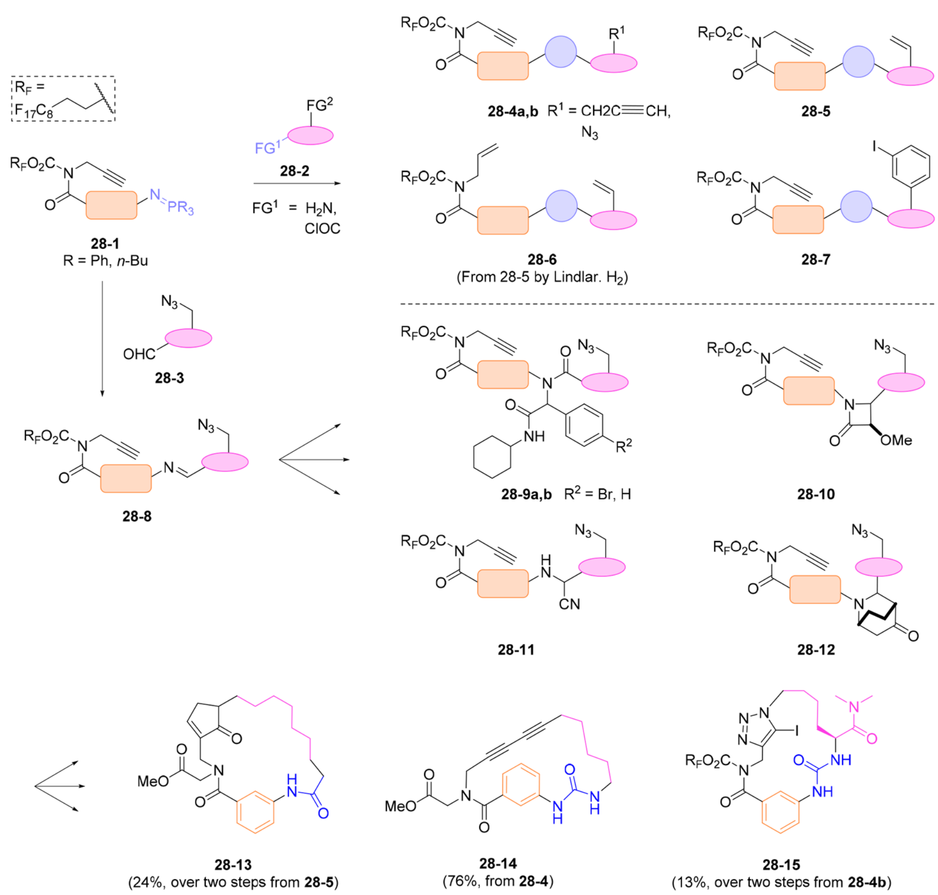


Figure 28. Aza-ylides (**28-1**) were further elaborated as multidimensional coupling partners to extend the scope of macrocyclization protocols and linkage diversity.[125]

DOS strategy, which included 51 macrocycles with 48 unique scaffolds without the need for protecting group manipulation.[124] The strategy builds on the use of aldehydes (**27-1**) and their respective organocatalytic coupling partners, "alophiles" (**27-2**), such as enals, alcohols, β-ketoesters, and chalcone derivatives (Figure 27A). All of these were generated from the same aldehyde precursor for an expedient synthesis of coupling partners. To increase the molecular diversity of the compound

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

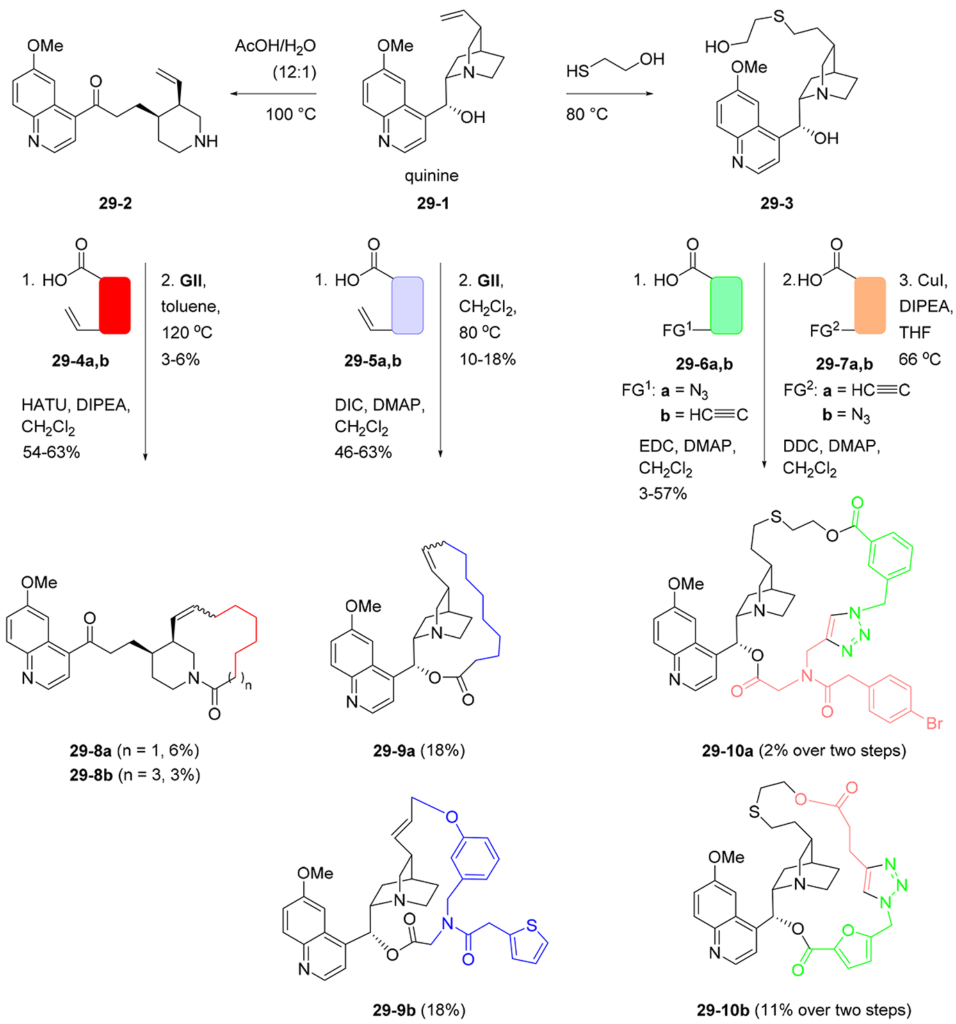


Figure 29. Ciardiello et al. recently utilized the natural product quinine products in their "complexity-to-diversity" strategy.[127]

collection, six different core structures, including aromatic, heteroaromatic, and aliphatic scaffolds, were employed in the "build" phase. *N*-heterocyclic carbenes (NHCs) have proven to be an effective source of organocatalysts and were chosen in this work for their ability to facilitate "umpolung" transformations. In the "couple" phase, ten unique coupling motifs were obtained via single-step transformations from the corresponding aldehyde or enal. These included benzoin and Stetter reactions, a variety of redox-esterification reactions, and a cascade process to afford the corresponding macrocyclic precursors (**27-3**) in low to excellent yields. Incorporation of alkene-functionalities in the appendages primed these macrocyclic precursors for RCM with Grubbs' second generation catalyst to afford structures like **27-4** and **27-5**. To further increase the skeletal diversity, additional 'couple' phases were introduced, see Figure 27B. 3-Hydroxybenzyl alcohol (**27-6**) was coupled to an enal (**27-7**) and exposed to catalyst **27-8**. The phenolic positions were subsequently treated once again with the NHC catalyst **27-8** and enal **27-10**. Following these iterative coupling steps, macrocyclic compounds were obtained after RCM reaction to afford B/C/C/P product **27-11**. Repeating the coupling step once more followed by RCM conditions gave rise to larger macrocycles via a formal B/C/C/C/P algorithm. Eleven ring sizes ranging from 12 to 27 ring sizes were generated by this approach, providing a diverse set of compounds as illustrated by **27-4**, **27-5**, and **27-11**. PMI analysis indicated the generated macrocycles exhibited broad shape diversity and significant spherical character, while PCA identified significant "druglike" molecular shape across the library.

The highly modular and versatile aza-ylides (**28-1**) were further explored by Nie et al., building on previous work from the Spring group, in order to facilitate multidimensional couplings.[125] Similar to the approach by Beckmann,[123] aza-ylides (**28-1**) were reacted with a variety of electrophiles (**28-2** and **28-3**) to explore linkage diversity for this multidimensional approach. In line with earlier reported work, ureas and amides (**28-4** to **28-7**) were introduced directly from the aza-ylides (**28-1**). Nie et al. mainly addressed the versatility of the imine **28-8**. This second branching point was successfully expanded to illustrate the multidimensional nature of the aza-ylides to include Ugi multicomponent (**28-9**), Staudinger ketene cycloaddition (**28-10**), Strecker (**28-11**), aza-Diels–Alder (**28-12**), and Povarov reactions (not shown). In Figure 28 is highlighted a selection of linkage diversity different from the work by Nie et al. Iterative "couple" phases were also investigated in order to introduce larger macrocycles and further increase the skeletal diversity of the library (not shown). By the selective incorporation of alkene, alkyne, iodoaryl, and azide functionalities (**28-2** and **28-3**) in the "build" phase, the bifunctional linear precursors could be subjected to an array of macro-

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

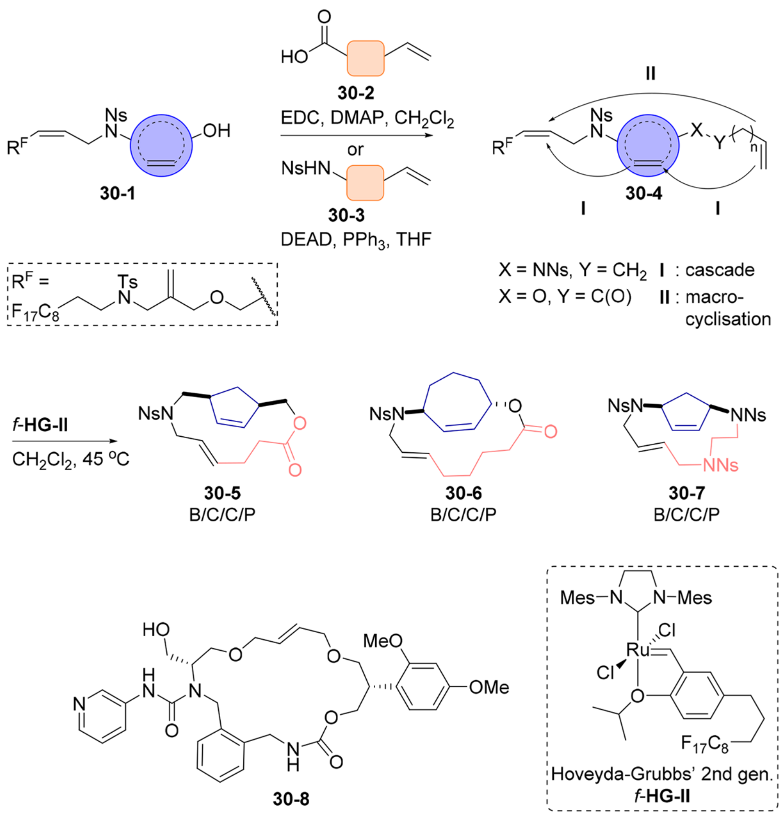


Figure 30. Nelson group disclosed an extraordinary body of work to generate 86 distinct scaffolds, including nine macrocycles, by metathesis.[54]

cyclization protocols. Six known protocols were explored (CuAAC, RuAAC, RCEYM, RCM, Sonogashira cross-coupling, Glaser cross-coupling (**28-14**)) along with two novel reactions to the macrocyclization field: the Pauson-Khand (**28-13**, two regioisomers were formed, only one shown) and a copper-catalyzed alkyne-iodo-azide cycloaddition (CuAIAC, with an external source of iodine) (**28-15**). Furthermore, the authors explored methods to introduce "post-pair" functionalization. The fluorous tags in the aza-ylides were functionalized via transesterification, ester−amide exchange, ester reduction, and ester hydrolysis. The alkynes generated via Sonogashira macrocylization were annulated by reaction with benzyl azide under forcing RuAAC conditions, forming the resulting triazoles (not shown). Dihydroxylation of RCM products and acylation of the urea species were achieved. The arsenal of macro-cyclization reactions explored in this paper afforded 45 novel, structurally diverse, and complex macrocycles ranging from 15- to 33-membered rings. PMI analysis showed that the compounds have prominent spherical characteristics compared to various biologically active compounds.

