Multiple Multicomponent Macrocyclizations (MiBs): A Strategic Development Toward Macrocycle Diversity

Ludger A. Wessjohann,* Daniel G. Rivera, and Otilie E. Vercillo

Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle/Saale, Germany

Received December 11, 2006

Contents

1. Introduction

Macrocycles are of high significance in areas as diverse as drug development and supramolecular chemistry. They can be considered as privileged molecules because they can combine flexibility and conformational bias. They allow a certain conformational adaptation for binding and at the same time can have an improved overall energy term while binding, compared to linear molecules. Recently, a diversity-oriented macrocyclization strategy termed multiple multicomponent macrocyclization including bifunctional building blocks (MiB) was developed which allows producing constitutionally diverse and complex macrocycles from simple building blocks in one pot.

The efficient search for novel molecular ligands of biological targets remains a continuing goal in drug discovery and chemical biology.[1−3] In the past, the predominant interest of medicinal chemists in synthetic ligands has been devoted to small rings (especially heterocycles) because of their known capability to interact with defined protein motifs and their ease of preparation. Huge libraries, including combinatorial ones,[4,5] have been synthesized by means of well-established processes and screened for biological activity. Lately, macrocycles have attracted increasing attention also by virtue of both their high success rate in medicinal and recognition chemistry and their widespread occurrence in nature.[6−10] The demand for bioactive compounds with new application profiles has triggered the search for molecules with biological features that simple 5/6/7-ring (hetero)cycles do not bear.[8−12] Macrocycles are usually endowed with a proper combination of more than one binding domain, conformational preorganization, and flexibility.[8,13,14] Their structural, physicochemical, and biological features provide recognition and binding properties not found in linear or small ring counterparts.[14] For example, their often increased biological stability compared to acyclic analogues (e.g., cyclopeptides compared to peptides) makes them a fascinating paradigm to design biologically active molecules.[8−14] Combinatorial synthetic chemistry in the macrocycle field does not yet reflect the tremendous impact of naturally occurring macrocycles in areas such as antibiotics, immunosuppressants, ion chelators, or membrane active compounds, where their success rate appears to be overproportional (in relative terms) compared to other drug types.[6−9,15]

The high incidence of macrocyclic structures is not limited to drug development.[8,11,12,14] Macrocycles are also common in areas as diverse as material sciences or supramolecular chemistry.[16,17] Especially in the latter area, success is founded in the chemists' capability to devise efficient strategies toward the synthesis of such compounds. Macrocycles with repetitive elements are usually cyclized homooligomers like the well-known calixarenes,[18] cyclodextrines,[19] cyclophanes,[17] and crown ethers[20] but also the cyclocholates[21] and cyclocholamides.[21−23] In contrast to these latter compounds that are available by a range of current synthetic methodologies, heterooligomeric or other nonrepetitive macrocycles, especially those containing natural motifs of interesting biological relevance,[8] are a major synthetic challenge. This is due to the high synthetic cost to produce them through specialized, single-case adapted total syntheses,[10,14,24] which nevertheless has rendered new generations of, e.g., antibiotics[9,24−26] or anticancer agents.[9,27−31] The scope of such individual macrocycle total syntheses is restricted to variations of such structures which possess an activity profile that can compensate for the effort and cost of the required multistep approach, usually derived from a natural product lead compound. However, such individual macrocycle syntheses are not yet an economic alternative for prospective drug discovery research or for finding highly selective and specific supramolecular hosts.

A useful solution may be to shift part of the focus from nature's lead compounds to nature's way to create those active molecules and thus mimic it. An important step in this direction would be to achieve the iterative generation of diverse molecular entities bearing those chemical motifs[8]

* To whom correspondence should be addressed. Phone: +49 345 5582 1301. Fax: +49 345 5582 1309. E-mail: wessjohann@ipb-halle.de.

10.1021/cr8003407 CCC: $71.50 © 2009 American Chemical Society
Published on Web 01/23/2009

Ludger Wessjohann studied chemistry in Hamburg (Germany) and Southampton (U.K.). He received his degree in 1987 and his Ph.D. degree in 1990 from the University of Hamburg for work on cyclopropane chemistry under the supervision of Professor Armin de Meijere, including a sandwich period with Professor Lars Skattebøl in Oslo (Norway, 1987/88). In 1990 he became a lecturer and advisor for a German government organization at the Universidade Federal de Santa Maria (Brazil), where he also was a visiting professor in 1993 and 1995. From late 1990 to 1992 he was a postdoctoral fellow of the Alexander von Humboldt Foundation with Professor Paul Wender at Stanford University, working on the total synthesis of Taxol. Returned to Germany, he became an assistant professor at the Ludwig-Maximilians-Universität München and received his "Habilitation" in July 1998. In June 1998 he became Full Professor of Bio-Organic Chemistry at the Vrije Universiteit Amsterdam (The Netherlands). In 1999/2000 he received calls to several universities in Germany and accepted one to the Leibniz Institute of Plant Biochemistry in Halle (Germany), a basic research institute of the Leibniz association. Since late 2000 he has been Director of the Department of Bio-Organic Chemistry and holds the chair of natural product chemistry at the Martin-Luther-Universität Halle-Wittenberg. His research interests include target and diversity oriented synthesis for recognition and medicinal chemistry, biocatalysis, and natural products chemistry. His work is published in over 170 scientific papers and books and several licensed patents.

Daniel G. Rivera was born in Santa Clara, Cuba, in 1978. He received his B.Sc. (first honors) and M.Sc. degrees in Chemistry from the University of Havana in 2002 and 2003, respectively. Recently he completed his Ph.D. thesis in the group of Professor L. A. Wessjohann, working on the development of diversity-oriented macrocyclization approaches based on multicomponent reactions. Simultaneously, he has held a research position at the Center for Natural Product Study of the University of Havana, working on the design and synthesis of biologically active steroid derivatives.

(i.e., privileged substructures based on evolution) capable to be recognized by specific biological targets.[12] This conveys that one does not only replicate nature's active structures by chemical synthesis[24−31] or utilize biomimetic pathways to access them[32,33] but also to learn from nature's principles.[8] One way can be to create the high degree of complexity and

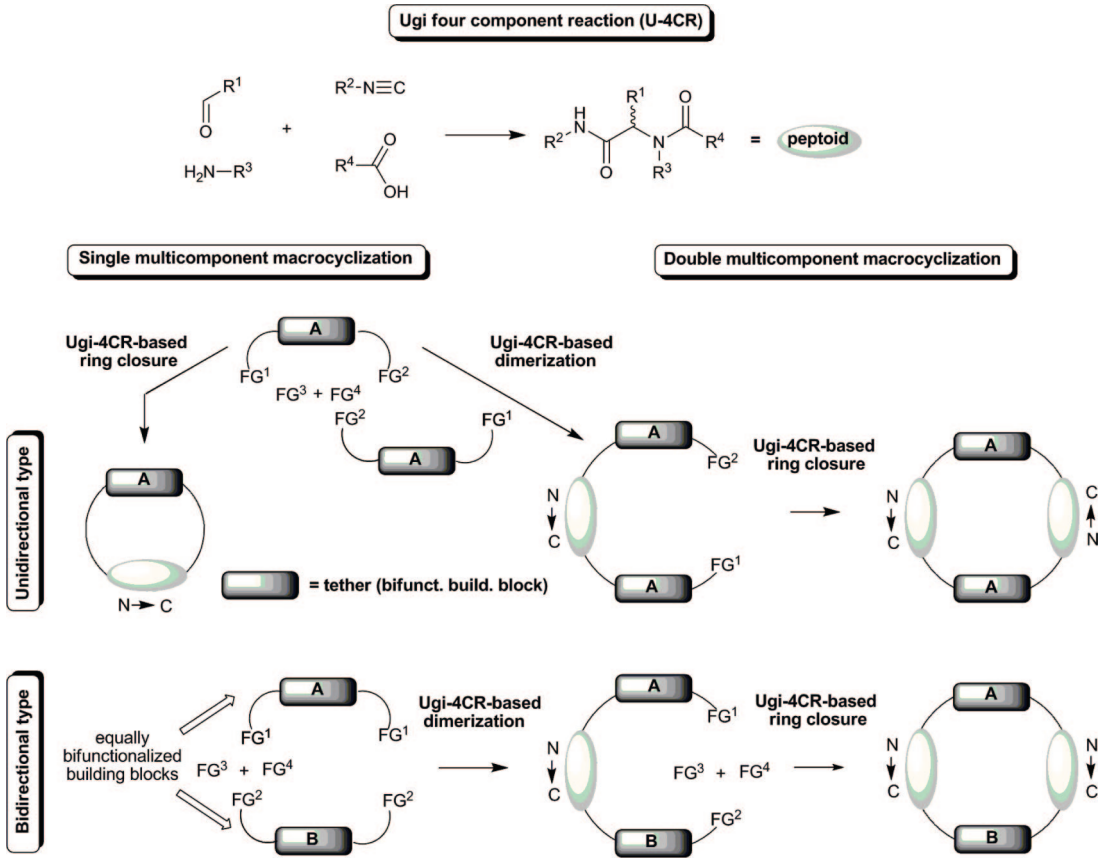
Otilie E. Vercillo was born in Brasília, Brazil, in 1979. She received her B.Sc. and M.Sc. degrees in Chemistry from the University of Brasília in 2000 and 2004, respectively. She obtained her Ph.D. degree in November 2007 at the University of Brasília with Professor Carlos Kleber de Andrade with several stays as a guest researcher in the group of Professor L. A. Wessjohann at the Leibniz-Institute of Plant Biochemistry. Her research focuses on the synthesis of new cyclic peptides and peptoids with potential bioactivity.

diversity found in natural macrocycles from simple and defined building blocks. Ideally the residues of such building blocks are mimics of or identical to natural moieties selected by evolution for binding to biological targets, e.g., natural amino acid side chains.

Several methodologies are amenable to implement fast and efficient chemical syntheses focusing on this idea. Useful methods are additionally suitable for automation and include iterative ones (e.g., Merrifield synthesis), click processes, and multicomponent reactions (MCRs). Of these, the latter ones offer optimum speed and diversity access. Diversity-oriented organic synthesis encompasses an efficient approach toward libraries of structurally diverse molecules, including macrocycles.[3,34] However, in most macrocycle syntheses the ring-closing reactions are usually performed at a late stage of the synthetic route.[10,14] While some (e.g., metathesis, lactonization, peptide coupling) can be quite efficient for ring closure, they cannot be considered as diversity-generating reactions.[34] Therefore, installation of diversity within a macrocyclic scaffold is mainly accomplished before or after the crucial cyclization step.[14,35−38] MCRs have been used by many groups to produce linear precursors to be subsequently cyclized using a wide set of ring-closing reactions, e.g., by Dömling,[39] Schreiber,[40] Zhu,[41−44] Wessjohann,[45] and others.[46−48] However, few groups have concentrated on using the MCR itself also for the macrocyclization step.

This review will concentrate on those approaches which produce macrocycles wherein the MCR is (also) responsible for the macrocyclization itself. MCR-based macrocyclization strategies are very suitable to generate highly diverse macrocyclic scaffolds displaying sufficient molecular complexity to resemble natural product-like ones.[8−10,14] Recently, this issue has been addressed by the development of a diversity-oriented strategy for macrocycle synthesis termed multiple multicomponent macrocyclization including bifunctional building blocks (MiB).[49,50] The MiB approach embodies an original concept of how organic chemists can design and create complex macrocycles, natural or other, from simple building blocks in a very straightforward and versatile process suitable for library construction. The Ugi four-component reaction (U-4CR) in its original form is currently the most studied MCR in macrocyclizations. Accordingly,

Scheme 1. General Scheme of Multiple Multicomponent Macrocyclizations Including Bifunctional Building Blocks (MiBs) Exemplified by the Ugi-4CR-variant[a]



[a] FG^{1-4} refer to the Ugi-4CR reactive functionalities ($-C{=}O$, $-NH_2$, $-NC$, $-CO_2H$) in any combination. Ovals: peptoid moiety formed in a single Ugi-4CR. Boxes: bifunctional building blocks containing two Ugi-FG's.

the first sections of this review will concentrate on the Ugi-variant of MiBs to demonstrate the underlying principles of macrocycle formation and diversity generation followed by other multiple MCR macrocyclizations in later sections.

2. Synthetic Strategy Based on the Ugi-4CR

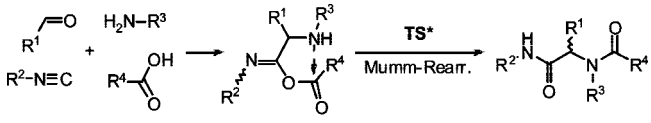
2.1. Chronology of the Multiple Multicomponent Macrocyclizations

The Ugi four-component reaction (Ugi-4CR)[51−53] is a highly efficient process in which a primary amine, an oxo compound, a carboxylic acid, and an isocyanide react in one pot to form a *N*-substituted dipeptide backbone, hereafter called "peptoid". Peptoids are *N*-substituted oligoglycines most commonly without an α substituent. However, α substitution is additionally acceptable in the extended use of the term for *N*-substituted oligopeptides applied here. The high diversity of substitution patterns at the peptoid skeleton that results from the simple combination of each one of the four components was already envisioned by Ugi in 1961.[52] This idea is now considered one of the pioneering findings of combinatorial chemistry and derived concepts have evolved to allow scaffold variations of many types.[53] The Ugi-4CR and other isocyanide-based MCRs have emerged as useful tools in diversity-oriented synthesis and been favorably exploited in drug discovery.[53−59] Special interest has been posed in utilizing these procedures to assemble either hetero- or polycyclic systems, especially because of their great versatility and scope as complexity-generating reactions.[34,60,61] In spite of this, the potential and clear advantage of the Ugi-4CR and other MCRs as ring-closing reactions also for medium and large rings have been underestimated so far.

