Conformation-Directed Macrocyclization Reactions

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Keywords: Macrocycles / Conformation-directed macrocyclization / Pre-organization / Natural products / Synthesis

The importance of conformational pre-organization in successful macrocyclization reactions has been recognized ever since Eschenmoser's synthesis of vitamin B12 and Woodward's synthesis of erythromycin. Different approaches to productive preorganization are possible depending mainly on the degree of freedom in the choice of the structural elements. In diversity-oriented synthesis, in which it is not imperative that the molecular framework has a fixed structure, matching building blocks can be used to assemble a macrocycle. In target-oriented synthesis, more subtle structural elements have to be considered in order to pre-organize the linear substrate into a folded conformer suitable for ring closure. In this microreview, some selected examples of macrocyclization reactions are presented to illustrate the different rational approaches. Special attention is paid to the role of intramolecular weak forces and protecting groups in the conformational pre-organization that facilitates macrocyclization reactions.

"*We all know that enforced propinquity often leads on to greater intimacy, the closer we hold reagents together, the more likely they are to react.*"
R. B. Woodward, quoted in K. B. Sharpless, *Chem. Ber.* **1986**, 39.

1. Introduction

Organic synthesis has been developed to a high level of sophistication that provides high productivity and insight into the mechanistic details is immense. Nowadays, the synthesis of complex molecules seems to have become more a question of synthetic elegance than of feasibility. True enough, synthetic methodology and structure elucidation have produced some breathtaking structures, including vitamin B12, palytoxin, brevetoxine, taxol, strychnine, vancomycin (Figure 1) and many more.[1] However, all these impressive achievements must not obscure the numerous pitfalls that still await the synthetic chemist. Access to a de-

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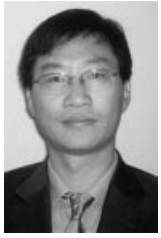


Jieping Zhu, Director of Research at the CNRS, was born in 1965 in Hangzhou, P. R. China. He received his B.Sc. degree from Hanzhou Normal University in 1984 and his M.Sc. degree from Lanzhou University in 1987 under the supervision of Professor Y.-L. Li. In 1988 he moved to France and obtained his Ph.D. degree (1991) from Université Paris XI under the guidance of Professor H.-P. Husson. After a one-and-half-year post-doctoral stay with Professor Sir D. H. R. Barton at Texas A & M University, he joined the "Institut de Chimie des Substances Naturelles", CNRS, in December 1992 as Chargé de Recherche and was promoted to the actual position in 2000. The development of novel synthetic methods, their application in the synthesis of bioactive natural products, and the design of novel multicomponent reactions are his main research interests.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

 DOI: 10.1002/ejoc.200400751

sired structure is rarely straightforward, but rather a series of detours and dead-ends.[2]

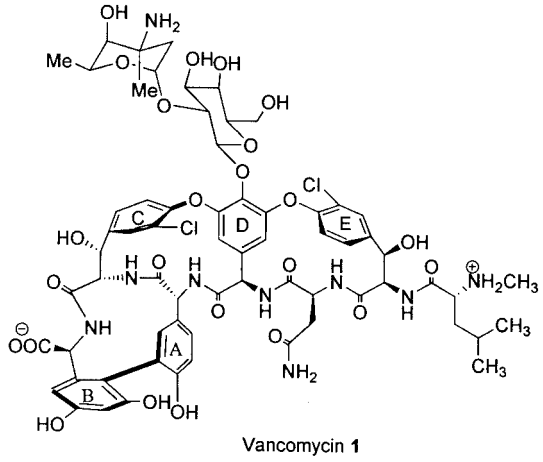


Figure 1.

One of the most frequently encountered problems in synthetic chemistry is the synthesis of macrocyclic structures. This is of special significance since macrocyclic structures in general play an important role in chemistry, biology and medicine.[3] Various important drugs indeed contain macrocyclic components, like cyclosporine, or the vast class of biologically active macrolides, such as erythromycin and the vancomycin family of glycopeptides.[4] Turning linear molecules into macrocyclic structures is an important tool for manipulating properties of compounds. Peptides have been shown to have interesting therapeutic potential, but unfavorable physicochemical properties,[5] a downside that sometimes can be overcome by converting them into cyclic analogues.[6] Apart from the pharmaceutical applications of macrocycles, there is also substantial economic interest in macrocyclic polymers and in the macrocycles used in the production of perfumes.[7]

Cyclization reactions are most often attempted in the late stage of a synthesis, which, in cases of failure, makes the modifications of the precursors especially painful.[8] Moreover, the low yields of the macrocyclization reactions, which are often reported, give an otherwise elegant synthesis a stale taste.

Macrocycles and their formation in general have been the subject of a manifold of publications and books.[9] Numerous different synthetic methods have been employed to obtain the desired ring structures, mostly under conditions of high dilution in order to avoid oligomerization. We do not intend to simply re-present the multitude of cyclization methods already cited elsewhere. Quite the contrary, this microreview focuses on systems and methods that facilitate the ring closure brought about by a directed conformational pre-organization approach.[10] Therefore, we will discuss only those systems which are either by their structure already pre-disposed to pre-organization or which have the ability to introduce an element of pre-organization. The generality of the macrocyclization problem makes it necessary to discuss different fields of organic chemistry, from classical peptide synthesis through to metal-catalysed processes, including total syntheses as well as model studies.