Natural products have long been recognized as excellent sources of complex compounds, and recent work utilizing the so-called "complexity-to-diversity" strategy has demonstrated that diverse and complex compound collections can be constructed via divergent ring distortion and/or ring forming reactions on complex natural product scaffolds.[126] Ciardiello et al. recently reported the application of this strategy to the synthesis of macrocycles using quinine (**29-1**, Figure 29) as the foundation for library construction.[127] The quinine-derived starting materials **29-2** and **29-3** were prepared and functionalized with different building blocks. Subsequent macrocyclization afforded six structurally distinct and complex macrocycles **29-8** to **29-10**.

2.3. Initiate/Propagate/Terminate

In an impressive work by the Nelson group, Morton et al. were able to generate a total of 86 distinct scaffolds via a DOS approach utilizing a key metathesis cascade.[54] The Nelson group generally uses the terminology "propagating" and "capping" for the generation of building blocks, which closely mirror the B/C/P strategy. In this work the authors commenced from fluorous-tagged unsaturated starting materials to generate macrocycles using a B/C/C/P algorithm. These fluorous-tagged compounds were functionalized with different 2-ene-1,4-diols in the "propagating" phase (**30-1**, Figure 30) and further derivatized with unsaturated substrates (**30-2** and **30-3**) in the "capping" step under acylation- or Mitsunobu conditions. The authors envisioned that the integration of three alkenes in **30-4** would prime the compound for a metathesis cascade reaction (pathway **I**, Figure 30) and afford compounds containing cyclic moieties with variable ring sizes. For a subset of linear compounds a competing macrocyclization occurred (pathway **II**, Figure 30). **30-4** contains a permanent tether in the form of *N*-nosyl; however, the authors also generated linear structures with a temporary silaketal tether (for clarity not illustrated in Figure 30). The latter compounds also undergo macrocyclization, but the temporary tether is subsequently removed by treatment of hydrogen fluoride. In a few cases, both pathways **I** and **II** were favorable which resulted in the isolation of two structurally distinct scaffolds from one reaction. A fluorous-tagged Hoveyda-Grubbs' second generation catalyst (*f*-**HG-II**) both provided macrocycles via a "head-to-tail" approach and a simplified purification process. Out of the 86 scaffolds synthesized, nine macrocycles ranging from 12- to 15-membered rings and one

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

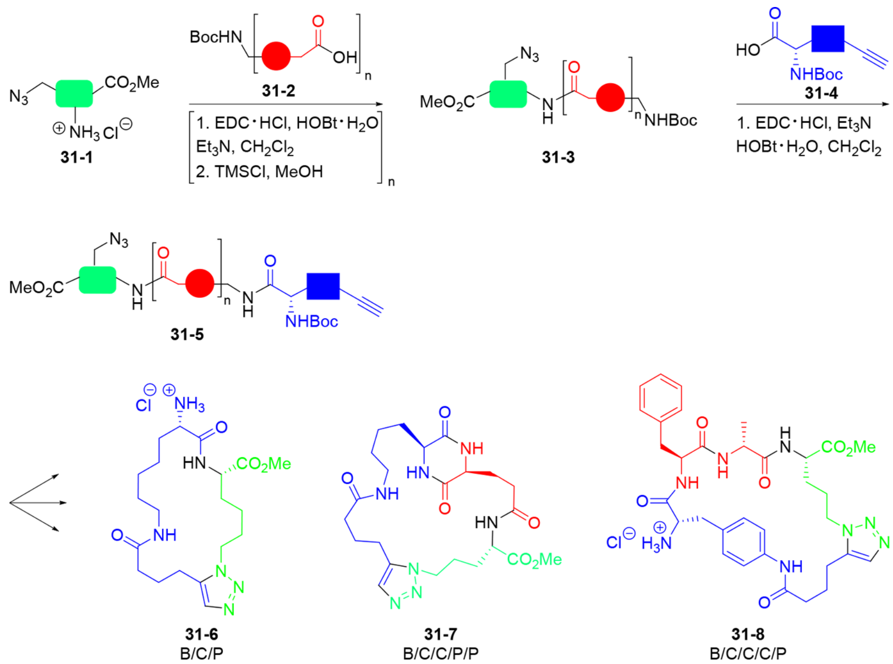


Figure 31. Spring group reported the synthesis of an extraordinary amount of diverse macrocyclic peptidomimetics (>200 molecules) by iterative coupling steps.[130]

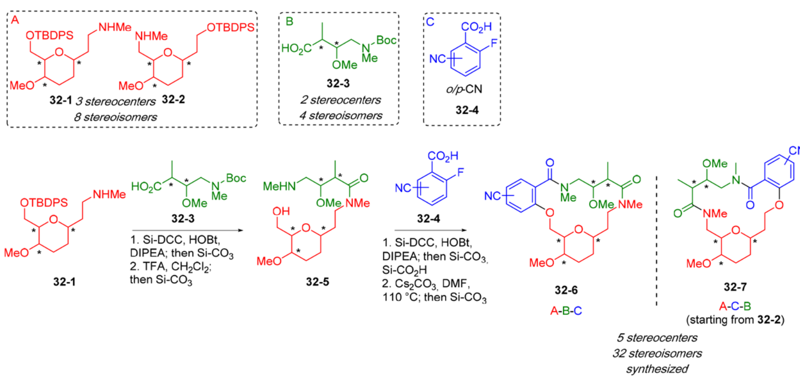


Figure 32. Domain-shuffling approach to tetrahydropyran-containing macrocycles. Si = silica-bound.

26-membered ring were reported (**30-5** to **30-7**). The strategy by Morton et al. was extended in 2013[128] to include only two macrocycles and further expanded in a recent publication by Dow et al.[129] where they only focused on the generation of macrocyclic compounds. The authors focused strongly on the introduction of appendage diversity with stereochemical information and multiple function groups. Seventeen different macrocyclic scaffolds spanning ring sizes of 12 to 20 atoms were generated. Due to the natural-product-likeness of the 17 macrocyclic scaffolds, a small combinatorial library was generated from the scaffolds to afford 66 compounds of which several displayed antimycobacterial activity with **30-8** being the most potent.

Building on previous work[116] (Figure 24), Isidro-Llobet et al. reported in 2015 the formation of macrocyclic peptidomimetics via iterative coupling steps and finally CuAAC macrocyclization.[130] The starting point for the synthesis is an initiating building block, which is coupled with either a "propagating" and/or a "terminating" building block to afford B/C/P-type products. Iterative "propagating" steps allow for the generation of products defined as B/C/C/P and B/C/C/C/P. The Spring group developed a strategy to explore iterative coupling steps by which they were able to generate an unprecedented number of diverse macrocyclic peptidomimetics (>200 molecules). For B/C/P products (**31-6**, Figure 31), azido-amines (**31-1**) were propagated with alkyne-acids (**31-4**, n = 0) followed by a 1,3-dipolar "head-to-tail" cycloaddition. To generate B/C/C/P-derived compounds (**31-7**, n = 0), azido-amines (**31-1**) were coupled with Boc-protected amino acids (**31-2**) followed by coupling with alkyne-acids (**31-4**), to afford linear precursors primed for macrocylization. Due to the simplicity of this strategy, an endless number of iterative "propagating" steps could be envisioned, although the authors limited their study to only two additional steps (**31-8**). All the compounds were poised for a "post-pair" DKP formation to further enhance molecular diversity. Regions of chemical space underexploited in drug discovery were occupied, and furthermore, PMI shows a relatively high level of shape diversity across the library when compared to a selection of top-selling drugs and natural products.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

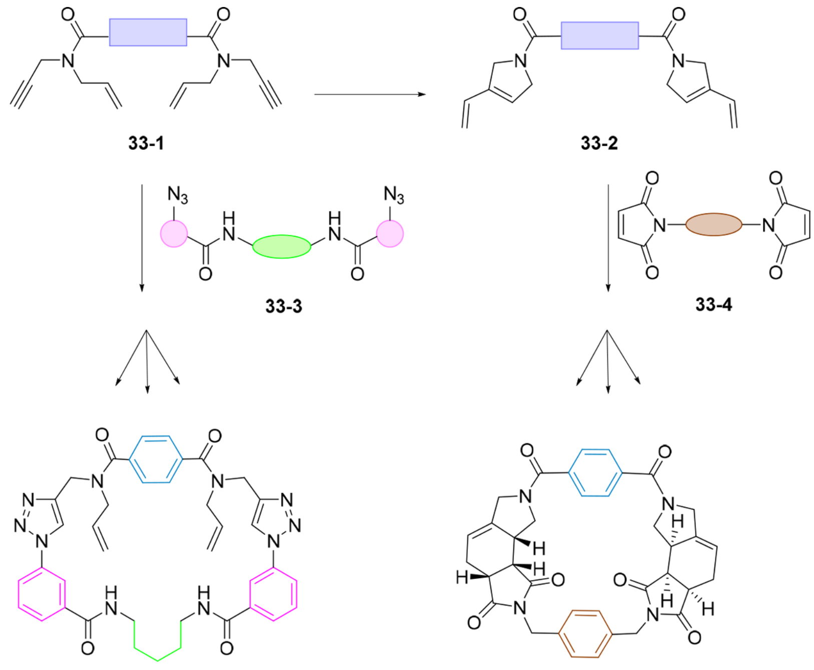


Figure 33. O'Connell et al. developed a two-directional strategy to generate macrocyclic compounds from the common starting material **33-1**.[140]

2.4. Fragment-Based Domain Shuffling

Chemical domain shuffling is a tool to incorporate discrete fragments, or "chemical domains", into a compound library. Su et al.[131] explored chemical domain shuffling via a condensation reaction of a carbonyl group (aldehyde/ketone) and an alkoxyamine to generate the corresponding oximes. By this strategy, 168 complex products were synthesized, and a compound with antiproliferative activity was found. This field has also been applied in the generation of macrocyclic compounds. A domain-shuffling strategy inspired by pyran-containing macrocyclic natural products such as rapamycin and bryostatin was utilized for the construction of a family of pyran-based macrocycles, where slight modifications to the building blocks or the order of couplings resulted in structurally distinct macrocyclic products.[132] In this report, Comer et al. utilized three distinct domains: a pyran domain functionalized with an amine and an alcohol (Figure 32, A, **32-1** and **32-2**), a linear hydroxy-amino acid domain (Figure 32, B, **32-3**), and benzoic acid possessing a fluorine and a nitrile substituent (Figure 32, C, **32-4**). The pyran and hydroxy-amino acid domains were constructed to include several stereocenters each, and for each domain the full stereoisomer matrix was synthesized and employed. The macrocycles were synthesized using solid-supported reagents in a series of steps including two amide couplings, to join the domains and a macrocyclization via nucleophilic aromatic substitution of the alcohol on the pyran domain to the benzoic acid domain, which was activated by the nitrile substituent. The resulting macrocycles formed through these routes included two distinct three-domain combinations termed A-B-C and A-C-B (e.g., **32-6** and **32-7**). In total, 352 macrocycles representing 14- to 16-membered rings with up to five stereocenters in all stereochemical combinations were constructed using this strategy, with a slightly expanded set of building blocks. Notably, shape analysis of this library by PMI showed that the closely related ABC and ACB rings occupied distinct regions of shape space, indicating that the subtle connectivity changes caused by domain shuffling can lead to significant changes in overall macrocyclic shape. Furthermore, this library was compared to the National Institutes of Health Molecular Library Small Molecule Repository (MLSMR), composed largely of commercially available compounds, and the AnalytiCon Discover library containing natural products. The comparison indicated that the generated library more closely resembled natural products in structural complexity (Fsp^3 and number of stereocenters), as well as falling within an acceptable range of physicochemical properties.