Scheme 1 outlines the general principles of the MiB methodology, in this case exemplified by the Ugi-4CR. A single Ugi-4CR-based macrocyclic ring closure is possible to occur when a building block is functionalized with two counter Ugi reactive functional groups and subjected to typical macrocyclization conditions. Indeed, the process succeeds if the resulting macrocycle and/or its precursor α adduct and the Mumm rearrangement intermediate are not too strained (see Table 1 for size changes during an Ugi-MiB; a detailed discussion of this problem can be found in ref 49). On the other hand, if either a too short or a too rigid bifunctional building block excludes direct ring closure, a dimerization reaction can occur to allow later a subsequent Ugi-4CR-based ring closure. This latter process is referred to as a double Ugi-4CR-based macrocyclization. When utilizing the Ugi-4CR as a ring-closing reaction at least one of the diversity elements is obviously lost as a consequence of the necessity to have a bifunctional building block, i.e., two Ugi reactive functional groups are required on a single acyclic precursor. This will eventually lead to unidirectional macrocycles (*v.i.*).

One way to avoid such a loss of diversity elements is the use of two identical Ugi reactive functional groups in a single building block, thus leading to bidirectional macrocycles (*v.i.*). It should be noted that Ugi already used such building

Table 1. Relative Ring Size of the Ugi (or Passerini) Macrocyclization Product with Respect to the α Adduct[a]



	bifunctional component A		
bifunctional component B	aldehyde (R^1)	isonitrile (R^2)	amine (R^3)
acid (R^4)	−1*	+1*	−3
amine (R^3)	0	0*	
isonitrile (R^2)	0		

[a] (+) Ring enlargement, i.e., the α intermediate is smaller than the final ring size. (−) Ring contraction, i.e., the final ring size is smaller than that of the intermediate. Combinations with a potentially strained ansa type transition state are marked with an asterisk.

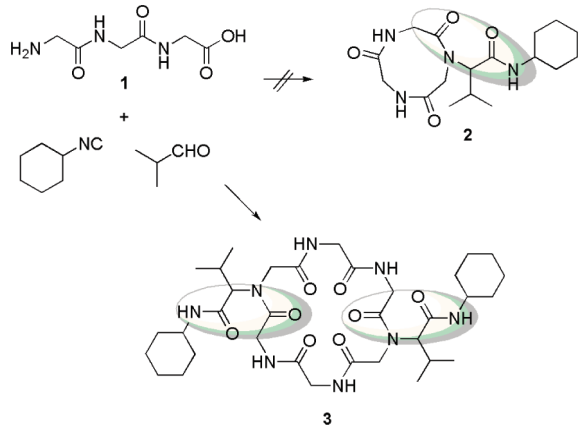
blocks in an approach toward the synthesis of polymers.[62] In order to apply the same methodology to the synthesis of macrocycles, ways to favor the macrocyclization versus further oligomerization are required during the design of the building blocks and synthetic setup. As usual, dilution conditions, structural preorganization, or template effects are helpful to overcome the entropically disfavored ring closure from large acyclic precursors.

The two basic variations, using either differently or equally bifunctionalized building blocks, will lead to uni- and bidirectional MCR-based macrocyclizations, respectively (Scheme 1). When designing multiple MCR-based macrocyclizations the conceptual differences between these two basic types must be considered. While in the bidirectional case dimerization is the only possible initial step, the unidirectional one comprises a competition between the direct intramolecular ring closure and dimerization (i.e., single- versus double-MCR-based macrocyclization). As will be shown in this review, the rigidity of the building blocks and folding of the acyclic precursors have a marked influence in the multiplicity of the MCR-based macrocyclizations.

In the case of Ugi-4CR-based macrocyclizations the directionality of the approach is identical to that of the resulting peptoid backbones. As peptide derivatives possess a N and C terminus, the peptoid chains arising from the multiple Ugi-4CRs can run in either the same or counter directions (one clockwise N → C and the other counter clockwise N → C). An advantage of unidirectional MiBs is their higher similarity to the equally unidirectional natural cyclopeptides.[9] However, because of the much easier synthesis of building blocks with identical MCR reactive functional groups and the (n + 1) times higher possibility of diversity generation, bidirectional approaches are now usually favored. From the diversity generation point of view, the unidirectional type also lacks the possibility to easily create skeletal diversity arising from differentiation of the building blocks. Additional drawbacks lie in the incompatibility of some functional groups, a subject that should not be considered trivial regarding the forthcoming automated production of macrocycle libraries.

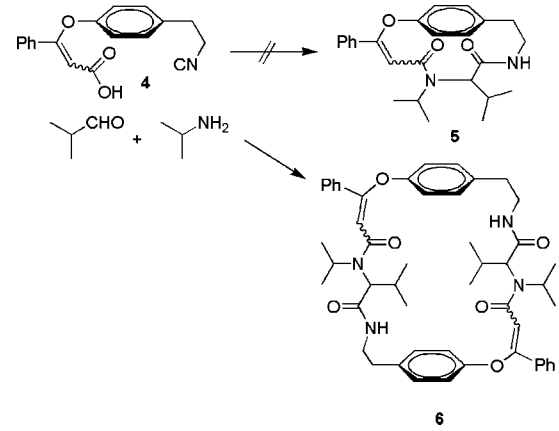
To our knowledge, the first report of a MCR-based (unidirectional) macrocyclization was described by Failli et al.[63] Attempts to obtain the strained 9-membered cyclopeptide **2** from tripeptide **1** via Ugi-4CR as the ring-closing reaction produced only the dimeric cyclopeptide **3**, which is based on two Ugi-4CRs. Interestingly, this result prompted the same group to use the Ugi-4CR to cycle hexapeptides, but further investigations on the use of this multicomponent

Scheme 2. Double Ugi-4CR-Based Macrocyclization of a Short Triglycine[a]



[a] Oval: Peptoid moieties formed by the Ugi-4CRs.

Scheme 3. Double Ugi-4CR-Based Macrocyclization of a Short, Rigid Building Block

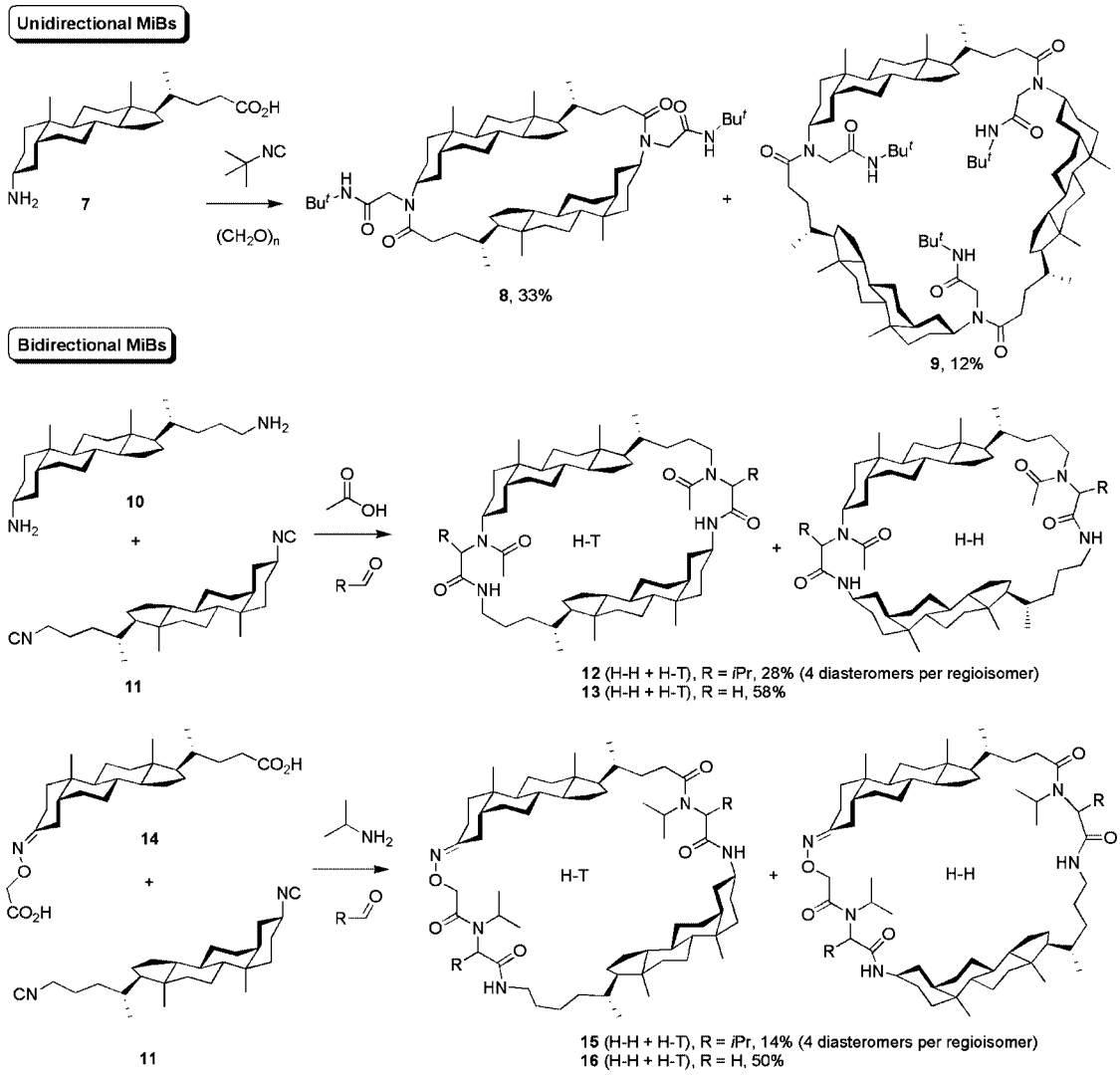


approach in cyclooligomerization reactions were not carried out. A similar approach has recently been used in a sequential Ugi-oligomerization/Ugi-macrocyclization to produce RGD-cyclopentapeptoids.[64]

The second appearance of a double-Ugi-4CR-based macrocyclization emerged from our laboratory[65] in 2001 in the frame of an extended program toward the synthesis of mimics of ansacyclic cyclopeptide alkaloids[66] (cf. **5** in Scheme 3). Several disconnection points could be envisaged for the possible macrocyclic ring closure to the relatively strained 14-membered ansa-macrocycle, e.g., aryl−alkyl ether bond formation via intramolecular S_NAr[67,68] versus the Ugi-4CR-based ring closure.[48,65] Attempts toward the synthesis of the ansa-cyclopeptoid **5** from bifunctional building block **4** led to the interesting result that the dimeric cyclopeptoid **6** was formed as the major product of the macrocyclization step. The nowadays obvious explanation is the inability of the linear intermediate either to form the cyclic α adduct of the reaction or to pass the very strained ansa-cyclic Mumm intermediate.[49] This fact disfavors direct intramolecular Ugi-4CR-based ring closure, and therefore, the intermediates evade strain build up by dimerization and subsequent cyclization leading to the 28-membered macrocycle **6**.[48,49]

The intriguing results afforded by these two 'unfortunate' examples prompted the development of a more general research program toward production of macrocycle libraries. Accordingly, it became necessary to devise the theoretical

Scheme 4. Double Ugi-4CR-Based Macrocyclization of Steroidal Bifunctional Building Blocks[a]



[a] For **12**, **13**, **15**, and **16** yields refer to a mixture of head-to-head (H−H) and head-to-tail (H−T) regioisomers and the diasteromeric mixture for **12** and **15**.[50,75]

principles and practical requisites for a general methodology to produce macrocycles based on multiple multicomponent reactions.

2.2. Underlying Principles of the Synthetic Design of Multiple Ugi-4CR-Based Macrocyclizations

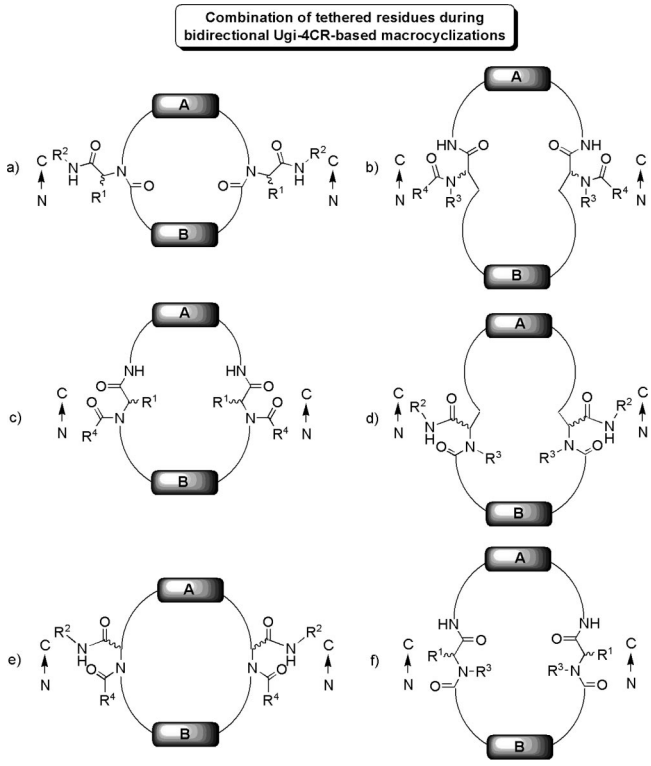
Initial efforts were directed to understanding the chemical and structural requirements for a successful synthetic planning that allows bifunctional building blocks to undergo multiple MCR macrocyclizations instead of direct intramolecular ring closure or linear polymerization. Thus, the first attempts to understand the synthetic and design requirements to achieve MiBs in high yield started in 1998 and utilized steroidal bifunctional scaffolds to build small libraries of steroid−peptoid hybrid macrocycles.[69]

Scheme 4 shows the first system in which very large steroidal macrocycles were obtained in excellent yields considering their very complex structures.[50] Several structural features make steroids suitable architectural components in macrocycle syntheses.[21,70,71] They present one of the few extended, rigid, and readily available chiral units. Their rigidity avoids back-folding to undergo direct intramolecular ring closure. Also, they can be functionalized easily by established procedures to assemble macrocyclic frameworks containing rigid arrays of concave-directed functionalities suitable for ion pair and molecular recognition.[70−74]

Initially, both mono- and bidirectional approaches were performed to assess the advantages and limitations of the two basic variations. The unidirectional double-Ugi-4CR-based macrocyclization is illustrated by formation of macrocycles **8** and **9** from the differently bifunctionalized steroid amino acid **7**.[75] For the bidirectional type, diamine **10** and diacid **14** were used as counterparts of diisonitrile **11** to afford macrocycles **12** and **13**, and **15** and **16**, respectively.[50]

As shown in Schemes 1 and 4 the bidirectional approach offers more possibilities to generate skeletal diversity derived from the use of varied scaffolds, e.g., head-to-tail (H−T) and head-to-head (H−H) isomers can be obtained from structurally unsymmetric or stereochemically asymmetric bifunctional building blocks with identical MCR reactive termini (FG's). This might be seen as a drawback because separation of the isomers is required and their characterization can be difficult. However, the regioisomerism definitely represents an additional gain with respect to diversity generation. Alternatively, tuning of the identical Ugi reactive

Scheme 5. Skeletal Diversity of the Peptoid Moieties Available from Bidirectional Ugi-MiBs by Varying the Ugi Reactive Functional Groups at the Bifunctional Building Blocks in the $N^B \rightarrow C^A$ series ($N^A \rightarrow C^B$ series is not shown)[a]



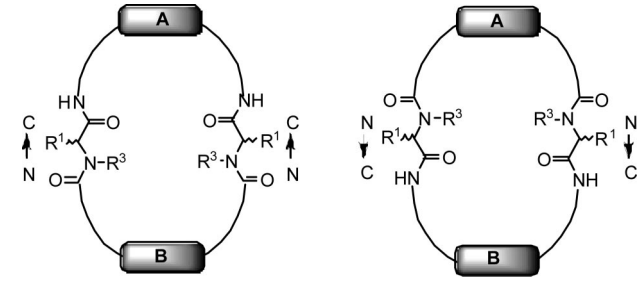
[a] Legend: (a) A-diamine + B-diacid, (b) A-diisocyanide + B-dialdehyde, (c) A-diisocyanide + B-diamine, (d) A-dialdehyde + B-diacid, (e) A-dialdehyde + B-diamine, (f) A-diisocyanide + B-diacid. Monofunctional building blocks are R^1−CHO, R^2−N≡C, R^3−NH_2, R^4−COOH.

functional groups may allow differential reactivity of one end versus the other, thus leading to preferential formation of one of the regioisomers. Molecular modeling and analysis of the chromatography behavior (*v.i.*) have shown that H−H and H−T macrocycles arising from the same building blocks usually have very different shapes and properties.[49,75]

Focusing on the latter outlook, the stereochemically unselective nature of the Ugi-4CR can be exploited by varying the nature of the oxo component toward generation of stereochemical diversity. For example, using isobutyraldehyde in the bidirectional approach all stereoisomers were formed in close to equal amounts as demonstrated by HPLC analysis of the library.[50,69] This prospect is of outstanding significance for the rapid generation of stereochemical diversity in macrocycle libraries built for activity/property screenings. As is evident from Scheme 4, the number of products also depends on the structural symmetry of the bifunctional building blocks used in the bidirectional approach. Use of at least one bifunctional building block with a C_2-symmetry axis halfway between the two MCR reactive groups ("symmetric" building block) will produce only one regioisomer. If all bifunctional building blocks are additionally achiral, this will reduce the number of diastereomers to one-half, a sometimes desired feature if structural analysis is only possible by such simplifications. Examples focusing on this possibility will be discussed later (Scheme 5 and Table 2).

Another prime feature that makes the MiB strategy unique is the straightforward assembly of nonrepetitive macrocyclic skeletons, e.g., though in macrocycles **12** and **13** the peptoid

Table 2. Number of Library Members Available for All but One Example: The Diacid/Diisocyanide Combination of Double Ugi-MiBs (cf. Scheme 5f)[a]



diversity elements				
bifunctional building block	oxo-cpd	constitut. isomers	diastereomers	all isoforms
sym. A = sym. B	R^1 = H	1	1	1
sym. A = sym. B	$R^1 \neq$ H	1	2	3[b]
sym. A ≠ sym. B	R^1 = H	2 (C ↔ N)	2	2
sym. A ≠ sym. B	$R^1 \neq$ H	2 (C ↔ N)	4	6[b]
C_2-unsym. A ≠ sym. B	R^1 = H	2 (C ↔ N)	2	2
C_2-unsym. A ≠ sym. B	$R^1 \neq$ H	2 (C ↔ N)	4	8
C_2-unsym. A ≠ C_2-unsym. B	R^1 = H	4 (C ↔ N + regio)	4	4
C_2-unsym. A ≠ C_2-unsym. B	$R^1 \neq$ H	4 (C ↔ N + regio)	8	16
asym. A ≠ sym. B	$R^1 \neq$ H	2 (C ↔ N)	8	16
asym. A ≠ asym. B	$R^1 \neq$ H	4 (C ↔ N + regio)	16	32

[a] Shown are selected combinations of only some of the overall 64 tunable diversity elements: combinations of oxo- and bifunctional groups of varying symmetry (R^3 not varied). Σ32 variations for C→N + Σ32 variations for N→C. C↔N: Both directionalities of the peptoid boxes appear (C→N + N→C). Regio: mixture of head-to-head (H−H) and head-to-tail (H−T) isomers. Diastereomers: Σ of all diastereomers of all constitutional isomers. Isoforms: Σ of all constitutional and stereoisomers. [b] Meso + D/L-form(s). Asym. = chiral bifunct. building block; C_2-unsym. = achiral bifunctional building block without C_2 axis halfway between the two Ugi reactive groups, e.g., CN−CH_2−CH_2−$C(CH_3)_2$−NC.

moieties are in themselves identical, they are not in the overall context of the macrocycle since there is no C_2-symmetry axis in the molecules. Thus, although many MiBs with two similar building blocks on first view look like repetitive homodimeric macrocycles they are nonrepetitive. This feature has not been addressed so far by any other current macrocyclization approach, including some one-step cyclodimerization reactions that have been previously utilized for macrocycle synthesis.[76−79]

2.3. Rapid Generation of Skeletal Diversity by Varying the Nature and Structure of the Bifunctional Building Blocks

Scheme 5 highlights a survey of the skeletal diversity amenable within the peptoid moieties or by varying the MCR reactive functional groups of two building blocks (A ≠ B) that participate in a bidirectional macrocyclization. In Ugi-MiBs backbones with fully or only partially macrocycle-incorporated peptoid elements are available, e.g., the extremes: exo- and endocyclic peptoid moieties are shown in Scheme 5a and 5f, respectively. This was exploited to some extent for the synthesis of small heterocycles in the area of drug discovery.[80] However, the potential of the six possible combinations of tethered residues to create peptoid diversity within macrocyclic cavities and for side chain generation was exploited only recently.[50,81] This fine tuning of peptoid structure diversity within the same macrocycle type becomes especially important if one wishes to impose and examine physical, chemical, or biological properties, e.g., the influence

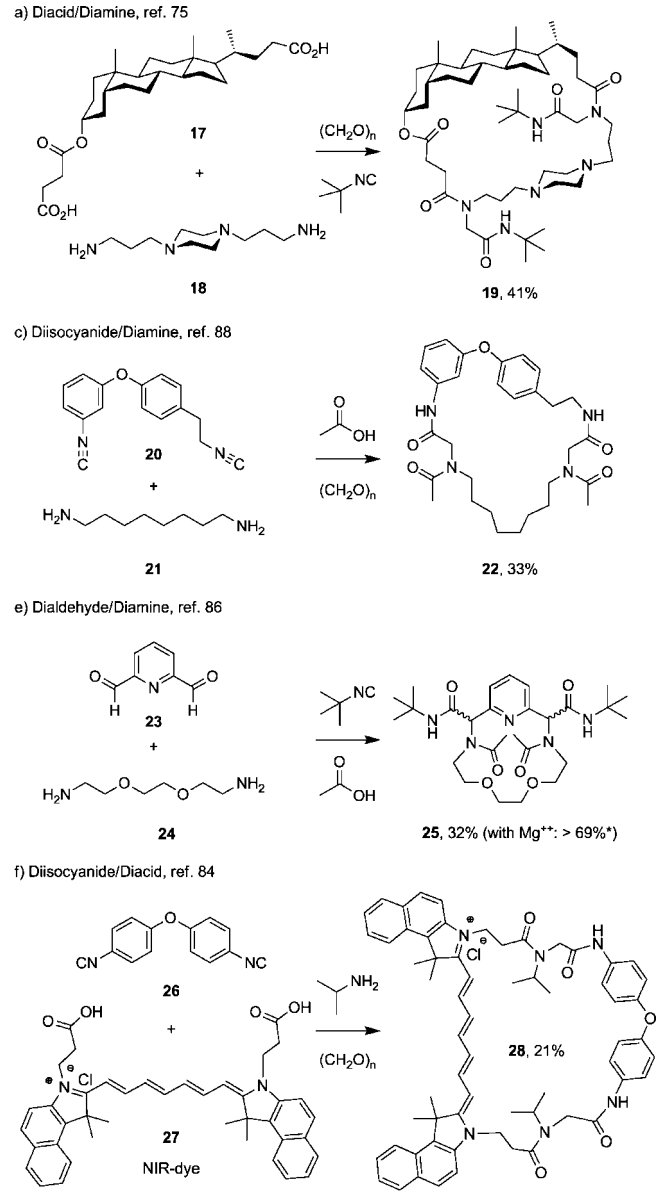
of size, shape, and flexibility in a set of macrocycles of otherwise similar chemical entities and residues. The main advantage, however, is the possibility to design side chains with tunable flexibility by applying simple combinatorial principles, even with limited sets of related or identical building blocks. This will be discussed in detail in the following.

The six basic combinations of tethered residues (Scheme 5, A = B), when combined with both possibilities for the directionality of the peptoid backbone (A ≠ B), give rise to a duplication of the library members, i.e., C → N and N → C peptoid moieties are possible for every combination of bifunctional building blocks. Adding the regioisomerism and stereoisomerism possibilities of unsymmetric building blocks it is possible to obtain a relatively large macrocycle library even without any change in the nature of R^{1-4}, i.e., by varying just a few of the many elements of diversity allowed by Ugi-MiBs. Table 2 illustrates the increasing number of macrocycle library members accessible within only one of the six basic combinations: diacid/diisocyanide (cf. Scheme 5f), for clarity without varying the amine (R^3 = fix). Changing the other elements of diversity, e.g., directionality of the peptoid boxes, topology and symmetry of the two bifunctional building blocks, and the prochirality of the oxo component, enhances the number of compounds exponentially within one skeletal base group. Therefore, this generates high diversity without even yet varying the substituents of the Ugi reactive groups (cf. R^{1-4} in Schemes 1 and 5). The number increases 6-fold when considering all combinations of Scheme 5 and Table 2, e.g., Ugi functional groups attached 2-fold to only two different but symmetric building blocks (sym. A ≠ sym. B, R^1 = H) can result in 12 constitutionally different macrocycles, and when R^1 ≠ H in 36 isomers (including 12 meso forms). If all bifunctional building blocks are asymmetric (asym. A ≠ asym. B, R^1 ≠ H) this can produce 192 isomers without even having changed a single appendix R^{1-4}. Between these extremes 30 further variations are possible plus variations of the side chain substituents not involved in the above discussion (e.g., R^3 in Scheme 5f). Some variations decrease the calculated number by higher symmetry (cf. meso forms). Accordingly, numerous possibilities open up for macrocycle library design considering the huge amount of available bifunctional building blocks that can be chosen to build extremely complex cyclic skeletons in one pot. Indeed, this prospect enhances the chances of delivering hits for biological targets[82] or host−guest chemistry with specific recognition requirements far beyond those required for simple spherical or symmetric ions.[83]

Scheme 6 exemplifies some of the discussed possibilities for the rapid generation of skeletal diversity focusing on the peptoid backbone variation. The examples represent recent combinations from our laboratory and were selected to illustrate the topological diversity arising from utilizing structurally varied bifunctional building blocks including, e.g., aromatic, heterocyclic, steroidal, polyether, or dye moieties.[81,84−88] In addition, functional macrocycles have been synthesized, e.g., with photoswitchable moieties.[84] For a double-4CR a total yield of 40% calculates to a bond forming efficiency of ca. 90%, a total yield of 65% to ca. 95% per bond formed, including the macrocyclization. In 4-fold-4CRs (*v.i.*) a 90% efficiency per bond formation including macrocyclization will give ca. 18% total yield.

When planning such macrocycle libraries one can take advantage of a helpful feature of the Ugi reactive functional

Scheme 6. Diversity Generation at the Peptoid Moieties: Examples of Four of the Six Different Combinations of Tether Residues Allowed in Bidirectional MiBs with at Least One Symmetric Bifunctional Building Block[a]

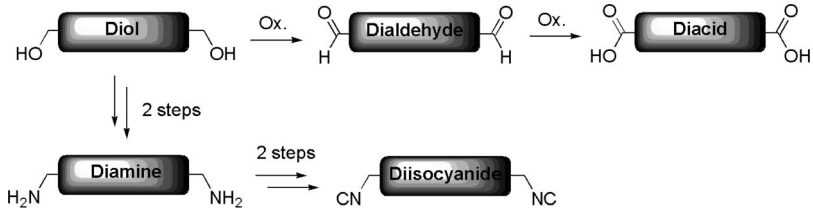


[a] Labels a−f correspond to those of Scheme 5, asterisk indicates under competetive DCL conditions - *v.i.*).