2.5. Two-Directional Synthesis

Two-directional strategies have found several applications in the generation of complex molecules[133−135] and as a versatile synthetic strategy in total synthesis of natural products.[136−139] This was recognized by O'Connell et al., who applied a two-directional strategy in their effort to synthesize macrocycles, see Figure 33.[140] Bis-enyne amides (**33-1**) generated in the "build" and "couple" phases were paired with bis-azides (**33-3**) using CuAAC conditions to afford the corresponding bis-triazole compounds (example **33-5**). To introduce more structural diversity, the building blocks were treated with Grubbs' first generation catalyst under an ethylene atmosphere to generate the bis-1,3-diene RCEYM products (**33-2**). **33-2** were treated with bis-maleimides (**33-4**) at high temperature to provide the corresponding macrocyclic bis-Diels−Alder products (example **33-6**). Generally, low yields were observed for all of the macrocyclizations. The authors illustrated two examples of "post-pair" functionalization of the newly formed alkene: hydrogenation and dihydroxylation. This strategy provided 14 macrocycles of nine ring sizes ranging from 21 to 32. By PCA, the compounds were found to occupy an underrepresented area of chemical space compared with compounds from the Drugbank database.

2.6. Successive Ring Expansion ("SuRE")

The application of iterative ring expansion reactions was reported by Kitsiou et al. for the construction of a library of

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

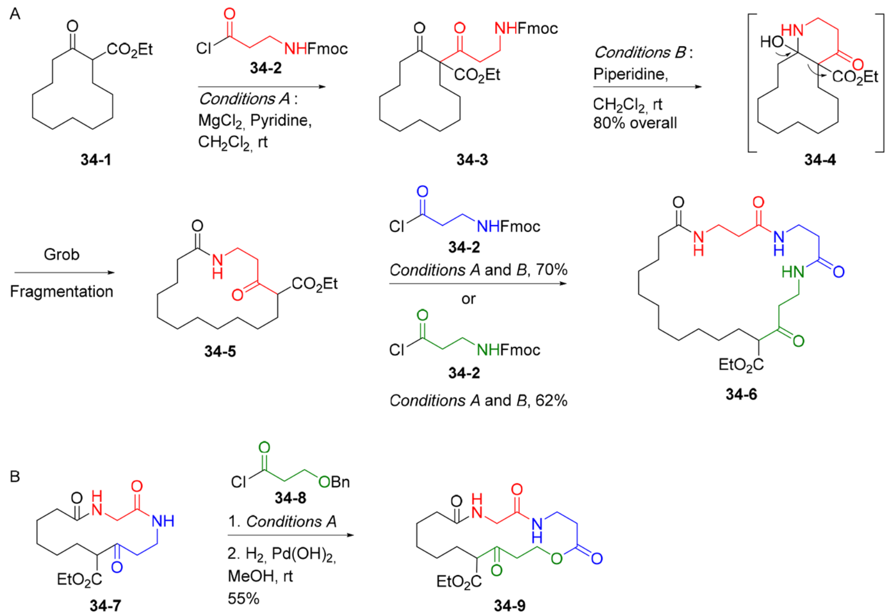


Figure 34. "SuRE" for the synthesis of macrocycles based on β-keto esters.

diverse macrocyclic lactams and lactones (Figure 34).[141] In an elegant strategy referred to as "SuRE", C-selective acylation of a cyclic β-ketoester **34-1** with a bifunctional amino-acid chloride **34-2** first yielded tricarbonyl species **34-3**. Deprotection of the amine with piperidine led to spontaneous rearrangement to intermediate **34-4** followed by Grob fragmentation to afford ring expanded product **34-5** and regenerated the key β-ketoester functional group. Regeneration of the β-ketoester allowed for further ring expansions to be performed using a variety of bifunctional acid chlorides. For example, two further iterations of this sequence from **34-5** using **34-2** produced 24-membered ring **34-6**. In another example, incorporating hydroxyl-containing building block **34-8** in a third round of acylation/expansion furnished macrolactone **34-9**. This general strategy allowed for the construction of 9- to 24-membered rings with control over ring size and sequence.

The "SuRE" strategy was recently extended to the ring expansion of lactams for the synthesis of peptidomimetics by Stephens et al. (Figure 35).[142] Starting from a secondary lactam such as **35-1**, *N*-acylation with a bifunctional acid chloride (**35-2**) followed by deprotection of the distal amine formed ring-expanded product **35-4** while regenerating the crucial secondary lactam functional group. The sequence could be repeated with a different acid chloride component to successively expand the macrocycle (e.g., **35-4** to **35-6**). A variety of α- and β-amino-acid-derived acid chlorides could be employed in the lactam expansion procedure in yields ranging from 40 to 96% (e.g., **35-7** and **35-8**), and the "SuRE" sequence performed up to three times to afford a range of peptide-like macrocyclic products, containing up to 25-membered rings.

3. RING DISTORTION STRATEGIES

3.1. Sequential Cycloaddition/Ring Cleavage

Transformations of steroid skeletons represent a well-established approach to complex polycyclic molecular frameworks. In a series of reports,[143−145] Bäurle et al. explored the construction of steroid derived *p*-cyclophane macrocycles from a precursor of type **36-1**, containing a 1,3-diene in its B ring (Figure 36), based on initial reports by Winterfeldt et al.[146−149]

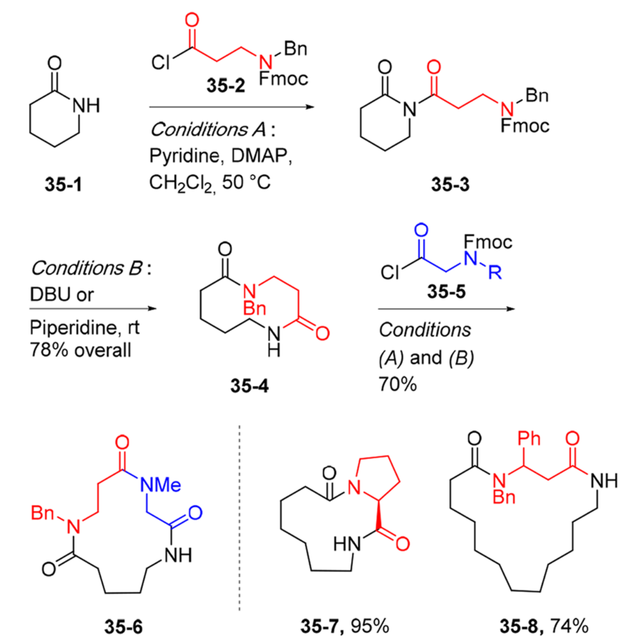


Figure 35. "SuRE" for the synthesis of macrocycles based on secondary amides.

Applying a Diels−Alder/retro Diels−Alder sequence to this skeleton led to the ring-expanded *p*-cyclophane macrocycle **36-3**. From **36-3**, the authors created further macrocyclic skeletons via ozone-mediated olefin cleavage, modification, and subsequent RCM or lactamization reactions to access alternate *p*-cyclophane macrocycles, as well as D-ring cleavage to provide further ring-expanded *p*-cyclophane skeletons **36-5** through **36-8**. Screening of some of these macrocycles identified **36-4** as a potent inhibitor of phosphatase Cdc25B, an essential cell cycle protein.

A sequence of Diels−Alder/retro Diels−Alder reactions applied to the B-ring diene of dehydroisoandrosterone-epoxy-derivative served as the basis for the synthesis of a library of over 2,000 macrocyclic *p*-cyclophane compounds reported by Kumar

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

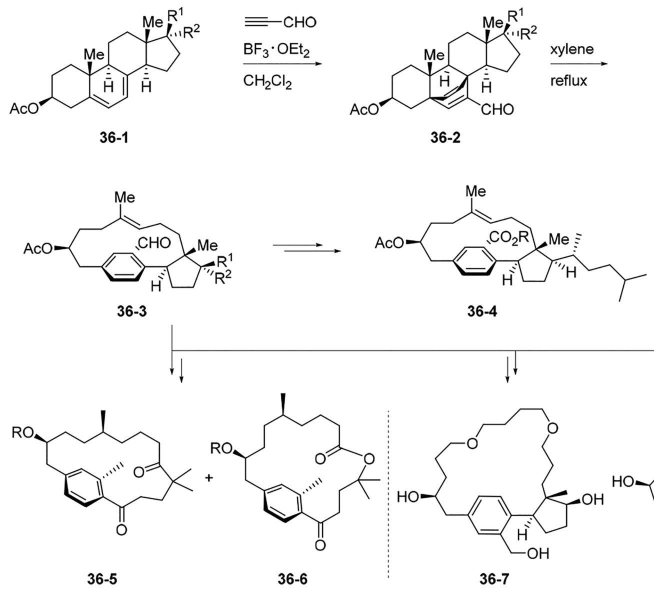


Figure 36. Sequential Diels–Alder/retro Diels–Alder of steroidal skeleton **36-1** to form macrocyclic *p*-cyclophanes.

et al.[150] Using bead-immobilized **37-1**, epoxide-opening (Figure 37) with a variety of nucleophiles followed by alkylation or acylation/cyclization afforded D-ring functionalized intermediates **37-2**. The Diels–Alder reaction of ynones with diene **37-2**, promoted by Et_2AlCl, formed bridged cyclohexadienes **37-3**. Subsequent thermally promoted retro Diels–Alder reactions afforded the skeletally transformed *p*-cyclophane products **37-4**.

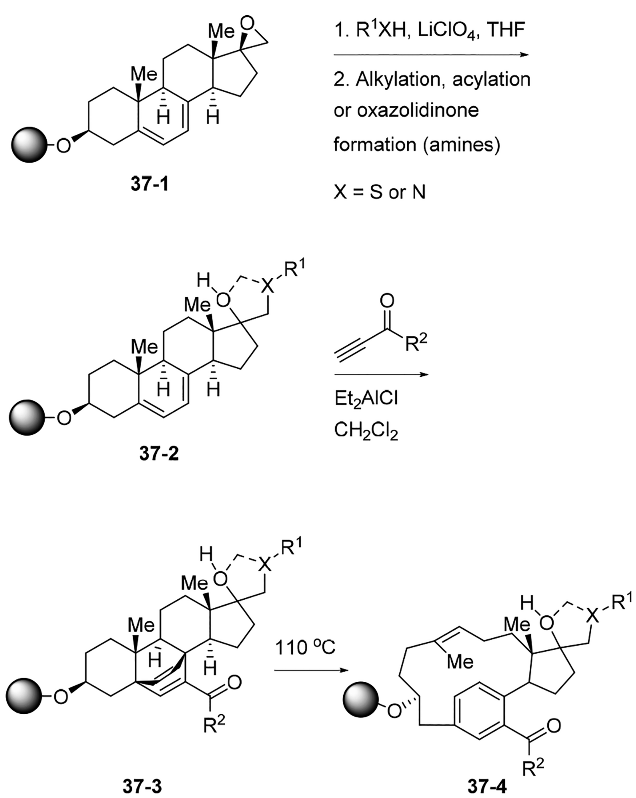


Figure 37. Solid phase-suppored synthesis of a library of macrocycled *p*-cyclophanes from a steroid skeleton based on a Diels–Alder/retro Diels–Alder sequence.

The final macrocycles shared the same skeleton, but subsequent functionalizations further diversified the library.