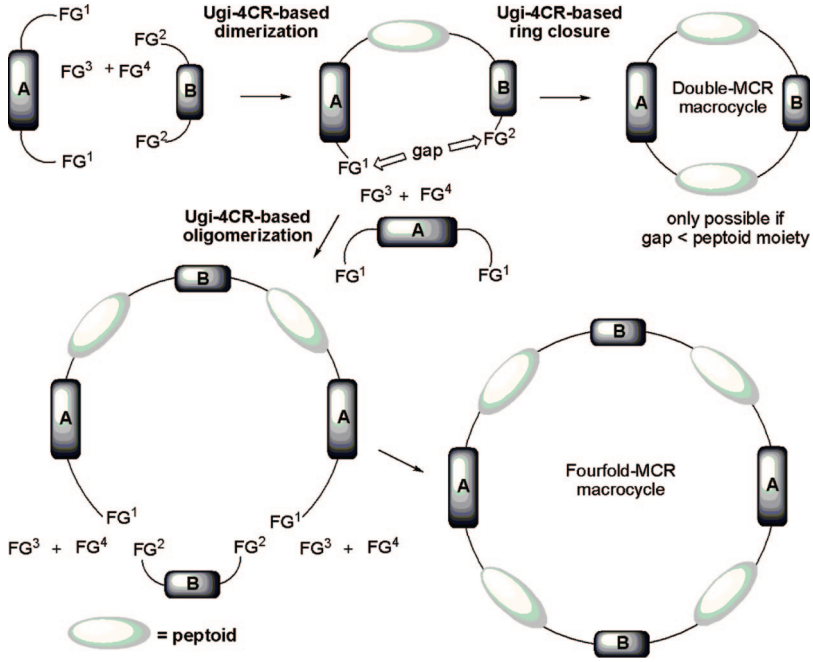
groups, i.e., all bifunctional building blocks are easily available from the same type of starting material, that is, a diol. In particular, a wide variety of diacid and diamino building blocks are readily available from commercial diols. Aromatic and aliphatic diisocyanides are readily obtained from diamines via formamide formation and dehydration.[51,53] Less favorable are, however, short chain aliphatic dialdehydes due to their known instability (for a recent solution to this problem see section 4).

As mentioned above, apart from the inherent size of the bifunctionalized scaffolds the different combinations (cf. Scheme 5) afford smaller or larger macrocycles depending on the connectivity of the resulting peptoid core.[49,50] For example, the diamine/dialdehyde combination (Scheme 5e/6e) produces a peptoid backbone with all amide bonds being exocyclic[86] and thus a smaller cycle, while the diacid/diisocyanide one (Scheme 5f/6f) produces only endocyclic

Scheme 7. Sequential Synthesis of Ugi-Bifunctionalized Building Blocks from Available Diols



Scheme 8. Schematic Representation of the Competing Double versus Four-Fold Ugi-4CR-Based Macrocyclizations during Bidirectional MiBs



amide bonds and a larger macrocycle.[81,84] The remaining four combinations produce at least one endocyclic amide bond. The *N*-substituted amide of the peptoid can also adopt a *s-cis* conformation depending on the size and strain of the macrocycle and the *N*-substituent R[3].[49,88]

To explore the strain component several bifunctional building blocks were selected with the aim to create both relatively small (e.g., **25**) and very large macrocyclic skeletons (e.g., **19** and **28**). An important aspect of the Ugi-4CR-based cyclization is not only the strain of the final compound but also that of the cyclic precursor α adduct and the possibly strained 1,3-ansa-like intermediate of the Mumm rearrangement.[49,87] This has found little consideration but is of high relevance for the cyclization success. For example, some combinations (see Table 1, e.g., dialdehyde/diacid) result in increased strain during formation, and others give strain release.

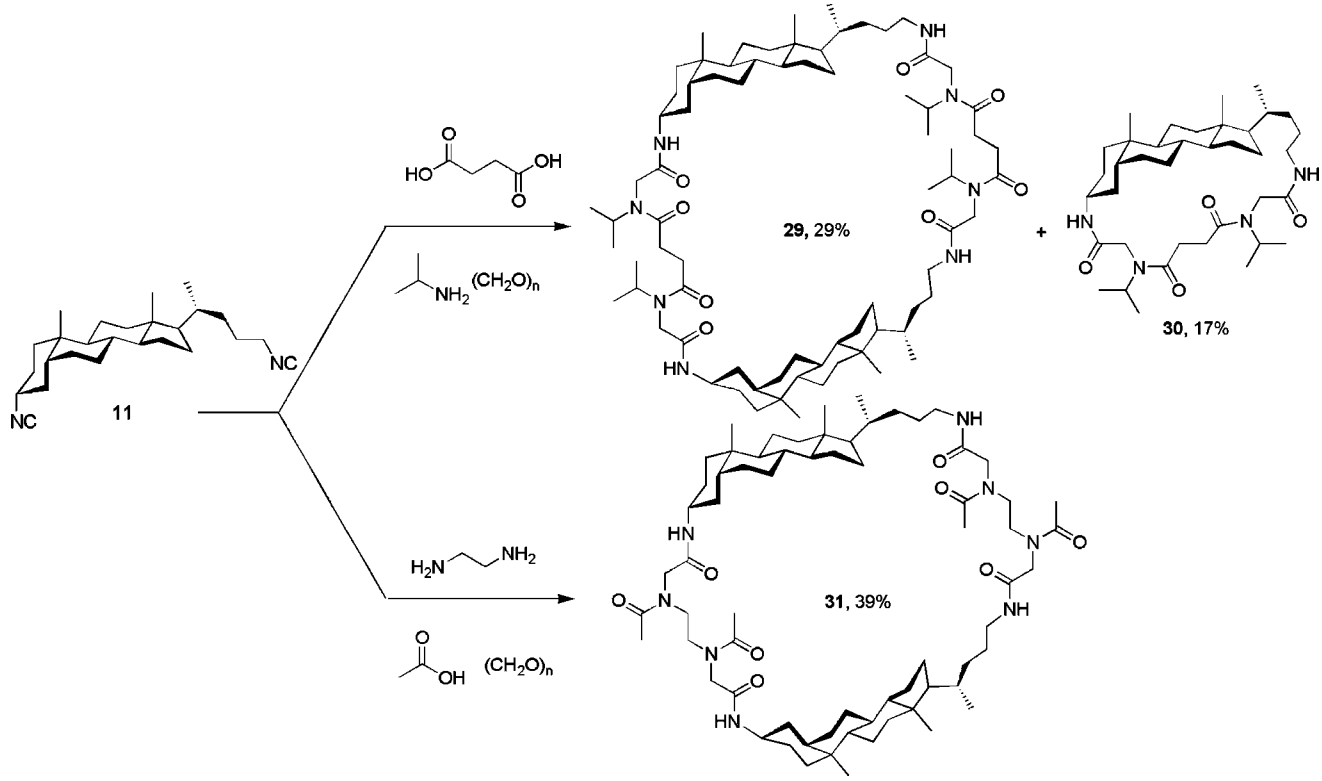
This aspect has not been fully exploited yet, e.g., to capture Ugi intermediates in mechanistic studies or in order to deviate into another product series. The few excellent examples of a deviation from the "normal" course of the reaction are Zhu's syntheses of oxazole-containing macrocycles by a modified Ugi-3CR of bifunctional isocyanoacetamides.[89,42,44] The Ugi intermediate is deviated to form an oxazole instead of the "normal" peptoid (see section 4).

If strain factors like ring strain, transannular strain, or conformational distortion become too severe the system can (and usually will) escape by a competitive 4-fold versus double-MCR-based macrocyclization.[50,81,87] This can be exploited for size control when extremely rigid and preorganized systems (e.g., steroids) are submitted to bidirectional MiBs. Variation of the macrocycle size based on the different multiplicities of the macrocyclization can be achieved using a very long tether A and a too short tether B. This mismatch combination favors multiplicities higher than two, especially the 4-fold MiBs.

In Scheme 8 a sketch demonstrates how mismatching sizes of the two bifunctional building blocks do not allow spanning the gap by the second Ugi-4CR. As a consequence, an oligomer is formed and later cyclized. Another reason, even if the building block size is matching, can be a misbehaved conformational preorganization of the acyclic intermediate. If the folding of the first Ugi product disfavors ring closure by the second MCR the system may instead undergo oligomerization and cyclize only when prefolding permits so. This may be seen as a special type of substrate-folding-directed macrocyclization[17,90] by which 4-fold macrocycles may be produced in higher yields than double ones. This event can occur even though formation of the larger rings usually is entropically disfavored and is not easy to design, in contrast to the plannable size mismatch approach.

To understand the underlying structural details that have a noteworthy influence on the multiplicity of the MiB approach, diisocyanide **11** has been used as a model system and submitted to a set of competitive bidirectional macrocyclizations using building blocks of varied length and topology as counterparts.[50,81] Scheme 9 illustrates one example of the results obtained by use of simpler and shorter bifunctional building blocks selected to favor the 4-fold macrocyclization. For example, both the double and 4-fold

Scheme 9. Substrate-Folding Directed Variation of the Cavity Size via MiBs[a]



[a] Examples based on the use of chemically different building blocks. For **29** and **31** yields refer to a mixture of head-to-head (H−H) and head-to-tail (H−T) regioisomers, though only H−H isomers are shown.

macrocycles **29** and **30**, respectively, were obtained using succinic acid as the bridging unit, while only the 4-fold one **31** was isolated when employing ethylenediamine. Reasons to explain the sole formation of the 4-fold macrocycle **31** may be either an unfavorable substrate folding of the monomer or that the ethylene-bridged dipeptoid backbone resulting from the diamine/diisocyanide combination is not long enough to span the steroid moiety, thus resulting in a too strained macrocycle. Less likely in this instance is that formation of the smaller ring is disfavored because of transannular strain or a nonviable α product or Mumm transition state.[49]

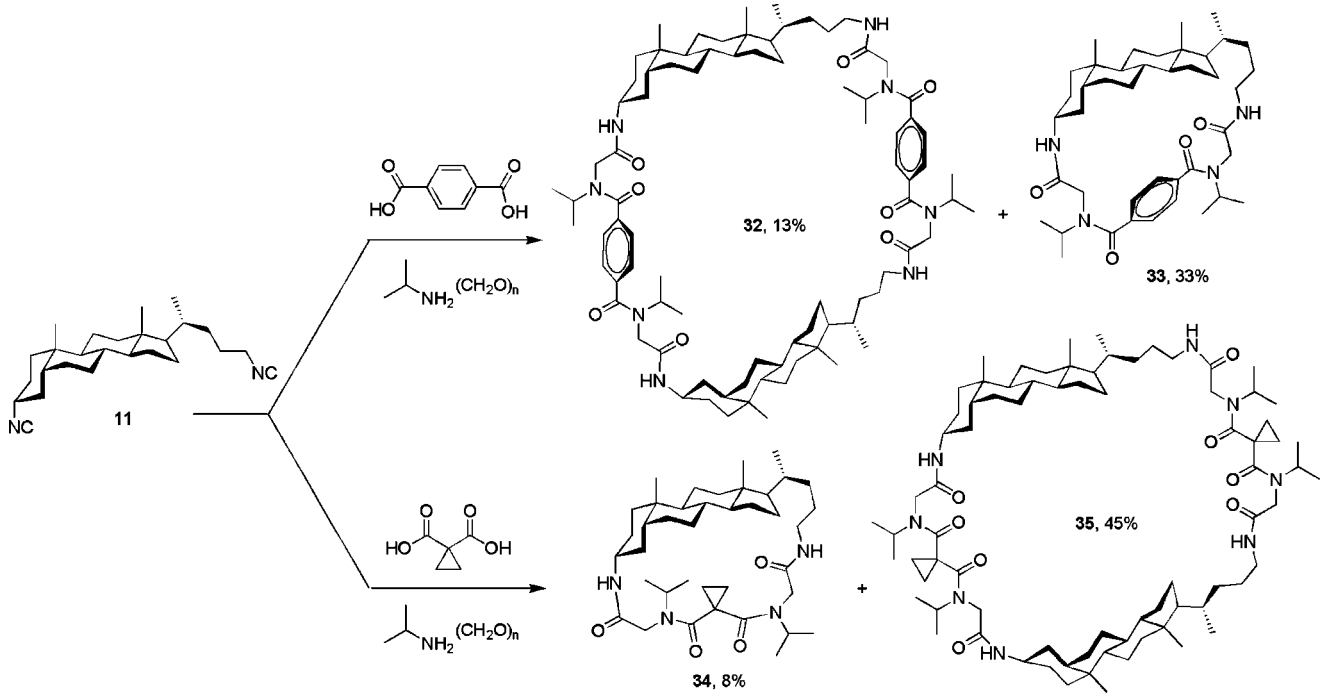
Similar results were obtained with 4,4′-diisocyanodiphenylether **20**, a smaller, rigid diisocyanide. When combined with very short diacids (e.g., oxalic acid) as counterpart[87] open chain compounds rather than cyclized products were obtained. In contrast to the more "spacy" and less rigid steroid examples, in this case size and ring strain factors of the intermediates forbid forming the smallest cycle.

Because of the interesting double/4-fold ratio achieved by employing the diacid/diisocyanide combination two additional dicarboxylic acids with different shape and flexibility were chosen to substitute succinic acid as the simpler building block B: terephthalic and cyclopropane-1,1-dicarboxylic acid. Scheme 10 summarizes the results, which were expected but are still remarkable. While the longer and straight terephthalic acid gives the double-Ugi-4CR-based macrocycle **33** as the main product the kinked and shorter cyclopropane tether favors the 4-fold over the double-Ugi-4CR-based macrocyclization, thus producing mostly the large macrocycle **35**.[50] The different outcomes of this model system (**34/35** vs **30/29** vs **33/32**) demonstrated the marked effect of building block size mismatch and folding of the acyclic intermediate to undergo Ugi-4CR-based ring closure.

Evidently, due to the extended and rigid steroidal moiety either a too low or too high flexibility or a too short length of bridging chain disfavors ring closure and provokes a competing Ugi-4CR to the next higher oligomer to take place. With slow addition of both bifunctional building blocks the resulting sufficiently long or foldable precursor then undergoes cyclization under usual pseudo-high-dilution conditions to afford the 4-fold Ugi-4CR-based macrocycle.[50,81,87] In the case of a sufficient excess of one bifunctional building block other evasive routes can become dominating, e.g., dimerization without ring closure (cf. Scheme 8 lower left).[87] The next higher cyclooligomer, the 6-fold Ugi-4CR-based macrocycle, has not been detected in the reaction pot in any significant amount, including an analysis of the crude mixtures by HR-FT-ICR mass spectrometry. This is reasonable considering the entropic cost to cyclize extremely long acyclic precursors without using a template effect or additional structural preorganization.[90] Despite the high degree of sophistication that has been achieved in shifting the system toward the 4-fold MiBs rather than the double ones it is noteworthy to point out that an appropriate selection of building blocks is mandatory. If the smaller MiBs can take place they usually will do so preferentially.

At this point it should be mentioned that the separability of MiBs within a series is not easy to predict. Often separation is easier than expected for such closely related structures. For Ugi-MiBs with a steroid backbone the double and 4-fold ones usually can be separated by normal chromatography. Even seemingly almost identical compounds of the same series can have a distinctly different chromatographic behavior, probably caused by different folding,[49,75] e.g., all eight isomers of compound **12** were easily separated in preparative HPLC.

Scheme 10. Substrate-Folding Directed Variation of the Cavity Size via MiBs[a]



[a] Examples based on the use of structurally different building blocks. For **32** and **35** yields refer to a mixture of head-to-head (H−H) and head-to-tail (H−T) regioisomers, though only H−H isomers are shown.[50]

The alternative reaction path to higher cyclooligomers are noncyclic oligomers, and indeed, their formation has been observed.[86,87] They are formed in higher amounts if either the pseudo-high-dilution-principle, i.e., slow addition of the bifunctional building block(s) to the other ones, is not followed or bifunctional building blocks with very flexible, long tethers are used.[90] These oligomers are, however, easily separated by chromatography, usually remaining at the baseline of a silica-tlc as they possess (reactive) polar ends with carboxylate or amino groups.[49,87] Isolations of linear oligomers with aldehyde and isonitrile end groups have not yet been reported in the context of MiBs. The above considerations on cyclic vs linear oligomerization are not generally true as some ideally precurved, rigid building blocks or template effects (*v.i.*) can give preferential macrocycle formation even at very high concentration or can lead to considerable formation of, e.g., a 6-fold MCR-MiB.[86]

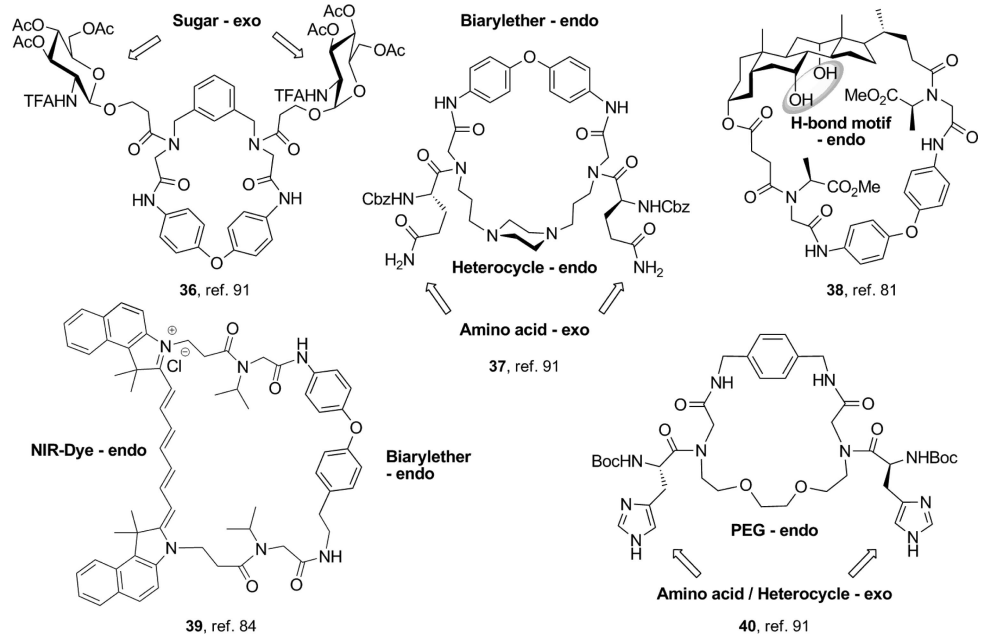
3. Introduction of Endo- and Exofunctional Elements in MiBs

Like every one-step cyclooligomerization approach MiBs offer the possibility to incorporate several identical structural moieties into the final macrocycle in a straightforward manner. Furthermore, MiBs allow installing functional elements in the endo (within the ring) and exo (appended to the ring) positions in a unified task. In principle, any catalytic, binding, or biologically relevant motif can be incorporated as either the exo or the endo element during the macrocyclization step. This is possible if the desired building block bears suitable MCR reactive functional groups and its other functional moiety is compatible ("orthogonal") with the MCR or if it is protected. Endofunctional elements are structural motifs acting as tethers between the peptoid moieties. These elements can be easily introduced by a judicious selection of MCR bifunctional building blocks endowed with properties desired for the resulting macrocycle. On the other hand, exofunctional elements arise from the use of MCR monofunctional groups bearing additional chemical motifs which later appear appended to the macrocycle.

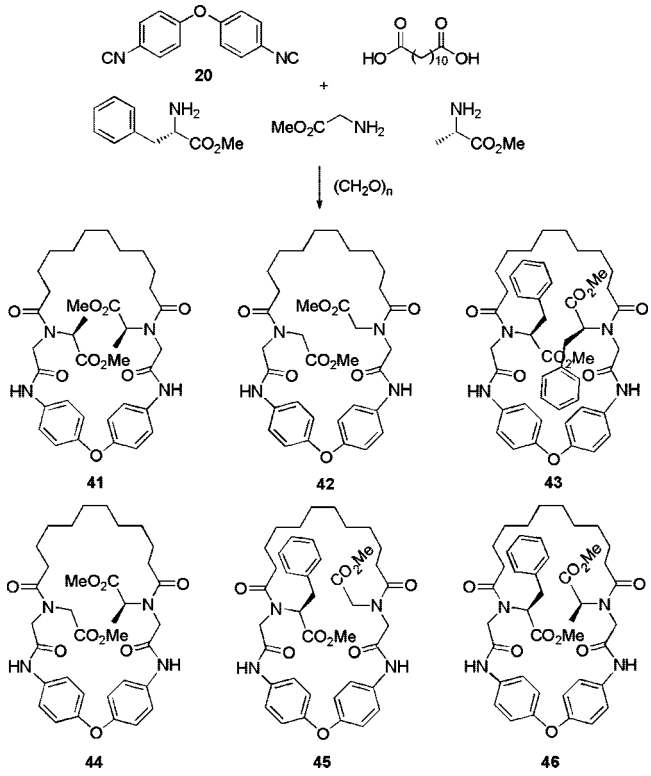
Scheme 11 shows selected Ugi-MiB examples of the vast scope offered by this methodology, creating both endo- and exodiversity in a single step, e.g., steroids,[50,81] dyes,[84] biarylethers,[84,87,88] PEGs,[91] heterocycles,[91] and phenyl rings[91] are examples of the endofunctional motifs that can be introduced in combination with exo elements of catalytic or biological importance.[81,84,91] Of great relevance is the possibility to attach specific "natural" side chains (appendages), e.g., of amino acids and sugars, to the macrocycle cavity during the macrocyclization step.[81,91] This can be used to approach a resemblance to natural product macrocycles,[88,91] particularly those with antibiotic activity which mostly possess sugar or amino acid side chains attached to the macrocyclic core. The fact that several elements of diversity can be simultaneously assembled in one pot is a distinctive key feature of MiBs as this issue is not easily addressed by other macrocyclization approaches.

In designing macrocycles toward ion or molecular recognition for either chemical or biological applications the endo functionalization is preferred due to the evident entropic contribution of the binding process. For example, the hydrogen-bonding motif of the diol functionality in the cholanic scaffold (**38**), the PEG chain, and the phenyl ring are well-known recognition motifs that can be easily introduced by this method in one pot. As depicted in Scheme 11 in the case of the diamine/diisocyanide combination (**36**, **37**, and **40**) the acid component (e.g., *N*-protected amino acids, sugars) is selected to install exo functionalization with desired properties, e.g., higher polarity, (organo)catalytic activity, binding to biological targets, etc. The same analysis is applicable when the diacid/diisocyanide combination (**38** and **39**) is performed. In this case the amino and oxo components determine the side chains. In terms of mimicking

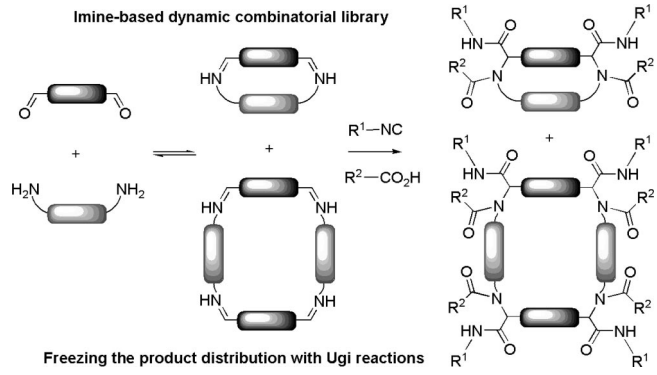
Scheme 11. Selected Examples of Macrocycles Obtained in One Pot with Variation in the Side Chain (Exo Functionalization) or within the Ring (Endo Functionalization) Based on Aryl-Containing Diisocyanides



Scheme 12. Combinatorial Generation of Appendage Diversity in One Shot: Library of Biarylether−Peptoid Hybrid Macrocycles Created by Mixing Three Amines for One-Pot Double Ugi-4CR-Based Macrocyclizations[85]



Scheme 13. Ugi-4CR-Based Freezing Process of a Dynamic Combinatorial Library (DCL) of Macrocyclic Oligoimines To Afford Macrocycles Containing Exo-Cyclic Peptoid Moieties[86]



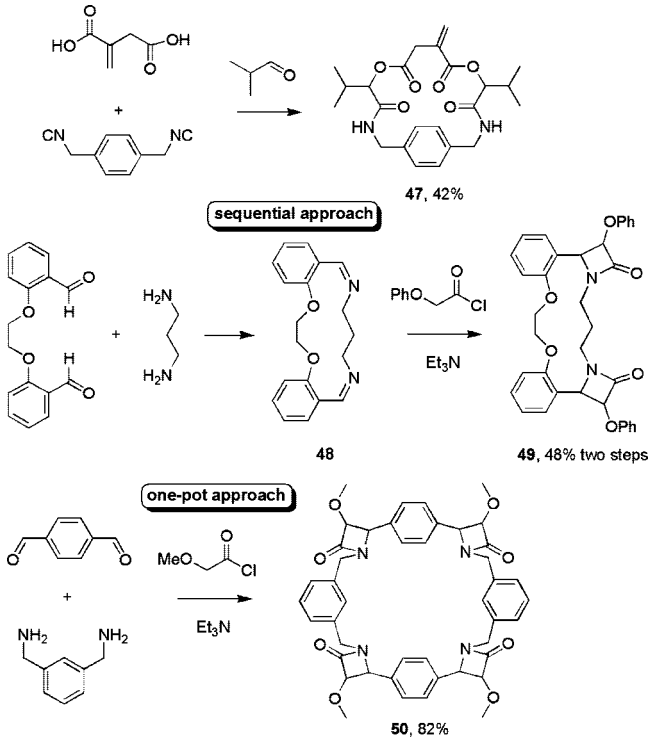
nature's way to create highly complex molecules from simpler building blocks the possibility to add natural or natural-like side chains while forming a (biologically inert) core structure represents a landmark of the MiB strategy.[64,91] This may be seen as one of the most promising features for exploration of the chemical space of macrocycles, mainly because it can be done so easily.

3.1. Combinatorial Synthesis of Macrocycles by Ugi-MiBs

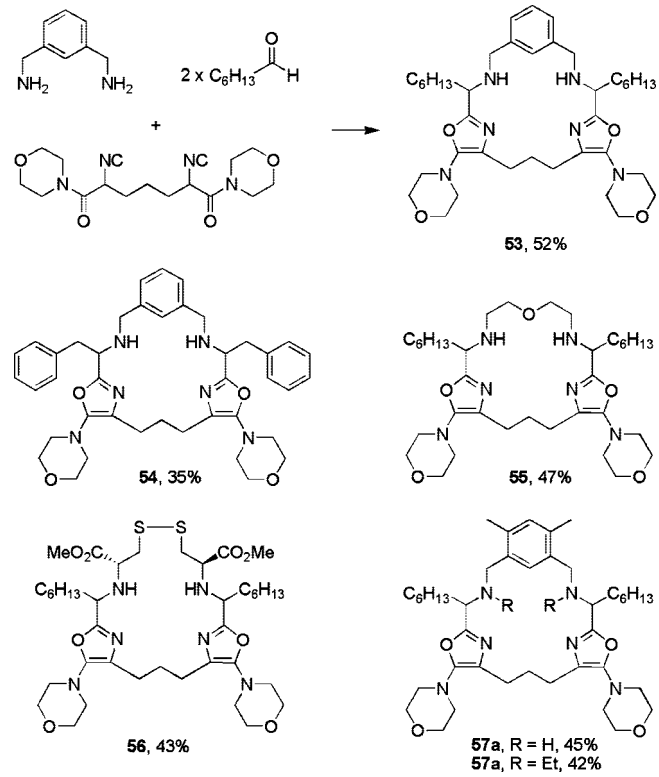
The value of the MiB strategy to generate both skeletal and side chain diversity of macrocycles can be enhanced by combinatorial assembly of macrocycles. This is possible through the use of different Ugi components of the same type, e.g., several different amines, in a one-pot procedure. It should be noted that while the parallel synthesis of macrocycles affords solely equally substituted (though not necessarily repetitive) peptoid moieties, the combinatorial procedure allows obtaining macrocycles with each peptoid moiety bearing different side chains per MCR involved.