Kopp et al. described the synthesis of a collection of macrolactones and macrolactams based on the oxidative ring cleavage of bicyclic enone-derived substrates.[151] The bicyclic enone substrates were constructed via a Diels–Alder reaction of 1,3-diketone-derived diene **38-1** and various dienophiles of type **38-2** (Figure 38), followed by diastereoselective ketone reduction to afford **38-4**. The resulting scaffolds were subjected to oxidative cleavage with $RuCl_3$ and oxone, conditions inspired by the classic oxidative cleavage of $\Delta^{9,10}$-octalin to 1,6-cyclodecandione.[152] The 10- to 12-membered rings of **38-5**

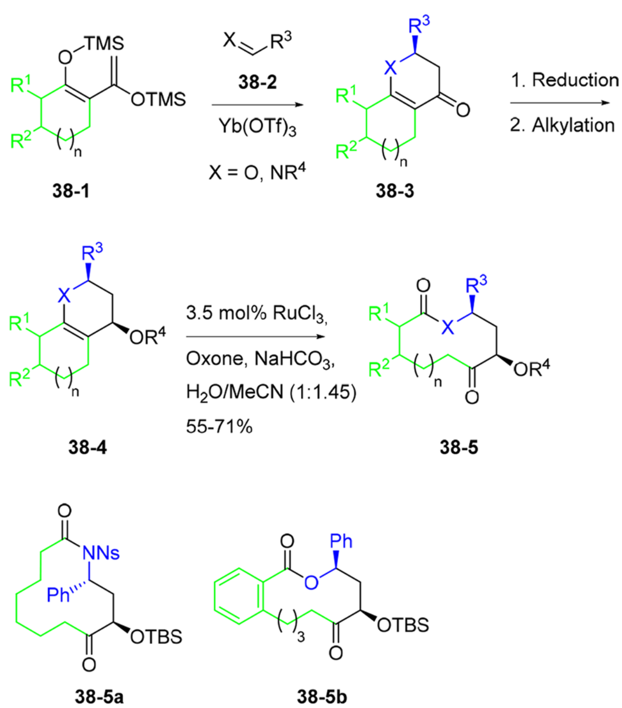


Figure 38. Sequential Diels–Alder/oxidative ring cleavage to form macrocycles **38-5**.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288–10317

(e.g., **38-5a** and **38-5b**) produced through this sequence could be further diversified through functional group transformations. Notably, the oxidative ring expansion route furnished macrocycles more efficiently than classical macrocyclization of linear precursors. Cheminformatic analysis of the final library using PCA and PMI analysis showed this approach was able to access distinct chemical space compared to macrocyclic drugs and druglike molecules, with substantial overlap with macrocyclic natural products.

A library of *p*-cyclophanes was constructed using the Diels–Alder/retro Diels–Alder approach pioneered by Winterfeldt applied to an expanded set of nonsteroidal polycyclic dienes (Figure 39).[153] Krieger et al. elegantly demonstrated the

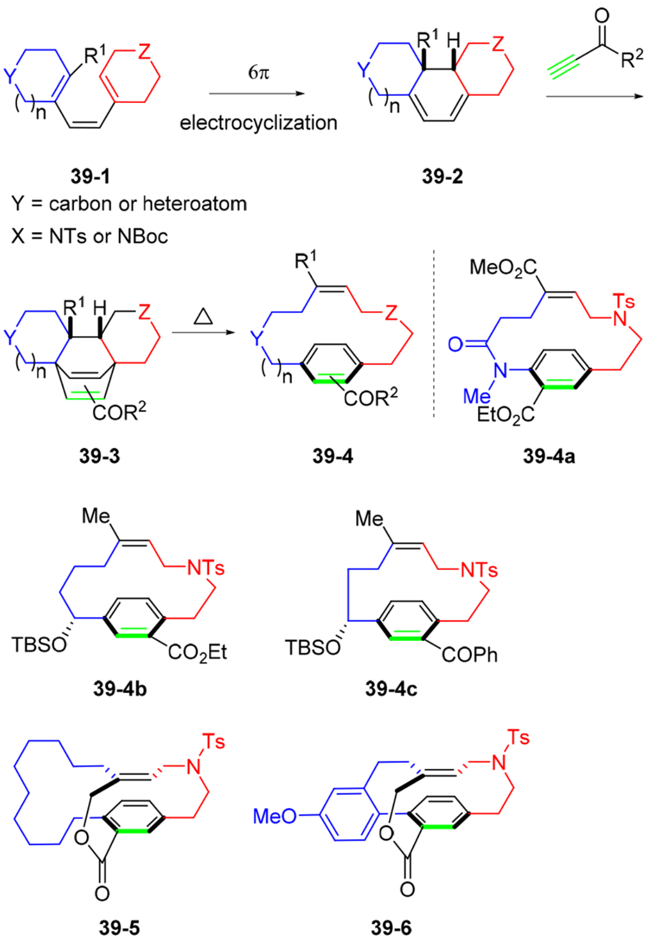


Figure 39. Sequential Diels–Alder/Retro Diels–Alder of dienes **39-2** to form *p*-cyclophane macrocycles.

construction of a set of 1,3-diene-containing substrates **39-2** via 6*π* electrocyclization of triene precursors **39-1**. Intra- or intermolecular Diels–Alder cycloadditions with an ynoate partner formed the requisite bridging cyclohexadiene skeleton **39-3**, which upon microwave heating underwent retro Diels–Alder to afford [9]-, [10]-, and [16]-*p*-cyclophane products **39-4**. Notably, this approach tolerated the incorporation of nitrogen-containing functional groups and allowed for the formation of some caged cyclophanes (for example **39-5** and **39-6**).

Macrocyclic hydroxamates were synthesized by Acharya et al. by employing a cycloaddition/fragmentation strategy based on their earlier work exploring the [4+3] cycloaddition between aza-oxyallyl cations and furans (Figure 40).[154] The researchers constructed an *α*-halo hydroxamate ester tethered by a linker to

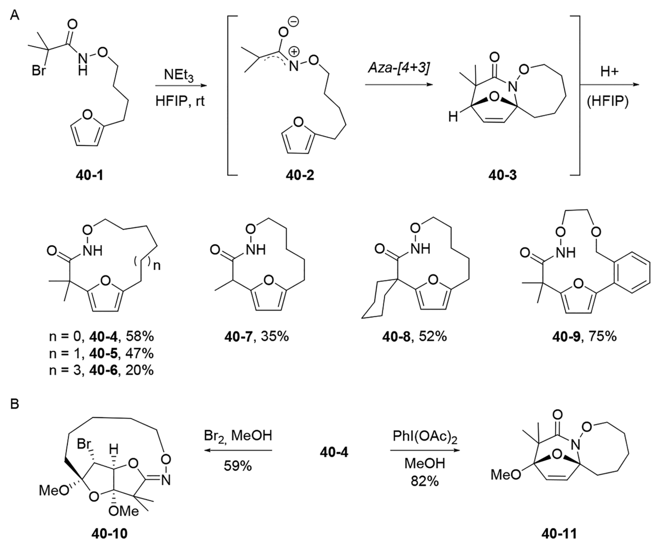


Figure 40. Synthesis of hydroxamate macrocycles via a sequence of aza-[4+3] cycloaddition/proteolysis.

a furan unit (**40-1**), which could undergo base-mediated intramolecular [4+3] cycloaddition to form bridged polycycle **40-3**. It was initially found that some of these cycloadducts ruptured in acidic alcohol solvent to afford macrocyclic products containing a hydroxamate ester and furan ring such as **40-4**. This finding was extended to the construction of a library of macrocycles by running the reaction in hexafluoroisopropanol (HFIP) to afford macrocyclic hydroxamates in a single synthetic procedure via cycloaddition/fragmentation. The effects of substitution, substrate rigidity, and ring size were studied and revealed that increased rigidity promoted cyclization (**40-7** through **40-9**) and that the formation of rings larger than 12 atoms was more sluggish (**40-5** and **40-6**). The furan rings embedded in these structures could be subsequently treated with a variety of oxidants to form other interesting medium-sized and macrocyclic structures, including **40-10** and **40-11**, by treatment with bromine in methanol or phenyliodine(III) diacetate ((diacetoxyiodo)benzene, PIDA) in methanol, respectively.

3.2. Ring Expansion

The synthesis of a collection of 8- to 12-membered rings was reported by Bauer et al. (Figure 41) leveraging the oxidative dearomatization of bicyclic phenol compounds (**41-1**) with $PhI(OAc)_2$ to yield cyclohexanedione compounds of **41-2**.[155] Ring expansion/rearomatization of this intermediate with either TsOH, Tf_2O, or $Cu(BF_4)_2$ avoided undesired rearrangement reactions and efficiently yielded a first generation library of benzannulated larger ring structures (**41-3** to **41-6**). Cheminformatics studies demonstrated that this library occupied chemical space overlapping with natural products containing similarly sized rings but distinct from drugs of the same size, confirming the biomimetic nature of this strategy.

The oxidative ring expansion of bicyclic compounds to form 10- to 12-membered rings was also explored using an antipsoriasis drug as a starting point for further exploration.[156,157]

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288–10317

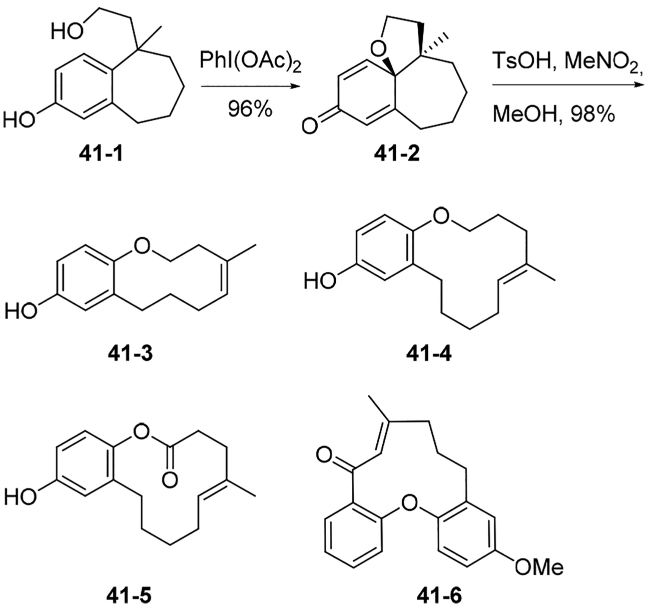


Figure 41. Ring expansion via oxidative rearomatization/ring expansion to synthesize macrocycles.

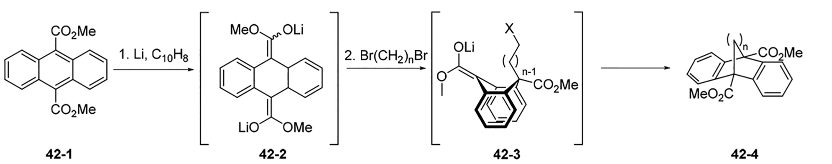
3.3. Miscellaneous

A library of dibenzo-fused [n.2.2] bicyclic macrocycles was constructed based on the dialkylation of bis-enolates (**42-2**) derived from the reduction of anthracene-9,10-dicarboxylate ester **42-1** (Figure 42).[158] When the bis-enolates were treated with a variety of 1,ω-dibromoalkane electrophiles macrocyclization smoothly occurred across a wide range of alkane lengths, forming up to 24-membered dibenzo[20.2.2]bicycles **42-4** without the need for high dilution conditions. In general, 11-membered and higher rings were formed in good yield. The success of this procedure is attributed to the puckered intermediate of the first alkylation (**42-3**), which positions the alkyl chain in the pseudoaxial position, thereby exposing the electrophile for a facile intramolecular alkylation.

The chemistry of α-imino carbenes was leveraged for the synthesis of polyether macrocycles under Rh catalysis in a report by Guarnieri-Ibáñez et al.[159] In this work, *N*-sulfonyl triazoles **43-1** were reacted with oxetanes **43-2** and dirhodium catalyst **43-3** (Figure 43). Reaction concentration was the key feature controlling macrocycle formation, and the choice of a substituent on the sulfonyl of **43-1** determined the type of macrocycle formed. It was observed that macrocycle formation occurred via a (3+4+4+4)-type cyclization between *in situ*-generated α-imino rhodium carbene and three equivalents of oxetane **43-2** when the reaction was performed with a 1 M concentration of **43-1** in **43-2** as solvent and an arylsulfonyl substrate (R^2 = Ar) was used, affording 15-membered macrocycles **43-4** (e.g, **43-6**) (Figure 43A). Alternatively, 13-membered macrocycle **43-5** formed resulting from [5+4+4] cyclization with a sulfonyl oxygen attack on the carbene electrophile when methanesulfonyl substrates (R^2 = Me) were employed (e.g., **43-7**). In contrast to macrocylization, at 0.1 M concentration of **43-1** in CH_2Cl_2 formation of tetrahydrofuran **43-8** was observed, as the product of reaction between **43-1** and one equivalent of **43-2** followed by $LiAlH_4$ reduction of the imine (Figure 43B). These observations allowed for the synthesis of a library of 13- and 15-membered macrocycles.