This has been exemplified through construction of a small combinatorial library of biarylether-containing macrocycles by mixing three different *C*-protected amino acids in a MiB approach of the diacid/diisocyanide type.[85] Scheme 12 shows a successful system in which the macrocyclic core contains two C_2-symmetric bifunctional building blocks, a biarylether moiety and a C_{12} diacid. This resulted in six constitutionally different macrocycles in one pot and illustrates the potential of combinatorial MiB methods for building larger macrocycle libraries with promising applications for bioactivity or

Scheme 14. Synthesis of α-Acyloxycarboxamide- and *β*-Lactam-Containing Macrocycles by Double-Passerini-3CR (top) and Staudinger [2 + 2] Cycloaddition-Based Macrocyclizations (middle and bottom)[94−96]



Scheme 16. Zhu's One-Pot Synthesis of Oxazole-Containing Macrocycles by Double-MCR-Based Macrocyclization Including Bifunctional Building Blocks



recognition (guest) screening. Mixed libraries of appendage diversity based on steroids[75] or skeletal diversity by mixing different bifunctional units were also successful.[85] Analysis of the combinatorial libraries by HPLC-ESI-MS and HR-FT-ICR disclosed the presence of all possible macrocycles in the crude mixture. Some smaller libraries were even separated by chromatography and the members individually characterized by NMR.[85]

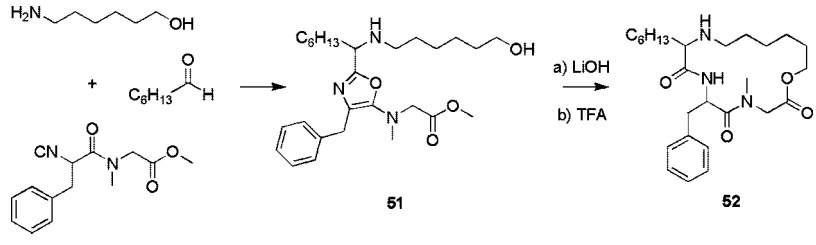
When designing combinatorial libraries through a combination of several amines it is advisable to consider the ability of every single amine to form the corresponding imine (e.g., aliphatic versus aromatic). A similar formation rate of the various Schiff base intermediates has been found to be a key aspect in obtaining equally distributed macrocycle libraries. This is indeed a desirable property looking for (semi)-quantitative screening results.[75,85,86] As is evident from these first examples other combinations of nonsymmetric bifunctional building blocks can be chosen to assemble macrocycles with different rims in a combinatorial fashion.

An especially interesting application of the MiB strategy is its use in dynamic combinatorial chemistry (DCC).[86] It has been demonstrated that DCC is suitable to generate new receptors, guests, or ligands based on varied types of selection processes.[92,93] The imine bond is one of the most amenable reversible chemical linkages used in DCC, and imine-based dynamic combinatorial libraries (DCL) are among the most useful systems to study diverse types of recognition and selection processes under thermodynamic control. Thus far the only way employed to freeze the imine exchange and analyze the product distribution of such DCLs is reduction with $NaBH_4$ to the corresponding amines.[93,100]

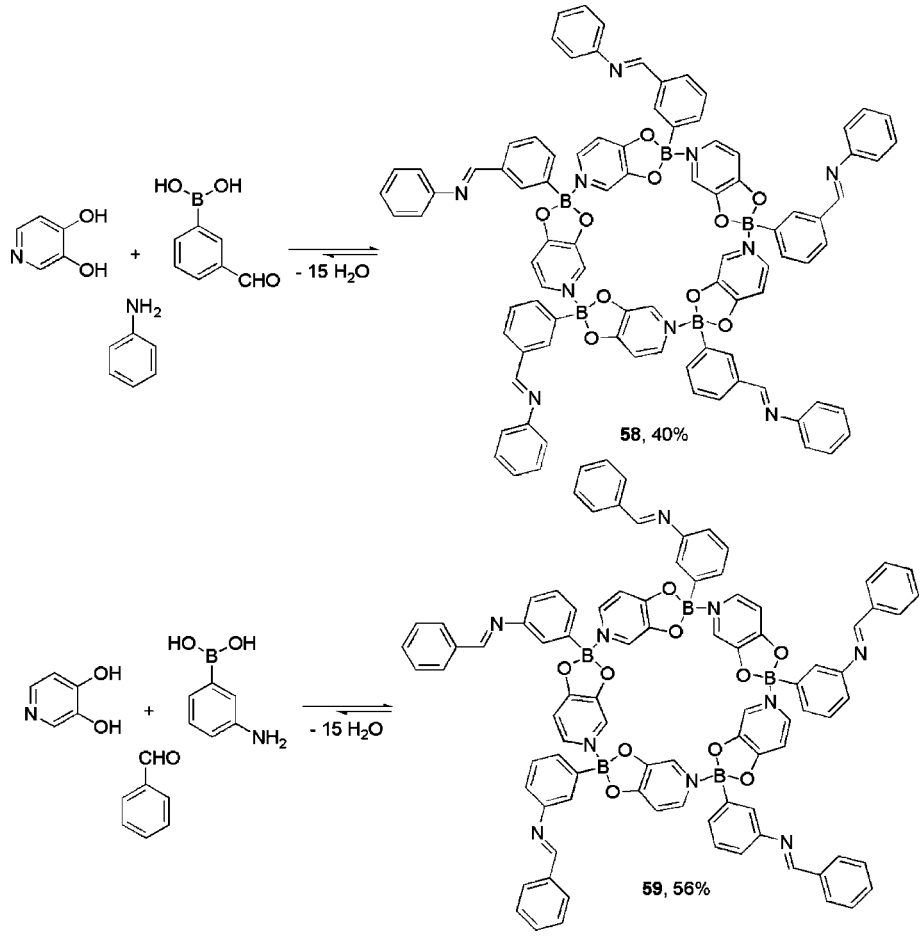
Very recently, a new procedure to quench imine-based DCLs by multiple Ugi-4CRs has been reported (Scheme 13).[86] Thus, DCLs of macrocyclic oligoimines were created, altered by a selection process, and then quenched by addition of a carboxylic acid and an isocyanide. The Ugi-4CR is referred to as a MCR of type II, i.e., it consists of a sequence of reversible steps (like the imine formation) that is ended by an irreversible one, i.e., the Mumm rearrangement.[51] The Ugi-4CR was found to be fast and efficient enough to freeze the product distribution after the DCLs had been biased by addition of varied templates, e.g., macrocycle **25** (Scheme 6e) was formed with high preference out of a library of different poly(cyclo)imines. It was formed without using a pseudo-high-dilution protocol. Template effects also allowed the first selective formation of a 6-fold Ugi-MiB.[86]

Additionally, the Ugi-4CR freezing approach affords a peptide-like scaffold different from the typical polyamine

Scheme 15. Sequential Process Consisting of a Multicomponent Reaction and a Domino Activation/Macrolactonization Approach Developed for the Synthesis Cyclodepsipeptides



Scheme 17. Multicomponent Assembly of Dendritic Macrocycles by Multiple (Parallel) Condensation-Based Macrocyclizations



skeleton resulting from the reduction approach. Indeed, other MCRs of type II are well suited to be applied to this promising field, especially, though not only, those based on an imine bond formation as one of the reversible steps.

4. MiBs from Non-Ugi MCRs

It is obvious that the synthetic value of the MiB strategy does not exclusively rest on the Ugi-4CR but in principle is applicable to all MCRs capable to generate diversity and complexity and serve as ring-closing reactions. This is especially interesting considering the diversity of chemical functionalities that can be incorporated into structurally related macrocyclic cavities by utilizing different MCRs with similar starting scaffolds.

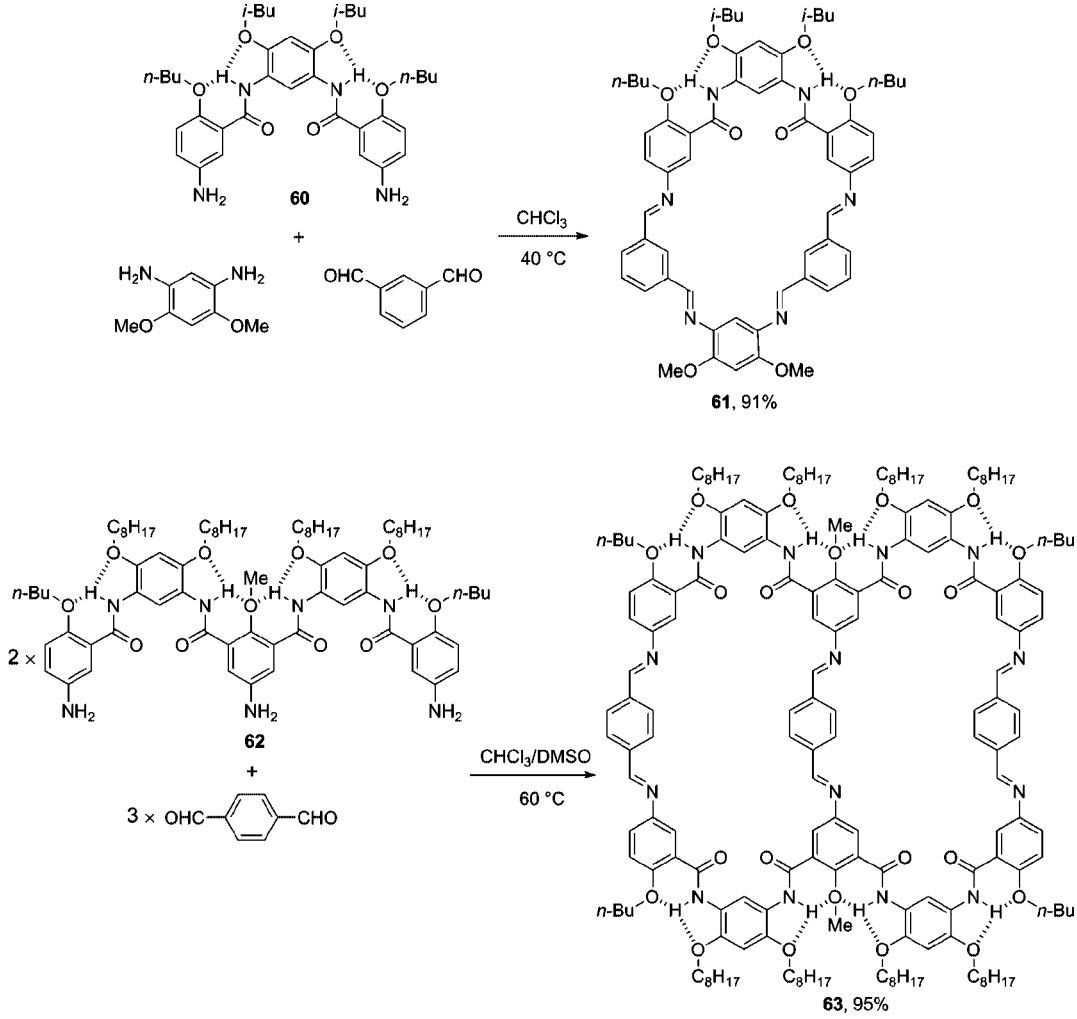
The great relevance of isocyanides in multicomponent condensations has been largely recognized and is well documented in the literature.[49,51,53] Recently, the MiB strategy was successfully applied to the synthesis of macrolactones via double-Passerini-3CR-based macrocyclizations. Utilizing the same synthetic protocol as with the Ugi-MiBs, conditions for the straightforward assembly of this completely new family of interesting macrocycles were properly addressed.[94] As depicted in Scheme 14 this approach shares the great versatility of an Ugi-MiB to easily incorporate constitutionally diverse building blocks into a final macrocyclic core in one step. Due to the stereochemically unselective nature of the Passerini-3CR nonpreferential formation of diastereomers was detected in macrocycle **47** using isobutyraldehyde as the oxo component.

Of special value is a variation of the Passerini-3CR in which a rather unstable aliphatic dialdehyde is substituted by the corresponding stable diol. In-situ oxidation of the diol with IBX during reaction allows Passerini-MiBs with a diol and a (di)isocyanide or a (di)acid.[94] Likely this can be extended to other MiBs which would normally require sensitive di- or trialdehydes.

Naturally in this 3CR procedure the possibility of rapidly generating appendage diversity is reduced compared to the 4CR-Ugi-MiBs. Nevertheless, Passerini-MiBs allow the most convergent planning toward the challenging field of cyclodepsipeptide- and macrolide-like compounds.[8,9] While other ester-bond-formation-based cyclodimerization reactions have been reported previously,[78,90] they lack the fascinating feature of the Passerini-MiB to allow formation of several bonds additional to the lactone one in the same pot.

The MiB principle has been applied in several laboratories for the synthesis of β-lactam-containing macrocycles using double-Staudinger [2 + 2] ketene−imine cycloaddition-based macrocyclizations.[94−96] As exemplified in Scheme 14, synthesis of the β-lactam-containing macrocycles **49**[95] and **50**[94] can be conducted in either a sequential or a one-pot approach. Both alternatives comprise the initial formation of the macrocyclic oligoimine which is allowed to react next with an acyl chloride in the presence of a base to complete the [2 + 2] ketene−imine cycloaddition. As previously shown for Ugi-MiBs, structural preorganization strongly influences the macrocyclization outcome. This also can be utilized for Staudinger-MiBs by an appropriate selection of the bifunctional building blocks, which may favor formation of either

Scheme 18. Self-Templated, Hydrogen-Bonding-Driven Multicomponent Assembly of Mono- and Bimacrocycles by Dynamic Covalent Chemistry



double- or 4-fold Staudinger [2 + 2] cycloaddition-based macrocycles depending on the rigid or flexible character of their structures. Interestingly, the stereochemical outcome of the double-cycloaddition process is not random in all cases but was found to be strongly influenced by the proximity of the imine bonds (i.e., the length of the building blocks). Additionally, this type of macrocycles gives access to diastereochemically pure macrocycles including peripheral functionalities such as β-amino acids, amide, and azetidine moieties.[95]

Special highlights in this field of macrocycle synthesis are the excellent contributions of the Zhu group. Analysis of some noteworthy reports from this group, even if not part of an MCR-based macrocyclization itself, may help to gain clarity in some of the underlying reactions and intermediates that define the MiB approach as a novel synthetic methodology. Two important examples of macrocycle synthesis mediated by MCRs, of which one is included in the MiB definition, are discussed here in detail.