4. CONCLUSION

As biological targets are becoming more complicated to address, there is a need for a shift away from traditional small molecules of which most compound libraries are comprised. Natural macrocycles have early on gained solid ground as biologically interesting molecules against a variety of targets. A study showed that of the 68 market macrocyclic drugs (by 2013), the main therapeutic areas were treatment against infections followed by oncology.[5] Natural macrocycles are usually used without chemical modifications (no lead optimization). Over the years the area has developed such that natural macrocycles have become an important source either as an inspiration toward simplified derivatives[160,161] or modified semisynthetic versions.[162] Fully synthetic macrocycles have only recently started to become regular members of compound libraries due to the advances within the research community to develop straightforward, low step count, and highly versatile approaches. We have, herein, comprehensively covered literature regarding the formation of macrocyclic compounds by a DOS strategy. To generate molecular diversity of macrocyclic compounds, different strategies such as the B/C/P or ring-distortion/-expansion have been applied. Building block diversity is the most common method to increase the scaffold diversity, but diversity can also be integrated by different macrocyclization reactions or initiating steps. The former is particularly valid for B/C/P where a range of different macrocyclization reactions has been performed, but in particular, RCM and CuAAC have been exceptionally reliable. Due to this reliability, CuAAC and RCM are by far the most applied macrocyclization approaches. Unfortunately, these only introduce minor linkage diversity. Therefore, there is a need to build up a stronger arsenal with other diversified macrocyclization reactions. We believe that a reagent-based macrocyclization strategy is a powerful tool to integrate linkage diversity. In this approach two function groups



n	Product ring size	Yield	n	Product ring size	Yield
3	7	95%	9	13	66%
4	8	52%	10	14	70%
5	9	0%	11	15	72%
6	10	41%	12	16	77%
7	11	72%	20	24	61%

Figure 42. Macrocyclization by alkylation of bis-enolate **41-2**.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

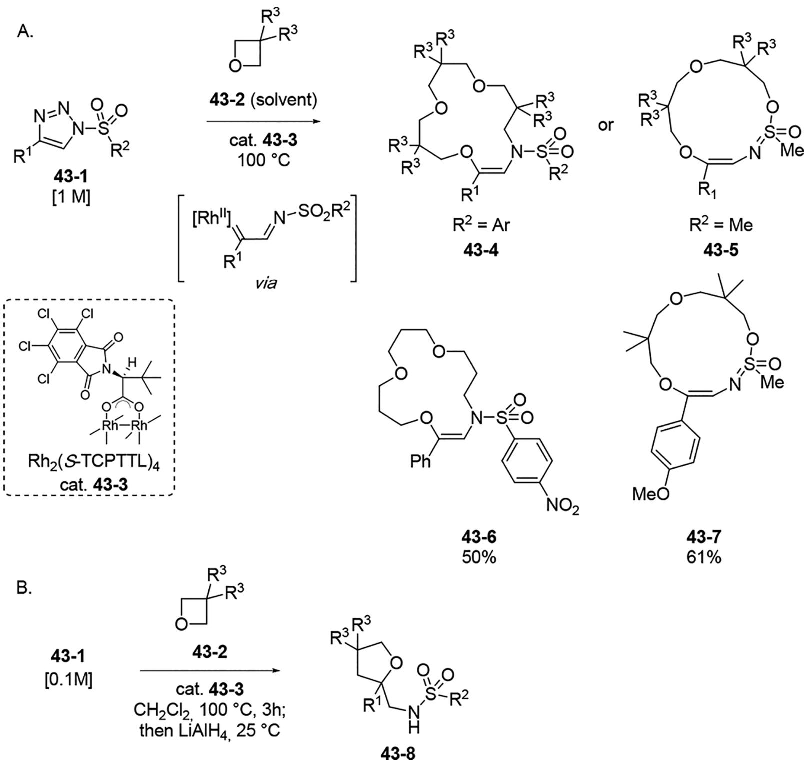


Figure 43. Guarnieri-Ibáñez et al. synthesized polyether macrocycles by the use of rhodium catalyst **43-3**.[159]

are paired together affording different products by variating the conditions. Ring-distortion and cycloadditions have been widely explored as an initiating reaction to set up the starting material for a ring-expansion. As chemistry is constantly evolving, implementation of novel methodologies into the macrocyclization step will enable the discovery of novel macrocyclic compounds, which is strongly needed. Due to the vastness of macrocyclic chemical space and the countless possibilities for building up macrocycles, an initial synthetic guidance would be highly valuable to generate biologically active compounds in a cost-efficient manner. High-throughput screening and conventional synthesis are very cumbersome and expensive, thus novel strategies to generate huge libraries could revolutionize drug discovery. The epochal work by Liu on DNA-encoded libraries shows that the technique can be used to generate enormous compound libraries that can progress through screening and hit identification in a cost-efficient manner. This is an approach that has been commercialized over the past decade and is utilized by multiple companies, both for macrocycle and small molecule screening platforms. This review describes the formation of several hit compounds and biochemical probes based on a DOS strategy. Combined with earlier mentioned drugs, with the current number of clinical candidates in development and the continuing development and novel macrocycles progressing into clinical development,[5] an increase in approved drugs is anticipated.

AUTHOR INFORMATION

Corresponding Author

*E-mail: spring@ch.cam.ac.uk.

ORCID

David R. Spring: 0000-0001-7355-2824

Notes

The authors declare no competing financial interest.

Biographies

Graduating with a M.Sc. in Synthesis and Medicinal Chemistry from Technical University of Denmark, Kim T. Mortensen started pursuing his Ph.D. in 2013 under the supervision of Katrine Qvortrup and Thomas Eiland Nielsen. His research included synthesis of biological active small molecules and peptides. After obtaining his Ph.D. he was awarded a Carlsberg Internationalization Fellowships grant and moved to David Spring's group in Cambridge UK (2018), where he is currently working with diversity-oriented synthesis as a tool in fragment-based drug discovery.

Thomas Osberger was born and raised in Indiana and received his B.S. in Chemistry from the University of Notre Dame in 2009. He then pursued graduate studies under the guidance of M. Christina White at the University of Illinois Urbana−Champaign, where he developed transition metal-catalyzed C−H oxidation reaction methodology. After obtaining his Ph.D. in 2016, he moved to Cambridge and joined David Spring's lab as a postdoctoral scholar, where he is currently investigating strategies for the diversity-oriented synthesis of geometrically constrained fragment molecules.

Thomas King graduated with a B.A. and M.Sc. from the University of Cambridge in 2018. He was awarded funding for postgraduate studies by the BBSRC and NPIF and later that year began a Ph.D. under the supervision of Professor David Spring, University of Cambridge. His research involves the development of small molecule inhibitors of protein−protein interactions.

Dr. Hannah Sore has over 18 years of research expertise, which includes extensive experience within the healthcare and drug discovery sector working in biotechnology, multinational pharmaceutical companies, and academia. Hannah has over 8 years consulting and business experience across healthcare sectors at Frost & Sullivan and as a founder

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

and Director of HFS Scientific Ltd. Hannah is the Spring Group Research Manager at the Department of Chemistry, University of Cambridge and is the founder and CEO of PharmEnable.

Prof. David Spring is currently a Professor at the University of Cambridge within the Chemistry Department and a Fellow of Trinity College. He received his DPhil (1998) at Oxford University under Sir Jack Baldwin. He then worked as a Wellcome Trust Postdoctoral Fellow at Harvard University with Stuart Schreiber (1999−2001), after which he joined the faculty at the University of Cambridge. His research program is focused on synthetic chemistry and chemical biology.

ACKNOWLEDGMENTS

D.R.S. acknowledges support from the Engineering and Physical Sciences Research Council (EP/P020291) and The Royal Society (Wolfson Research Merit Award). K.T.M. thanks the Carlsberg Foundation for a Postdoctoral Fellowship. T.A.K. thanks the BBSRC for financial support.

REFERENCES

(1) Mallinson, J.; Collins, I. Macrocycles in New Drug Discovery. *Future Med. Chem.* **2012**, *4*, 1409−1438.
(2) Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. What Can a Chemist Learn from Nature's Macrocycles? - A Brief, Conceptual View. *Mol. Diversity* **2005**, *9*, 171−186.
(3) Yu, X.; Sun, D. Macrocyclic Drugs and Synthetic Methodologies toward Macrocycles. *Molecules* **2013**, *18*, 6230−6268.
(4) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. The Exploration of Macrocycles for Drug Discovery - an Underexploited Structural Class. *Nat. Rev. Drug Discovery* **2008**, *7*, 608−624.
(5) Giordanetto, F.; Kihlberg, J. Macrocyclic Drugs and Clinical Candidates: What Can Medicinal Chemists Learn from Their Properties? *J. Med. Chem.* **2014**, *57*, 278−295.
(6) Swinney, D. C.; Anthony, J. How Were New Medicines Discovered? *Nat. Rev. Drug Discovery* **2011**, *10*, 507−519.
(7) Madsen, C. M.; Clausen, M. H. Biologically Active Macrocyclic Compounds - From Natural Products to Diversity-Oriented Synthesis. *Eur. J. Org. Chem.* **2011**, *2011*, 3107−3115.
(8) Terrett, N. K. Methods for the Synthesis of Macrocycle Libraries for Drug Discovery. *Drug Discovery Today: Technol.* **2010**, *7*, e97−e104.
(9) Levine, D. P. Vancomycin: A History. *Clin. Infect. Dis.* **2006**, *42*, S5−S12.
(10) Donadio, S.; McAlpine, J. B.; Sheldon, P. J.; Jackson, M.; Katz, L. An Erythromycin Analog Produced by Reprogramming of Polyketide Synthesis. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 7119−7123.
(11) Doak, B. C.; Zheng, J.; Dobritzsch, D.; Kihlberg, J. How Beyond Rule of 5 Drugs and Clinical Candidates Bind to Their Targets. *J. Med. Chem.* **2016**, *59*, 2312−2327.
(12) Stachel, S. J.; Coburn, C. A.; Sankaranarayanan, S.; Price, E. A.; Pietrak, B. L.; Huang, Q.; Lineberger, J.; Espeseth, A. S.; Jin, L.; Ellis, J.; et al. Macrocyclic Inhibitors of β-Secretase: Functional Activity in an Animal Model. *J. Med. Chem.* **2006**, *49*, 6147−6150.
(13) Guo, Z.; Hong, S. Y.; Wang, J.; Rehan, S.; Liu, W.; Peng, H.; Das, M.; Li, W.; Bhat, S.; Peiffer, B.; et al. Rapamycin-Inspired Macrocycles with New Target Specificity. *Nat. Chem.* **2019**, *11*, 254−263.
(14) Ali, A.; Aydin, C.; Gildemeister, R.; Romano, K. P.; Cao, H.; Özen, A.; Soumana, D.; Newton, A.; Petropoulos, C. J.; Huang, W.; et al. Evaluating the Role of Macrocycles in the Susceptibility of Hepatitis C Virus NS3/4A Protease Inhibitors to Drug Resistance. *ACS Chem. Biol.* **2013**, *8*, 1469−1478.
(15) Bowsher, M.; Hiebert, S.; Li, R.; Wang, A. X.; Friborg, J.; Yu, F.; Hernandez, D.; Wang, Y.-K.; Klei, H.; Rajamani, R.; et al. The Discovery and Optimization of Naphthalene-Linked P2-P4Macrocycles as Inhibitors of HCV NS3 Protease. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 43−48.
(16) Feyen, F.; Cachoux, F.; Gertsch, J.; Wartmann, M.; Altmann, K. Epothilones as Lead Structures for the Synthesis-Based Discovery of New Chemotypes for Microtubule Stabilization. *Acc. Chem. Res.* **2008**, *41*, 21−31.
(17) Schreiber, S. L.; Crabtree, G. R. The Mechanism of Action of Cyclosporin A and FK506. *Immunol. Today* **1992**, *13*, 136−142.
(18) Marsault, E.; Peterson, M. L. Macrocycles Are Great Cycles: Applications, Opportunities, and Challenges of Synthetic Macrocycles in Drug Discovery. *J. Med. Chem.* **2011**, *54*, 1961−2004.
(19) Faivre, S.; Kroemer, G.; Raymond, E. Current Development of MTOR Inhibitors as Anticancer Agents. *Nat. Rev. Drug Discovery* **2006**, *5*, 671−688.
(20) Yudin, A. K. Macrocycles: Lessons from the Distant Past, Recent Developments, and Future Directions. *Chem. Sci.* **2015**, *6*, 30−49.
(21) Pelay-Gimeno, M.; Glas, A.; Koch, O.; Grossmann, T. N. Structure-Based Design of Inhibitors of Protein-Protein Interactions: Mimicking Peptide Binding Epitopes. *Angew. Chem., Int. Ed.* **2015**, *54*, 8896−8927.
(22) Iegre, J.; Ahmed, N. S.; Gaynord, J. S.; Wu, Y.; Herlihy, K. M.; Tan, Y. S.; Lopes-Pires, M. E.; Jha, R.; Lau, Y. H.; Sore, H. F.; et al. Stapled Peptides as a New Technology to Investigate Protein-Protein Interactions in Human Platelets. *Chem. Sci.* **2018**, *9*, 4638−4643.
(23) Robertson, N.; Jamieson, A. Regulation of Protein-Protein Interactions Using Stapled Peptides. *Reports Org. Chem.* **2015**, *5*, 65−74.
(24) Gartner, Z. J.; Tse, B. N.; Grubina, R.; Doyon, J. B.; Snyder, T. M.; Liu, D. R. DNA-Templated Organic Synthesis and Selection of a Library of Macrocycles. *Science* **2004**, *305*, 1601−1605.
(25) Tse, B. N.; Snyder, T. M.; Shen, Y.; Liu, D. R. Translation of DNA into a Library of 13 000 Synthetic Small-Molecule Macrocycles Suitable for in Vitro Selection. *J. Am. Chem. Soc.* **2008**, *130*, 15611−15626.
(26) Usanov, D. L.; Chan, A. I.; Maianti, J. P.; Liu, D. R. Second-Generation DNA-Templated Macrocycle Libraries for the Discovery of Bioactive Small Molecules. *Nat. Chem.* **2018**, *10*, 704−714.
(27) Zhu, Z.; Shaginian, A.; Grady, L. C.; O'Keeffe, T.; Shi, X. E.; Davie, C. P.; Simpson, G. L.; Messer, J. A.; Evindar, G.; Bream, R. N.; et al. Design and Application of a DNA-Encoded Macrocyclic Peptide Library. *ACS Chem. Biol.* **2018**, *13*, 53−59.
(28) Connors, W. H.; Hale, S. P.; Terrett, N. K. DNA-Encoded Chemical Libraries of Macrocycles. *Curr. Opin. Chem. Biol.* **2015**, *26*, 42−47.
(29) Lennard, K. R.; Tavassoli, A. Peptides Come Round: Using SICLOPPS Libraries for Early Stage Drug Discovery. *Chem. - Eur. J.* **2014**, *20*, 10608−10614.
(30) Czekster, C. M.; Ludewig, H.; McMahon, S. A.; Naismith, J. H. Characterization of a Dual Function Macrocyclase Enables Design and Use of Efficient Macrocyclization Substrates. *Nat. Commun.* **2017**, *8*, 1045.
(31) Zaretsky, S.; Hickey, J. L.; Tan, J.; Pichugin, D.; St. Denis, M. A.; Ler, S.; Chung, B. K. W.; Scully, C. C. G.; Yudin, A. K. Mechanistic Investigation of Aziridine Aldehyde-Driven Peptide Macrocyclization: The Imidoanhydride Pathway. *Chem. Sci.* **2015**, *6*, 5446−5455.
(32) Wessjohann, L. A.; Ruijter, E. Macrocycles Rapidly Produced by Multiple Multicomponent Reactions Including Bifunctional Building Blocks (MiBs). *Mol. Diversity* **2005**, *9*, 159−169.
(33) Morejón, M. C.; Laub, A.; Kaluđerović, G. N.; Puentes, A. R.; Hmedat, A. N.; Otero-González, A. J.; Rivera, D. G.; Wessjohann, L. A. A Multicomponent Macrocyclization Strategy to Natural Product-like Cyclic Lipopeptides: Synthesis and Anticancer Evaluation of Surfactin and Mycosubtilin Analogues. *Org. Biomol. Chem.* **2017**, *15*, 3628−3637.
(34) Wessjohann, L. A.; Rivera, D. G.; Coll, F. Synthesis of Steroid-Biaryl Ether Hybrid Macrocycles with High Skeletal and Side Chain Variability by Multiple Multicomponent Macrocyclization Including Bifunctional Building Blocks. *J. Org. Chem.* **2006**, *71*, 7521−7526.
(35) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. Multiple Multicomponent Macrocyclizations (MiBs): A Strategic Development Toward Macrocycle Diversity. *Chem. Rev.* **2009**, *109*, 796−814.
(36) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(37) Spring, D. R. Diversity-Oriented Synthesis; a Challenge for Synthetic Chemists. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870.
(38) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nat. Commun.* **2010**, *1*, 80.
(39) Sauer, W. H. B.; Schwarz, M. K. Molecular Shape Diversity of Combinatorial Libraries: A Prerequisite for Broad Bioactivity. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987−1003.
(40) Galloway, W. R. J. D.; Spring, D. R. Is Synthesis the Main Hurdle for the Generation of Diversity in Compound Libraries for Screening? *Expert Opin. Drug Discovery* **2009**, *4*, 467−472.
(41) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization. *Chem. Rev.* **2015**, *115*, 8736−8834.
(42) White, C. J.; Yudin, A. K. Contemporary Strategies for Peptide Macrocyclization. *Nat. Chem.* **2011**, *3*, 509−524.
(43) Lau, Y. H.; de Andrade, P.; Wu, Y.; Spring, D. R. Peptide Stapling Techniques Based on Different Macrocyclisation Chemistries. *Chem. Soc. Rev.* **2015**, *44*, 91−102.
(44) Nielsen, T. E.; Schreiber, S. L. Towards the Optimal Screening Collection: A Synthesis Strategy. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56.
(45) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. An Approach to Skeletal Diversity Using Functional Group Pairing of Multifunctional Scaffolds. *Org. Lett.* **2007**, *9*, 2123−2126.
(46) Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. Route to Three-Dimensional Fragments Using Diversity-Oriented Synthesis. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6799−6804.
(47) Lenci, E.; Menchi, G.; Guarna, A.; Trabocchi, A. Skeletal Diversity from Carbohydrates: Use of Mannose for the Diversity-Oriented Synthesis of Polyhydroxylated Compounds. *J. Org. Chem.* **2015**, *80*, 2182−2191.
(48) Lowe, J. T.; Lee, M. D.; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; et al. Synthesis and Profiling of a Diverse Collection of Azetidine-Based Scaffolds for the Development of CNS-Focused Lead-like Libraries. *J. Org. Chem.* **2012**, *77*, 7187−7211.
(49) Pizzirani, D.; Kaya, T.; Clemons, P. A.; Schreiber, S. L. Stereochemical and Skeletal Diversity Arising from Amino Propargylic Alcohols. *Org. Lett.* **2010**, *12*, 2822−2825.
(50) Uchida, T.; Rodriquez, M.; Schreiber, S. L. Skeletally Diverse Small Molecules Using a Build/Couple/Pair Strategy. *Org. Lett.* **2009**, *11*, 1559−1562.
(51) Oguri, H.; Schreiber, S. L. Skeletal Diversity via a Folding Pathway: Synthesis of Indole Alkaloid-Like Skeletons. *Org. Lett.* **2005**, *7*, 47−50.
(52) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. Short Synthesis of Skeletally and Stereochemically Diverse Small Molecules by Coupling Petasis Condensation Reactions to Cyclization Reactions. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635−3638.
(53) Mitchell, J. M.; Shaw, J. T. A Structurally Diverse Library of Polycyclic Lactams Resulting from Systematic Placement of Proximal Functional Groups. *Angew. Chem., Int. Ed.* **2006**, *45*, 1722−1726.
(54) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. Synthesis of Natural-Product-Like Molecules with Over Eighty Distinct Scaffolds. *Angew. Chem., Int. Ed.* **2009**, *48*, 104−109.
(55) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. Skeletal Diversity Construction via a Branching Synthetic Strategy. *Chem. Commun.* **2006**, 3296−3298.
(56) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. An Approach to Skeletal Diversity Using Functional Group Pairing of Multifunctional Scaffolds. *Org. Lett.* **2007**, *9*, 2123−2126.
(57) Spring, D. R.; Krishnan, S.; Schreiber, S. L. Towards Diversity-Oriented, Stereoselective Syntheses of Biaryl- or Bis(Aryl)Metal-Containing Medium Rings. *J. Am. Chem. Soc.* **2000**, *122*, 5656−5657.
(58) Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber, S. L. Diversity-Oriented Synthesis of Biaryl-Containing Medium Rings Using a One Bead/One Stock Solution Platform. *J. Am. Chem. Soc.* **2002**, *124*, 1354−1363.
(59) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057−3064.
(60) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem.* **2002**, *114*, 2708−2711.
(61) Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) and beyond: New Reactivity of Copper(i) Acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315.
(62) McKay, C. S.; Finn, M. G. Click Chemistry in Complex Mixtures: Bioorthogonal Bioconjugation. *Chem. Biol.* **2014**, *21*, 1075−1101.
(63) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999.
(64) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930.
(65) Johansson, J. R.; Beke-Somfai, T.; Said Stålsmeden, A.; Kann, N. Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications. *Chem. Rev.* **2016**, *116*, 14726−14768.
(66) Trnka, T. M.; Grubbs, R. H. The Development of L2 × 2 = RuCHR Olefin Metathesis Catalysts: An Organometallic Success Story. *Acc. Chem. Res.* **2001**, *34*, 18−29.
(67) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527.
(68) Fürstner, A. Metathesis in Total Synthesis. *Chem. Commun.* **2011**, *47*, 6505−6511.
(69) Schmidt, D. R.; Kwon, O.; Schreiber, S. L. Macrolactones in Diversity-Oriented Synthesis: Preparation of a Pilot Library and Exploration of Factors Controlling Macrocyclization. *J. Comb. Chem.* **2004**, *6* (2), 286−292.
(70) Marsault, E.; Hoveyda, H. R.; Gagnon, R.; Peterson, M. L.; Vézina, M.; Saint-Louis, C.; Landry, A.; Pinault, J.-F.; Ouellet, L.; Beauchemin, S.; et al. Efficient Parallel Synthesis of Macrocyclic Peptidomimetics. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4731−4735.
(71) Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vézina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; et al. Discovery of a New Class of Macrocyclic Antagonists to the Human Motilin Receptor. *J. Med. Chem.* **2006**, *49*, 7190−7197.
(72) Luo, T.; Schreiber, S. L. Gold(I)-Catalyzed Coupling Reactions for the Synthesis of Diverse Small Molecules Using the Build/Couple/Pair Strategy. *J. Am. Chem. Soc.* **2009**, *131*, 5667−5674.
(73) Gorin, D. J.; Toste, F. D. Relativistic Effects in Homogeneous Gold Catalysis. *Nature* **2007**, *446*, 395−403.
(74) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180−3211.
(75) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular Cyclopropanation of Enynes with Alkenes: Trapping of Two Different Gold Carbenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029−6032.
(76) Gorin, D. J.; Sherry, B. D.; Toste, F. D. Ligand Effects in Homogeneous Au Catalysis. *Chem. Rev.* **2008**, *108*, 3351−3378.
(77) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. Gold(I)-Catalysed Arylation of 1,6-Enynes: Different Site Reactivity of Cyclopropyl Gold Carbenes. *Chem. Commun.* **2007**, 698−700.
(78) Jiménez-Núñez, E.; Echavarren, A. M. Molecular Diversity through Gold Catalysis with Alkynes. *Chem. Commun.* **2007**, 333−346.
(79) Wingstrand, M. J.; Madsen, C. M.; Clausen, M. H. Rapid Synthesis of Macrocycles from Diol Precursors. *Tetrahedron Lett.* **2009**, *50*, 693−695.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