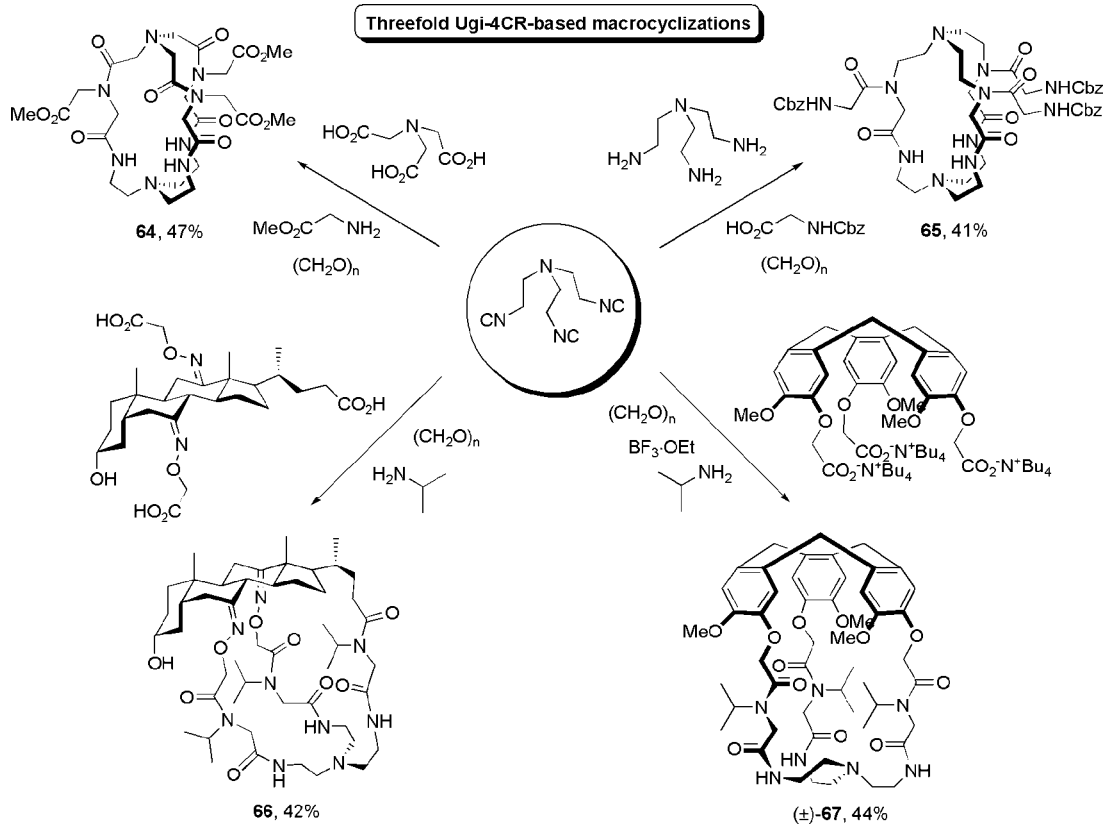
Scheme 15 shows a very interesting and direct approach toward cyclodepsipeptides.[44,97] The previously developed three-component reaction-derived synthesis of oxazoles was implemented in a sequential approach by which bifunctional building blocks condensate through the MCR to afford the acyclic intermediate **51** including the oxazole moiety. This latter aids the consecutive lactone bond formation to afford macrocycle **52**. Evidently, the procedure includes bifunctional building blocks that undergo a MCR, though this latter process is not acting as the ring-closing reaction. Therefore, this otherwise fascinating procedure cannot be considered a MiB approach but sets the stage for another great example from the same group that fits the definition of MiBs.

Using the same three-component reaction a one-pot synthesis of a small library of oxazole-containing macrocycles was produced.[98] Scheme 16 shows the synthetic design and structures of some members which were considered to be suitable for bioactivity screening due to their natural product-like elements.[94] Intriguingly, this approach was found to render higher yields when rather concentrated solutions of the building blocks were used. Similar to previously described Ugi-MiBs,[50] the Zhu approach features generation of diastereomers in close to equal amounts when using prochiral oxo components.

The above examples show that the MiB methodology does not rely exclusively on either the Ugi-4CR or isocyanide-based MCRs. Additionally, other MCRs of type II (with an irreversible last step), such as the Petasis reaction, are expected to be successful once implemented with suitable building blocks.[99]

However, there are no reports of MiBs based on MCRs of type I. These latter processes are sequences of elementary, all reversible steps, and thus, mixtures of final products and intermediates are usually produced. This characteristic makes the adaptation of type I MCRs to MiB protocols quite

Scheme 19. One-Pot Assembly of Macrobicyclic Cores (i.e., cryptands, hemicryptophanes, and cages) by Three-Fold Ugi-4CR-Based Macrocyclizations of Trifunctional Building Blocks[103]



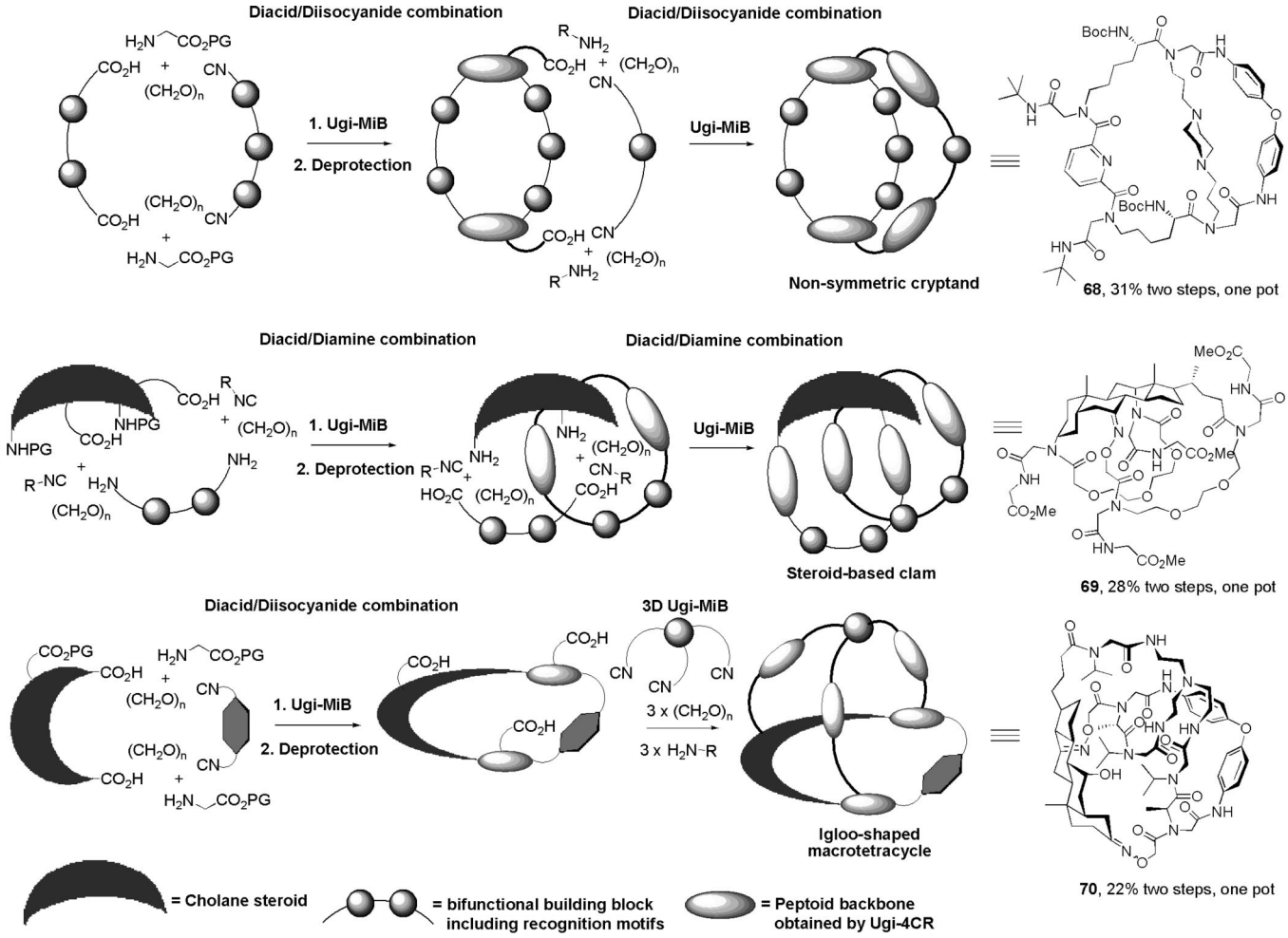
difficult, at least if the process is not performed with the aid of templates that help to reduce the number of byproduct and acyclic intermediates formed in equilibrium with the multiple MCRs (cf. the dynamic combinatorial libraries prior to MiB type or other fixation,[86,91,92,100] cf. Scheme 13).

On the other hand, use of multiple reversible reactions to produce macrocycles in a multicomponent fashion can be achieved if a quenching process is included to avoid retro-reaction.[86,100] Recently, a multicomponent assembly of boron-based macrocycles from bifunctional building blocks has been reported.[101] This approach relies on parallel utilization of three different reversible reactions: (i) condensation of boronic acids with aromatic diols, (ii) addition of *N*-donor ligands to boronate esters, and (iii) condensation of aldehydes with primary amines. As these reversible elementary steps do not occur necessarily in a cascade-type process (i.e., condensation of the exocyclic imines does not take place in a time-dependent manner with steps i and ii) the approach cannot be considered to be based on MCRs of type I. However, the overall process can be considered a MiB approach as at least two bifunctional building blocks are incorporated into the final macrocyclic structure that is assembled in a multicomponent manner (i.e., having at least three different building blocks eventually forming the macrocycle).

As shown in Scheme 17 the dendritic macrocycles **58** and **59** were obtained in moderate yields by a modular assembly of three different substrates.[101] Again, appropriate selection of suitable building blocks (i.e., bifunctional boronic acids, dihydroxypyridine ligands, and amines or aldehydes) allowed the self-assembly process without the need of metal templates. Of course, use of dehydrating conditions was required to shift the equilibrium toward the products, an unavoidable requisite if only reversible condensation reactions are utilized. The success of this approach showed the potential of using modular and parallel elementary steps as multicomponent procedures to produce extremely complex even nanosized macrocyclic scaffolds in one-pot, self-assembly processes.

Another possibility to accomplish an efficient multicomponent assembly of macrocycles based exclusively on reversible reactions is the use of hydrogen-bonding-driven thermodynamic control. In particular, when employing condensation of amines and aldehydes as the reversible process the previously mentioned drawbacks derived from the instability of the imine bond and low yields upon nondehydrating conditions are difficult to overcome without the aid of external templates. Nevertheless, the advances achieved over the last decades on the understanding of several recognition, self-assembly, and folding processes based on hydrogen bonding have opened up new avenues to address the efficient formation of macrocycles via multicomponent reversible chemistry. In this sense, hydrogen-bonded preorganized building blocks can be considered as internal templates that enable efficient formation of stable, even imine-based, macrocycles by simultaneous condensations with several simpler counterparts. This type of self-templated multicomponent macrocyclization has been recently described with anthranilamides as the hydrogen-bond-driven organizing frameworks to afford mono- and bimacrocycles under thermodynamic control.[102] Scheme 18 depicts the multicomponent assembly of the complex macrocycles **61** and **63** through formation of up to six imine bonds and incorporation of up to five components in one pot.[102] Remarkably, the macrocycles were formed in nearly quantitative yield without the use of dehydrating conditions and without any external template. This result is derived from the intrinsic structural preorganization provided by the U- and zigzag-shaped anthranilamide building blocks **60** and

Scheme 20. Sequential Multiple Multicomponent Macrocyclization Approach for the Assembly of Topologically Diverse and Chiral Macromulticycles



62, respectively. Their defined conformations are stabilized by two pairs of three-center hydrogen bonds. Interestingly, this hydrogen-bond-driven assembly can also be extended to hydrazone formation, and it proved to be a dynamic and self-sorting process exclusively controlled by conformational bias.

5. Synthesis of Macromulticycles by "Three-Dimensional" and Sequential MiBs

Following the exploration of single macrocycles by the MiB methodology, another challenge was the development of related approaches suitable for assembly of macromulticycles.[85,86,103] For Ugi-MiBs extension to the third dimension comprises the performance of 3-fold Ugi-4CR-based macrocyclizations of trifunctional building blocks to obtain cryptands, cryptophanes, and steroid-based cages. As depicted in Scheme 19 a wide variety of macrobicyclic cavities suitable for inclusion complex formation can be created in one pot. As previously shown for single macrocycles, skeletal diversity can be generated either by varying the combination of Ugi reactive functional groups (e.g., diacid/diisocyanide versus diamine/diisocyanide) or the structural features of the building blocks. This is exemplified in cryptands **64** and **65** as both possess the same macrocyclic ring size but present a different number of endocyclic amide bonds. Also, "three-dimensional" MiBs allow combining generation of multicyclic complexity with appendage diversity as functional side chains can be installed as easily as shown before. Very recently this has been addressed by parallel,[103] combinatorial,[85] and dynamic combinatorial[86] procedures with and without template effects being used. It was not only possible to run 3-fold Ugi reactions such as those shown in Scheme 19 but 5-fold and even 6-fold ones worked, i.e., up to 24 bonds were formed in one pot, to give a single molecule in up to 59% yield (templated), corresponding to ca. 98% efficiency per bond formed including two macrocyclizations.[86]

Macrobicycles are usually endowed with improved encapsulating properties compared to their analogous nonbridged macrocycles.[19,23,103,104] The capability to bind and encapsulate a guest depends not only on the cavity size but also on the nature of the tether chains. In this sense, the peptoid backbone itself can be considered a suitable recognition motif for either metal ions or organic species, in many aspects comparable to peptides.[9] Furthermore, rapid incorporation of varied recognition motifs into the macrobicycle skeletons conveys a very promising prospect for molecular recognition and coordination chemistry. For example, the distinct recognition motifs of cage **66** and hemicryptophane **67** have been assembled in one pot. These are as follows: an upper pole featuring a concave (hydrophobic) structure, a central core composed of multiple peptoid moieties, and a lower pole presenting a coordinating bridgehead nitrogen atom. Further applications may arise from installation of

interesting catalytic motifs appended to the macrocyclic cavity aiming to mimic, e.g., catalytic sites of selected enzymes.