(80) Madsen, C. M.; Hansen, M.; Thrane, M. V.; Clausen, M. H. Synthesis of New Diverse Macrocycles from Diol Precursors. *Tetrahedron* **2010**, *66*, 9849−9859.
(81) Grimwood, M. E.; Hansen, H. C. Synthesis of Macrocyclic Scaffolds Suitable for Diversity-Oriented Synthesis of Macrolides. *Tetrahedron* **2009**, *65*, 8132−8138.
(82) Pandya, B. A.; Dandapani, S.; Duvall, J. R.; Rowley, A.; Mulrooney, C. A.; Ryba, T.; Dombrowski, M.; Harton, M.; Young, D. W.; Marcaurelle, L. A. Practical Asymmetric Synthesis of β-Hydroxy γ-Amino Acids via Complimentary Aldol Reactions. *Tetrahedron* **2011**, *67*, 6131−6137.
(83) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; et al. An Aldol-Based Build/Couple/Pair Strategy for the Synthesis of Medium- and Large-Sized Rings: Discovery of Macrocyclic Histone Deacetylase Inhibitors. *J. Am. Chem. Soc.* **2010**, *132*, 16962−16976.
(84) Dandapani, S.; Lowe, J. T.; Comer, E.; Marcaurelle, L. A. Diversity-Oriented Synthesis of 13- to 18-Membered Macrolactams via Ring-Closing Metathesis. *J. Org. Chem.* **2011**, *76*, 8042−8048.
(85) Heidebrecht, R. W., Jr.; Mulrooney, C.; Austin, C. P.; Barker, R. H., Jr.; Beaudoin, J. A.; Cheng, K. C.-C.; Comer, E.; Dandapani, S.; Dick, J.; Duvall, J. R.; et al. Diversity-Oriented Synthesis Yields a Novel Lead for the Treatment of Malaria. *ACS Med. Chem. Lett.* **2012**, *3*, 112−117.
(86) Comer, E.; Beaudoin, J. A.; Kato, N.; Fitzgerald, M. E.; Heidebrecht, R. W.; Lee, M. D.; Masi, D.; Mercier, M.; Mulrooney, C.; Muncipinto, G.; et al. Diversity-Oriented Synthesis-Facilitated Medicinal Chemistry: Toward the Development of Novel Antimalarial Agents. *J. Med. Chem.* **2014**, *57*, 8496−8502.
(87) Fitzgerald, M. E.; Mulrooney, C. A.; Duvall, J. R.; Wei, J.; Suh, B.-C.; Akella, L. B.; Vrcic, A.; Marcaurelle, L. A. Build/Couple/Pair Strategy for the Synthesis of Stereochemically Diverse Macrolactams via Head-to-Tail Cyclization. *ACS Comb. Sci.* **2012**, *14*, 89−96.
(88) Denmark, S. E.; Muhuhi, J. M. Development of a General, Sequential, Ring-Closing Metathesis/Intramolecular Cross-Coupling Reaction for the Synthesis of Polyunsaturated Macrolactones. *J. Am. Chem. Soc.* **2010**, *132*, 11768−11778.
(89) Zapf, C. W.; Bloom, J. D.; McBean, J. L.; Dushin, R. G.; Nittoli, T.; Ingalls, C.; Sutherland, A. G.; Sonye, J. P.; Eid, C. N.; Golas, J.; et al. Design and SAR of Macrocyclic Hsp90 Inhibitors with Increased Metabolic Stability and Potent Cell-Proliferation Activity. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2278−2282.
(90) Zapf, C. W.; Bloom, J. D.; McBean, J. L.; Dushin, R. G.; Nittoli, T.; Otteng, M.; Ingalls, C.; Golas, J. M.; Liu, H.; Lucas, J.; et al. Macrocyclic Lactams as Potent Hsp90 Inhibitors with Excellent Tumor Exposure and Extended Biomarker Activity. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3411−3416.
(91) Zapf, C. W.; Bloom, J. D.; McBean, J. L.; Dushin, R. G.; Golas, J. M.; Liu, H.; Lucas, J.; Boschelli, F.; Vogan, E.; Levin, J. I. Discovery of a Macrocyclic O-Aminobenzamide Hsp90 Inhibitor with Heterocyclic Tether That Shows Extended Biomarker Activity and in Vivo Efficacy in a Mouse Xenograft Model. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3627−3631.
(92) Zapf, C. W.; Bloom, J. D.; Li, Z.; Dushin, R. G.; Nittoli, T.; Otteng, M.; Nikitenko, A.; Golas, J. M.; Liu, H.; Lucas, J.; et al. Discovery of a Stable Macrocyclic O-Aminobenzamide Hsp90 Inhibitor Which Significantly Decreases Tumor Volume in a Mouse Xenograft Model. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4602−4607.
(93) Isaacs, J. S.; Xu, W.; Neckers, L. Heat Shock Protein 90 as a Molecular Target for Cancer Therapeutics. *Cancer Cell* **2003**, *3*, 213−217.
(94) Maloney, A.; Workman, P. HSP90 as a New Therapeutic Target for Cancer Therapy: The Story Unfolds. *Expert Opin. Biol. Ther.* **2002**, *2*, 3−24.
(95) Solit, D. B.; Chiosis, G. Development and Application of Hsp90 Inhibitors. *Drug Discovery Today* **2008**, *13*, 38−43.
(96) Huang, K. H.; Veal, J. M.; Fadden, R. P.; Rice, J. W.; Eaves, J.; Strachan, J.-P.; Barabasz, A. F.; Foley, B. E.; Barta, T. E.; Ma, W.; et al. Discovery of Novel 2-Aminobenzamide Inhibitors of Heat Shock Protein 90 as Potent, Selective and Orally Active Antitumor Agents. *J. Med. Chem.* **2009**, *52*, 4288−4305.
(97) Pajouhesh, H.; Feng, Z.-P.; Zhang, L.; Pajouhesh, H.; Jiang, X.; Hendricson, A.; Dong, H.; Tringham, E.; Ding, Y.; Vanderah, T. W.; et al. Structure−activity Relationships of Trimethoxybenzyl Piperazine N-Type Calcium Channel Inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4153−4158.
(98) Aronov, A. M. Predictive in Silico Modeling for HERG Channel Blockers. *Drug Discovery Today* **2005**, *10*, 149−155.
(99) Heckrodt, T. J.; Singh, R. General Route for the Preparation of Diverse 17-Membered Macrocycles Based on RCM and Examination of the E/Z Selectivity. *Synth. Commun.* **2012**, *42*, 2854−2865.
(100) Bahulayan, D.; Arun, S. An Easy Two Step Synthesis of Macrocyclic Peptidotriazoles via a Four-Component Reaction and Copper Catalyzed Intramolecular Azide-Alkyne [3 + 2] Click Cycloaddition. *Tetrahedron Lett.* **2012**, *53*, 2850−2855.
(101) Choudhary, A.; Raines, R. T. An Evaluation of Peptide-Bond Isosteres. *ChemBioChem* **2011**, *12*, 1801−1807.
(102) Dong, X.; Wang, Q.; Zhang, Q.; Xu, S.; Wang, Z. Construction of Dihydropyran-Bridged Macrocycles by Inverse-Electron-Demand Diels-Alder Reaction. *Tetrahedron* **2013**, *69*, 11144−11154.
(103) Wei, Q.; Harran, S.; Harran, P. G. Methods to Initiate Synthetic Re-Structuring of Peptides. *Tetrahedron* **2003**, *59*, 8947−8954.
(104) Zhao, H.; Negash, L.; Wei, Q.; LaCour, T. G.; Estill, S. J.; Capota, E.; Pieper, A. A.; Harran, P. G. Acid Promoted Cinnamyl Ion Mobility within Peptide Derived Macrocycles. *J. Am. Chem. Soc.* **2008**, *130*, 13864−13866.
(105) Lawson, K. V.; Rose, T. E.; Harran, P. G. Template-Constrained Macrocyclic Peptides Prepared from Native, Unprotected Precursors. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, E3753−E3760.
(106) Lawson, K. V.; Rose, T. E.; Harran, P. G. Template-Induced Macrocycle Diversity through Large Ring-Forming Alkylations of Tryptophan. *Tetrahedron* **2013**, *69*, 7683−7691.
(107) Rose, T. E.; Lawson, K. V.; Harran, P. G. Large Ring-Forming Alkylations Provide Facile Access to Composite Macrocycles. *Chem. Sci.* **2015**, *6*, 2219−2223.
(108) Ciardiello, J. J.; Galloway, W. R. J. D.; O'Connor, C. J.; Sore, H. F.; Stokes, J. E.; Wu, Y.; Spring, D. R. An Expedient Strategy for the Diversity-Oriented Synthesis of Macrocyclic Compounds with Natural Product-like Characteristics. *Tetrahedron* **2016**, *72*, 3567−3578.
(109) Maurya, S. K.; Rana, R. An Eco-Compatible Strategy for the Diversity-Oriented Synthesis of Macrocycles Exploiting Carbohydrate-Derived Building Blocks. *Beilstein J. Org. Chem.* **2017**, *13*, 1106−1118.
(110) Estrada-Ortiz, N.; Neochoritis, C. G.; Twarda-Clapa, A.; Musielak, B.; Holak, T. A.; Dömling, A. Artificial Macrocycles as Potent P53-MDM2 Inhibitors. *ACS Med. Chem. Lett.* **2017**, *8*, 1025−1030.
(111) Bista, M.; Wolf, S.; Khoury, K.; Kowalska, K.; Huang, Y.; Wrona, E.; Arciniega, M.; Popowicz, G. M.; Holak, T. A.; Dömling, A. Transient Protein States in Designing Inhibitors of the MDM2-P53 Interaction. *Structure* **2013**, *21*, 2143−2151.
(112) Kim, Y.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. Relationship of Stereochemical and Skeletal Diversity of Small Molecules to Cellular Measurement Space. *J. Am. Chem. Soc.* **2004**, *126*, 14740−14745.
(113) Lee, D.; Sello, J. K.; Schreiber, S. L. A Strategy for Macrocyclic Ring Closure and Functionalization Aimed toward Split-Pool Syntheses. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649.
(114) Peng, L. F.; Stanton, B. Z.; Maloof, N.; Wang, X.; Schreiber, S. L. Syntheses of Aminoalcohol-Derived Macrocycles Leading to a Small-Molecule Binder to and Inhibitor of Sonic Hedgehog. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6319−6325.
(115) Stanton, B. Z.; Peng, L. F.; Maloof, N.; Nakai, K.; Wang, X.; Duffner, J. L.; Taveras, K. M.; Hyman, J. M.; Lee, S. W.; Koehler, A. N.; et al. A Small Molecule That Binds Hedgehog and Blocks Its Signaling in Human Cells. *Nat. Chem. Biol.* **2009**, *5*, 154−156.
(116) Isidro-Llobet, A.; Murillo, T.; Bello, P.; Cilibrizzi, A.; Hodgkinson, J. T.; Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. Diversity-Oriented Synthesis of Macrocyclic Peptidomimetics. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6793−6798.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

(117) Bock, V. D.; Speijer, D.; Hiemstra, H.; van Maarseveen, J. H. 1,2,3-Triazoles as Peptide Bond Isosteres: Synthesis and Biological Evaluation of Cyclotetrapeptide Mimics. *Org. Biomol. Chem.* **2007**, *5*, 971−975.
(118) Springer, J.; de Cuba, K. R.; Calvet-Vitale, S.; Geenevasen, J. A. J.; Hermkens, P. H. H.; Hiemstra, H.; van Maarseveen, J. H. Backbone Amide Linker Strategy for the Synthesis of 1,4-Triazole-Containing Cyclic Tetra- and Pentapeptides. *Eur. J. Org. Chem.* **2008**, *2008*, 2592−2600.
(119) Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; van Maarseveen, J. H. Click Chemistry as a Route to Cyclic Tetrapeptide Analogues: Synthesis of Cyclo-[Pro-Val-ψ(Triazole)-Pro-Tyr]. *Org. Lett.* **2006**, *8*, 919−922.
(120) Horne, W. S.; Olsen, C. A.; Beierle, J. M.; Montero, A.; Ghadiri, M. R. Probing the Bioactive Conformation of an Archetypal Natural Product HDAC Inhibitor with Conformationally Homogeneous Triazole-Modified Cyclic Tetrapeptides. *Angew. Chem., Int. Ed.* **2009**, *48*, 4718−4724.
(121) Niu, T.; Sun, M.; Lv, M.; Yi, W.; Cai, C. Synthesis of Highly Functionalized Macrocycles by Tandem Multicomponent Reactions and Intramolecular Sonogashira Cross-Coupling. *Org. Biomol. Chem.* **2013**, *11*, 7232−7238.
(122) Niu, T.; Gu, L.; Wang, L.; Yi, W.; Cai, C. Chemoselective Preparation of Unsymmetrical Bis(1,2,3-Triazole) Derivatives and Application in Bis(1,2,3-Triazole)-Modified Peptidomimetic Synthesis. *Eur. J. Org. Chem.* **2012**, *2012*, 6767−6776.
(123) Beckmann, H. S. G.; Nie, F.; Hagerman, C. E.; Johansson, H.; Tan, Y. S.; Wilcke, D.; Spring, D. R. A Strategy for the Diversity-Oriented Synthesis of Macrocyclic Scaffolds Using Multidimensional Coupling. *Nat. Chem.* **2013**, *5*, 861−867.
(124) Grossmann, A.; Bartlett, S.; Janecek, M.; Hodgkinson, J. T.; Spring, D. R. Diversity-Oriented Synthesis of Drug-Like Macrocyclic Scaffolds Using an Orthogonal Organo- and Metal Catalysis Strategy. *Angew. Chem., Int. Ed.* **2014**, *53*, 13093−13097.
(125) Nie, F.; Kunciw, D. L.; Wilcke, D.; Stokes, J. E.; Galloway, W. R. J. D.; Bartlett, S.; Sore, H. F.; Spring, D. R. A Multidimensional Diversity-Oriented Synthesis Strategy for Structurally Diverse and Complex Macrocycles. *Angew. Chem., Int. Ed.* **2016**, *55*, 11139−11143.
(126) Huigens, R. W., III; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr.; Richter, M. F.; Hergenrother, P. J. A Ring-Distortion Strategy to Construct Stereochemically Complex and Structurally Diverse Compounds from Natural Products. *Nat. Chem.* **2013**, *5*, 195−202.
(127) Ciardiello, J. J.; Stewart, H. L.; Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. A Novel Complexity-to-Diversity Strategy for the Diversity-Oriented Synthesis of Structurally Diverse and Complex Macrocycles from Quinine. *Bioorg. Med. Chem.* **2017**, *25*, 2825−2843.
(128) Maurya, S. K.; Dow, M.; Warriner, S.; Nelson, A. Synthesis of Skeletally Diverse Alkaloid-like Molecules: Exploitation of Metathesis Substrates Assembled from Triplets of Building Blocks. *Beilstein J. Org. Chem.* **2013**, *9*, 775−785.
(129) Dow, M.; Marchetti, F.; Abrahams, K. A.; Vaz, L.; Besra, G. S.; Warriner, S.; Nelson, A. Modular Synthesis of Diverse Natural Product-Like Macrocycles: Discovery of Hits with Antimycobacterial Activity. *Chem. - Eur. J.* **2017**, *23*, 7207−7211.
(130) Isidro-Llobet, A.; Georgiou, K. H.; Galloway, W. R. J. D.; Giacomini, E.; Hansen, M. R.; Méndez-Abt, G.; Tan, Y. S.; Carro, L.; Sore, H. F.; Spring, D. R. A Diversity-Oriented Synthesis Strategy Enabling the Combinatorial-Type Variation of Macrocyclic Peptidomimetic Scaffolds. *Org. Biomol. Chem.* **2015**, *13*, 4570−4580.
(131) Su, S.; Acquilano, D. E.; Arumugasamy, J.; Beeler, A. B.; Eastwood, E. L.; Giguere, J. R.; Lan, P.; Lei, X.; Min, G. K.; Yeager, A. R.; et al. Convergent Synthesis of a Complex Oxime Library Using Chemical Domain Shuffling. *Org. Lett.* **2005**, *7*, 2751−2754.
(132) Comer, E.; Liu, H.; Joliton, A.; Clabaut, A.; Johnson, C.; Akella, L. B.; Marcaurelle, L. A. Fragment-Based Domain Shuffling Approach for the Synthesis of Pyran-Based Macrocycles. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6751−6756.
(133) Zhu, T.; Boons, G.-J. A Two-Directional Approach for the Solid-Phase Synthesis of Trisaccharide Libraries. *Angew. Chem., Int. Ed.* **1998**, *37*, 1898−1900.
(134) Harding, M.; Nelson, A. A General, Two-Directional Synthesis of C-(1→6)-Linked Disaccharide Mimetics: Synthesis from Non-Carbohydrate Based Starting Materials. *Chem. Commun.* **2001**, 695−696.
(135) Procopiou, G.; Aggarwal, P.; Newton, A. F.; Richards, D.; Mellor, I. R.; Harbottle, G.; Stockman, R. A. Two-Directional Synthesis and Biological Evaluation of Alkaloid 5-Epi-Cis-275B′. *Chem. Commun.* **2014**, *50*, 15355−15357.
(136) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. Rapid Two-Directional Synthesis of the F-J Fragment of the Gambieric Acids by Iterative Double Ring-Closing Metathesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157−6162.
(137) Ikemoto, N.; Schreiber, S. L. Total Synthesis of (−)-Hikizimycin Employing the Strategy of Two-Directional Chain Synthesis. *J. Am. Chem. Soc.* **1992**, *114*, 2524−2536.
(138) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. A Two-Directional Synthesis of (±)-Perhydrohistrionicotoxin. *J. Org. Chem.* **2004**, *69*, 1598−1602.
(139) Al-Saffar, F. M.; Brown, R. C. D. A Two-Directional Synthesis of (+)-β-Isosparteine. *Org. Lett.* **2017**, *19*, 3502−3504.
(140) O'Connell, K. M. G.; Beckmann, H. S. G.; Laraia, L.; Horsley, H. T.; Bender, A.; Venkitaraman, A. R.; Spring, D. R. A Two-Directional Strategy for the Diversity-Oriented Synthesis of Macrocyclic Scaffolds. *Org. Biomol. Chem.* **2012**, *10*, 7545−7551.
(141) Kitsiou, C.; Hindes, J. J.; I'Anson, P.; Jackson, P.; Wilson, T. C.; Daly, E. K.; Felstead, H. R.; Hearnshaw, P.; Unsworth, W. P. The Synthesis of Structurally Diverse Macrocycles By Successive Ring Expansion. *Angew. Chem., Int. Ed.* **2015**, *54*, 15794−15798.
(142) Stephens, T. C.; Lodi, M.; Steer, A. M.; Lin, Y.; Gill, M. T.; Unsworth, W. P. Synthesis of Cyclic Peptide Mimetics by the Successive Ring Expansion of Lactams. *Chem. - Eur. J.* **2017**, *23*, 13314−13318.
(143) Bäurle, S.; Blume, T.; Mengel, A.; Parchmann, C.; Skuballa, W.; Bäsler, S.; Schäfer, M.; Sülzle, D.; Wrona-Metzinger, H.-P. From Rigidity to Conformational Flexibility: Macrocyclic Templates Derived from Ansa-Steroids. *Angew. Chem., Int. Ed.* **2003**, *42*, 3961−3964.
(144) Bäurle, S.; Blume, T.; Günther, J.; Henschel, D.; Hillig, R. C.; Husemann, M.; Mengel, A.; Parchmann, C.; Schmid, E.; Skuballa, W. Design and Synthesis of Macrocyclic Inhibitors of Phosphatase Cdc25B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1673−1677.
(145) Bäurle, S.; Blume, T.; Leroy, E.; Mengel, A.; Parchmann, C.; Schmidt, K.; Skuballa, W. Novel Macrocyclic Templates by Ring Enlargement of Ansa-Steroids. *Tetrahedron Lett.* **2004**, *45*, 9569−9571.
(146) Chowdhury, P. K.; Prelle, A.; Schomburg, D.; Thielmann, M.; Winterfeldt, E. Ansa-Seco-Steroide. *Liebigs Ann. Chem.* **1987**, *1987*, 1095−1099.
(147) Schomburg, D.; Thielmann, M.; Winterfeld, E. Ansa-Steroids. *Tetrahedron Lett.* **1985**, *26*, 1705−1706.
(148) Prelle, A.; Winterfeldt, E. From Steroids to Macrolides. *Heterocycles* **1989**, *28*, 333−346.
(149) Winterfeldt, E. Ansasteroide: Neues von Einem Neuartigen Verbindungstyp. *Chim. Int. J. Chem.* **1993**, *47*, 39−45.
(150) Kumar, N.; Kiuchi, M.; Tallarico, J. A.; Schreiber, S. L. Small-Molecule Diversity Using a Skeletal Transformation Strategy. *Org. Lett.* **2005**, *7*, 2535−2538.
(151) Kopp, F.; Stratton, C. F.; Akella, L. B.; Tan, D. S. A Diversity-Oriented Synthesis Approach to Macrocycles via Oxidative Ring Expansion. *Nat. Chem. Biol.* **2012**, *8*, 358−365.
(152) Hückel, W.; Danneel, R.; Schwartz, A.; Gercke, A. Zur Stereochemie Bicyclischer Ringsysteme. V. Δ9,10-Oktalin. *Justus Liebigs Ann. Chem.* **1929**, *474*, 121−144.
(153) Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [n]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem., Int. Ed.* **2014**, *53*, 8705−8708.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317

(154) Acharya, A.; Eickhoff, J. A.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. Access to Bicyclic Hydroxamate Macrocycles via Intramolecular Aza-(4 + 3) Cyloaddition Reactions of Aza-Oxyallylic Cation Intermediates. *Org. Chem. Front.* **2016**, *3*, 330−334.
(155) Bauer, R. A.; Wenderski, T. A.; Tan, D. S. Biomimetic Diversity-Oriented Synthesis of Benzannulated Medium Rings via Ring Expansion. *Nat. Chem. Biol.* **2013**, *9*, 21−29.
(156) Jones, A. M.; Lorion, M. M.; Lebl, T.; Slawin, A. M. Z.; Philp, D.; Westwood, N. J. The Chemical Reactivity of a Known Anti-Psoriasis Drug. Part 1: Further Insights into the Products Resulting from Oxidative Cleavage. *Tetrahedron* **2010**, *66*, 9667−9674.
(157) Lebl, T.; Lorion, M. M.; Jones, A. M.; Philp, D.; Westwood, N. J. Synthesis and Characterisation of Medium-Sized Ring Systems by Oxidative Cleavage. Part 2: Insights from the Study of Ring Expanded Analogues. *Tetrahedron* **2010**, *66*, 9694−9702.
(158) Lobato, R.; Veiga, A. X.; Pérez-Vázquez, J.; Fernández-Nieto, F.; Paleo, M. R.; Sardina, F. J. A One-Step, Versatile Synthesis of Dibenzo [n.2.2] Macrobicyclic Compounds via a Conformation-Directed Macrocyclization Reaction. *Org. Lett.* **2013**, *15*, 4090−4093.
(159) Guarnieri-Ibáñez, A.; Medina, F.; Besnard, C.; Kidd, S. L.; Spring, D. R.; Lacour, J. Diversity-Oriented Synthesis of Heterocycles and Macrocycles by Controlled Reactions of Oxetanes with α-Iminocarbenes. *Chem. Sci.* **2017**, *8*, 5713−5720.
(160) Ding, H.; DeRoy, P. L.; Perreault, C.; Larivée, A.; Siddiqui, A.; Caldwell, C. G.; Harran, S.; Harran, P. G. Electrolytic Macrocyclizations: Scalable Synthesis of a Diazonamide-Based Drug Development Candidate. *Angew. Chem., Int. Ed.* **2015**, *54*, 4818−4822.
(161) Wieczorek, M.; Tcherkezian, J.; Bernier, C.; Prota, A. E.; Chaaban, S.; Rolland, Y.; Godbout, C.; Hancock, M. A.; Arezzo, J. C.; Ocal, O.; et al. The Synthetic Diazonamide DZ-2384 Has Distinct Effects on Microtubule Curvature and Dynamics without Neurotoxicity. *Sci. Transl. Med.* **2016**, *8*, 365ra159−365ra159.
(162) Fernandes, P.; Martens, E.; Pereira, D. Nature Nurtures the Design of New Semi-Synthetic Macrolide Antibiotics. *J. Antibiot.* **2017**, *70*, 527−533.

DOI: 10.1021/acs.chemrev.9b00084
Chem. Rev. 2019, 119, 10288−10317