With regard to structural diversity and complexity, the scope of MiB can be significantly expanded by conducting multiple Ugi-4CR-based macrocyclizations in a sequential manner. Thus, chiral cryptands as well as clam- and igloo-shaped macromulticycles have been produced by this type of protocol that comprises the fastest access to nonsymmetric peptidic macromulticycles with potential as synthetic receptors. As illustrated in Scheme 20 a key feature of this sequential-MiB approach is not only rapid assembly of complex molecules but also very straightforward access of topologically diverse architectures not easily prepared by other means. Thus, the methodology can be considered as a crucial contribution toward "architectural chemistry".

For example, chiral cryptands like compound **68** can be produced by sequential double-Ugi-4CR-based macrocyclizations that may include the same type of building block combination or not.[106] This type of chiral macrobicycles shows two interesting and completely novel features, i.e., the bridgehead cores are tertiary amide bonds formed by the Ugi-4CRs and the three tether chains are different. This latter feature opens up a variety of possibilities for recognition of chiral molecules. Alternatively, clam-shaped macrobicycles like **69** can be produced by utilizing tetrafunctional cholanic steroids in the same reaction sequence, i.e., MiB/deprotection/MiB. In this case, the two resulting macrocyclic rings are attached to the concave cholanic scaffold, thereby resulting in a clam-type topology,[106] which in principle allows studying the proximity effects of two different guests. Finally, a wide set of macrotetracycles, such as compound **70**, endowed with igloo-type topologies can be achieved in a similar protocol that comprises a sequence of double- and 3-fold Ugi-4CR-based macrocyclizations.[103] Intentional variation of the multiplicity of Ugi-MiBs gives rise to an extra diversity element, which can be combined in different manners with the previously presented diversity-generation issues of MiB. This characteristic enables, for the first time, constructing three-dimensional macrocycles of tremendous complexity in an architectural manner.

6. Conclusions and Future Perspectives

In this review some of the basic principles of the multiple multicomponent macrocyclization (MiB) methodology are outlined. The MiB approach is expected to develop to one of the most valuable strategies for the synthesis of peptide-like or artificial macrocycles. The authors believe that multiple MCR-based macrocyclizations will emerge as a milestone of further synthetic methods toward both repetitive and nonrepetitive complex macrocycles of highly diverse shape, size, constitution, and stereochemistry, additionally containing recognition or functional motifs appended to or within their cavities.[84−89,91] This is possible due to the very efficient, straightforward, and diversity-oriented character that allows applications in many relevant fields derived from modern organic chemistry, e.g., chemical genetics, catalysis, medicinal, biological, supramolecular, and architectural chemistry.

The value of this approach for production of biologically active macrocycles is evident. An imitation of nature's evolutionary principle that leads from structurally simple building blocks to extremely complex and biologically effective macro(multi)cyclic skeletons may be seen as the key feature to new drugs or biological tools of the future.

Synthetic advancements might focus on novel methods to assemble complex (multi)cyclic scaffolds and their precursors with low synthetic cost and in a faster way.[100−108] In particular, for applications in molecular recognition and coordination chemistry rapid access to macro(multi)cycles presenting chiral and specifically functionalized frameworks is of clear importance if one wants to move away from ion recognition to the selective recognition of uncharged small organic molecules. Solutions to future challenges like creation of efficient artificial enzymes ("recognition catalysts") or architectural construction of large molecules appear closer when considering the possibilities offered by multiple MCRs. Further developments may rely also on the use of other MCRs than those tested so far, or on a tunable variation of the MCR reactive functional groups to allow selective formation of a single regioisomer, or on the stereochemical control of MCRs. Studies on the use of templates and switchable moieties to control the macrocycle size and improve efficiency have already started.[84,86,100] First advances for selective formation of a single regioisomer were achieved by sequential and protective group strategies, but this will need further elaboration.[64,103]

Multiple multicomponent approaches like MiBs and similar strategies derived from this concept are likely to play a pivotal role in the future development of functional macrocycles, cryptands, cages, and similar compounds. However, only development of proper theoretical, synthetic, and analytical methods that allow combining design with combinatorial skills, efficient screening, and SAR analyses shall ultimately lead to successful applications in the challenging area of recognition chemistry. We believe that the concepts and advantages included in this methodology for macrocycle synthesis, e.g., speed, versatility, complexity generation, functionality, and size control, perfectly illustrate its potential for development of future chemistry.

7. Abbreviations

BOC	*tert*-butyloxycarbonyl
Cbz	benzyloxycarbonyl
3CR	three-component reaction
DCC	dynamic combinatorial chemistry
DCL	dynamic combinatorial library
ESI-MS	electrospray ionization mass spectrometry
FG	MCR reactive functional group
HPLC	high-performance liquid chromatography
HR-FT-ICR	high-resolution Fourier transform ion cyclotron resonance
MCR	multicomponent reaction
MiB(s)	multiple multicomponent macrocyclization(s)/macrocycle(s) including bifunctional building blocks
NIR	near-infrared
P-3CR	Passerini three-component reaction
PEG	polyethylene glycol
TFA	trifluoroacetyl
Ugi-4CR	Ugi four-component reaction (also U-4CR)

8. Acknowledgments

We thank all our colleagues whose names appear in the references for their inspiration and outstanding contribution to the development of this fascinating concept. We are grateful to the Deutsche Forschungsgemeinschaft (GRK/894, CERC3, SPP Organocatalysis WE 1826/4-1 and HWP/LSA) and the DAAD and CNPq (grant to O.E.V.) for financial

support. Special thanks to Prof. Dr. Bernhard Westermann for helpful discussion.

9. References

(1) Gohlke, H.; Klebe, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2644.
(2) Berg, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2462.
(3) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(4) Boger, D. L.; Desharnais, J.; Capps, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4138.
(5) Fenniri, H., Ed. *Combinatorial Chemistry: A Practical Approach*; Oxford University Press: New York, 2000.
(6) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2007**, *70*, 461.
(7) Shu, Y. Z. *J. Nat. Prod.* **1998**, *61*, 1053.
(8) Wessjohann, L. A.; Ruijter, E.; Rivera, D. G.; Brandt, W. *Mol. Diversity* **2005**, *9*, 171.
(9) Wessjohann, L. A.; Kleber, Z.; Andrade, C.; Vercillo, O. E.; Rivera, D. G. *Targets Heterocycl. Syst.* **2006**, *10*, 24.
(10) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2005**, *243*, 137.
(11) Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303.
(12) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878.
(13) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.
(14) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev.* **2008**, *7*, 608.
(15) Rouhi, M. *Chem. Eng.* **2003**, *81* (41), 77.
(16) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH: Weinheim, 1995.
(17) Vögtle, F. *Supramolecular Chemistry*; Wiley & Sons: Chichester, 1991.
(18) Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998.
(19) D'Souza, V. T.; Lipkowitz, K. B. *Chem. Rev.* **1998**, *98*, 1741.
(20) Cram, D. J.; Cram, M. J. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, 1997.
(21) Tamminen, J.; Kolehmainen, E. *Molecules* **2001**, *6*, 21.
(22) Feigel, M.; Ladberg, R.; Winter, M.; Bläser, D.; Boese, R. *Eur. J. Org. Chem.* **2006**, 371.
(23) Whitmarsh, S. D.; Redmond, A. P.; Sgarlata, V.; Davis, A. P. *Chem. Commun.* **2008**, 3669.
(24) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.
(25) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weingand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072.
(26) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.
(27) Wessjohann, L. A.; Scheid, G. O. In *Organic Synthesis Highlights*; Schmalz, H.-G., Ed.; Wiley-VCH: Weinheim, 2000; Vol. IV, pp 251−267.
(28) (a) Wessjohann, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 715. (b) Wessjohann, L. *Angew. Chem.* **1997**, *109*, 739.
(29) Altmann, K.-H.; Pfeiffer, B.; Arseniyadis, S.; Pratt, B. A.; Nicolaou, K. C. *ChemMedChem* **2007**, *2*, 396–423.
(30) Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K.-H.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3515.
(31) Chou, T.-C.; Dong, H.; Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Tong, W. P.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4762.
(32) de la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160.
(33) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078.
(34) Burke, M. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
(35) Takahashi, T.; Kusaka, S.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230.
(36) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2097.
(37) Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716.
(38) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648.
(39) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047.
(40) Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125.
(41) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron Lett.* **2003**, *44*, 5575.
(42) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145.
(43) Cristau, P.; Vors, J.-P.; Zhu, J. *QSAR Comb. Sci.* **2006**, *25*, 519.
(44) Bughin, C.; Zhao, G.; Bienaymé, H.; Zhu, J. *Chem. Eur. J.* **2006**, *12*, 1174.
(45) de Greef, M.; Abeln, S.; Belkasmi, K.; Dömling, A.; Orru, R. V. A.; Wessjohann, L. A. *Synthesis* **2006**, 3997.
(46) Owens, T. D.; Araldi, G. L.; Nutt, R. F.; Semple, J. E. *Tetrahedron Lett.* **2001**, *42*, 6271.
(47) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596.
(48) Dietrich, S. A.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97.
(49) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*, 159.
(50) (a) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785. (b) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem.* **2005**, *117*, 4863.
(51) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
(52) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *64*, 734.
(53) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(54) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
(55) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187.
(56) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1.
(57) Weber, L. *Drug Discovery Today* **2002**, *2*, 143.
(58) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
(59) Zhu, J.; Bienyamé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
(60) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
(61) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.
(62) Skorna, G.; Ugi, I. *Chem. Ber.* **1978**, *111*, 3965.
(63) Failli, A.; Immer, H.; Götz, M. D. *Can. J. Chem.* **1979**, *57*, 3257.
(64) Vercillo, O. E.; Kleber, Z.; Andrade, C.; Wessjohann, L. A. *Org. Lett.* **2008**, *10* (2), 205.
(65) Orru, R. V. A.; de Greef, M.; Abeln, S.; Belkasmi, K.; Dömling, A.; Wessjohann, L. A. In The 12th European Symposium on Organic Chemistry (ESOC 12), 2001, O-36, Groningen, The Netherlands.
(66) Gournelis, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, *14*, 75.
(67) Cristau, P.; Temal-Laïb, T.; Bois-Choussy, M.; Martin, M.-T.; Vors, J.-P.; Zhu, J. *Chem. Eur. J.* **2005**, *11*, 2668.
(68) Temal-Laib, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583.
(69) Voigt, B.; Schaks, A.; Bögel, M.; Brandt, W.; Wessjohann, L. A. In 2nd International Conference on Multi Component Reactions, Combinatorial and Related Chemistry (MCR 2003), 2003, Genova, Italy.
(70) Virtanen, E.; Kolehmainen, E. *Eur. J. Org. Chem.* **2004**, 3385.
(71) Davis, A. P. *Molecules* **2007**, *12*, 2106.
(72) Li, Y.; Dias, J. R. *Chem. Rev.* **1997**, *97*, 283.
(73) Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev.* **1997**, *97*, 1567.
(74) Davis, A. P.; Joss, J.-B. *Coord. Chem. Rev.* **2003**, *240*, 143.
(75) Rivera, D. G.; Wessjohann, L. A. *Molecules* **2007**, *12*, 1890.
(76) Hoye, T. R.; Moon, P. E. B. *J. Am. Chem. Soc.* **2000**, *122*, 4982.
(77) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Pavone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984.
(78) Rowan, S. J.; Hamilton, D. G.; Brandy, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578.
(79) Singh, Y.; Sokolenko, N.; Kelso, M. J.; Gahan, L. R.; Abbenante, G.; Fairlie, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 333.
(80) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39.
(81) Wessjohann, L. A.; Rivera, D. G.; Coll, F. *J. Org. Chem.* **2006**, *71*, 7521.
(82) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51.
(83) Lehn, J.-M. In *Supramolecular Science: Where It Is and Where It Is Going*; Ungaro, R., Dalcanale, E., Eds.; Kluwer: Dordrecht, 1999; pp 287−304.
(84) Kreye, O.; Westermann, B.; Rivera, D. G.; Johnson, D. V.; Orru, R. V. A.; Wessjohann, L. A. *QSAR Comb. Sci.* **2006**, *25*, 461.
(85) Rivera, D. G.; Vercillo, O. E.; Wessjohann, L. A. *Synlett* **2007**, 308.
(86) Wessjohann, L. A.; Rivera, D. G.; León, F. *Org. Lett.* **2007**, *9*, 4733.
(87) Michalik, D.; Schaks, A.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2007**, 149.
(88) Westermann, B.; Michalik, D.; Schaks, A.; Kreye, O.; Wagner, C.; Merzweiler, K.; Wessjohann, L. A. *Heterocycles* **2007**, *73*, 863.
(89) Janvier, P.; Bois-Choussy, M.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811.
(90) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901. (b) Cort, A. D.; Ercolani, G.; Iamiceli, A. L.; Mandolini, L.; Mencarelli, P. *J. Am. Chem. Soc.* **1994**, *116*, 7081. (c) Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949.
(91) Rivera, D. G.; Vercillo, O. E.; Wessjohann, L. A. *Org. Biomol. Chem.* **2008**, 1787.
(92) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898.

(93) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652.
(94) León, F.; Rivera, D. G.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 1762.
(95) Sierra, M. A.; Pellico, D.; Gómez-Gallego, M.; Manchego, M. J.; Torres, R. *J. Org. Chem.* **2006**, *71*, 8787.
(96) Arumugan, N.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 8855.
(97) Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700.
(98) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584.
(99) Petasis, N. A. In *Multicomponent Reactions*; Zhu, J., Bienyamé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 119−123.
(100) Alfonso, I.; Bolte, M.; Bru, M.; Burguete, M. I.; Luis, S. V.; Rubio, J. *J. Am. Chem. Soc.* **2008**, *130*, 6137–6144.
(101) Christinat, N.; Scopellit, R.; Severin, K. *J. Org. Chem.* **2007**, *72*, 2192.
(102) Lin, J.-B.; Xu, X.-N.; Jiang, X.-K.; Li, Z.-T. *J. Org. Chem.* **2008**, *73*, 9403.
(103) Rivera, D. G.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2006**, *128*, 7122.
(104) Llinares, J. M.; Powell, D.; Bowman-James, K. *Coord. Chem. Rev.* **2003**, *240*, 57.
(105) Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671.
(106) Rivera, D. G.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2009**, submitted for publication.
(107) Akritopoulus-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125.
(108) Eckert, H. *Heterocycles* **2007**, *73*, 149.

CR8003407