By illustrating these different approaches, we hope to demystify the cyclization step and to provide a basic synthetic tool-box for the macrocyclization process. But most of all, we wish to stimulate further discussions and publications in order to fill in the gaps still present on the map leading to successful macrocyclization. The formation of some eight-membered rings will be included − although not strictly a macrocyclization process by definition − since this ring-size is particularly difficult to obtain.

2. General Considerations

Most of the cyclization reactions reported in the literature are effected under conditions of high dilution. However, the inefficiency in bringing head and tail together often leads to prolonged reaction times and side-reactions, for example, cyclodimerization and epimerization. Moreover, compounds that have an unfavorable conformation often cannot be cyclized at all, whereas even large, pre-organized linear molecules cyclize in high yields. As always, the fine balance between entropy and enthalpy is the key to the formation of a desired product or an unwanted material.

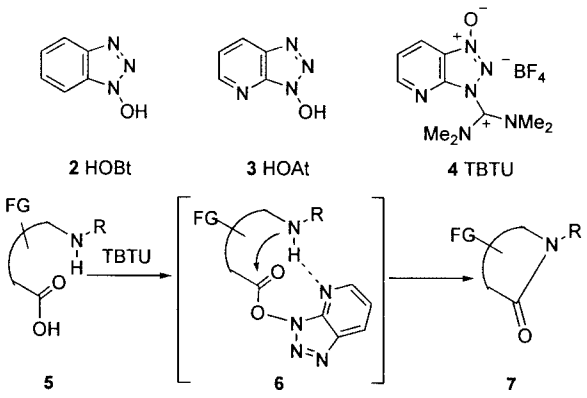
3. Synthesis

As stated by Woodward, the proximity of two reactive centers enhances the chance of a productive interaction, either by pure statistical calculation or by lowering the reaction barriers. Therefore, the activation energy for a ring-closure reaction can be lowered by bringing the two reacting termini into close proximity (pre-organization) before the cyclization step takes place. Naturally, the energy required to bring the reaction centers together and to restrain their motion, for example, the rotational freedom of the molecular framework, in order to facilitate the formation of the ring-bond has to be paid for in the pre-organization step. The forces responsible for one conformation being favored over another are, namely, covalent bonds, hydrogen bonding, steric and different electronic interactions, such as electrostatic interactions, repulsive forces, polarization and charge transfer.[11] The interplay of various of these factors of different strengths and to different degrees contributes to the conformation of molecules and, hence, also to the pre-organization of the reactive centers. In the following sections we will highlight some representative examples, demonstrate their synthetic importance and point out practical solutions.

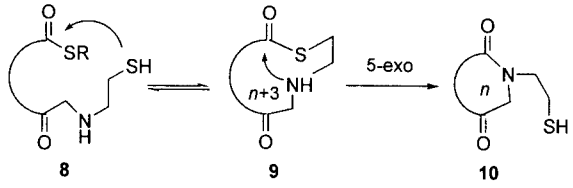
3.1 Reagent-Based Approach

To construct cyclopeptides and macrolides, numerous coupling reagents have been developed, starting from simple carbodiimides, triazole derivatives and phosphate-based compounds.[12] Some of these reagents have been shown to greatly enhance the rate of end-to-end cyclization and the

superior performance of HOAt- over HOBt-based reagents has often been observed (Scheme 1).[13] This sometimes spectacular enhancement is thought to be a result of a sort of pre-organization of the amino and carboxy components through hydrogen bonding with the reagent (Scheme 2).[14] However, when the linear precursor has an unfavorable conformation miracles cannot be expected and cyclization does not occur.[15]



Scheme 1.



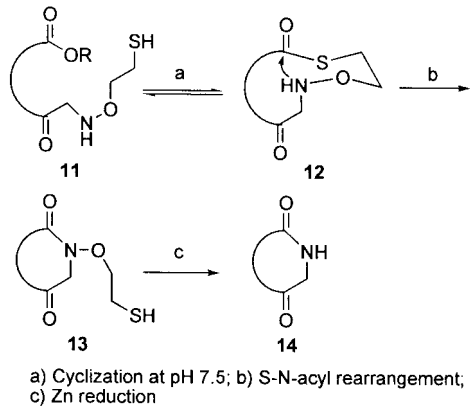
Scheme 2.

3.2 Ring Contraction and Enlargement

In a broad sense, the double-action behavior exerted by an HOAt-type reagent which leads to pre-organized conformations is closely related to ring contraction and enlargement cyclization reactions.[16] Different efficient strategies based on the initial formation of thioesters followed by a *S*- to *N*-acyl rearrangement to give lactams have been reported in the literature. The efficiency of this approach can be explained by the following considerations. First, even though transthiolactonization is a reversible process, under equilibrating conditions ring–chain tautomerization is favored over the alternative dimerization/polymerization process. Secondly, with the formation of the macrothiolactone **9** the N and C termini are covalently bound in close proximity, thus facilitating the (proximity-driven) S→N acyl transfer. Indeed the acyl migration itself should be facile as it is formally a 5-*exo*-*trig* process (Scheme 2).

The group of Tam has made substantial contributions to this field, developing cysteine-containing systems that facilitate the macrocyclization process. These cyclization reactions, called "native chemical ligation", proceed either through weak activation[17] or transesterification[18] of the C terminus, as well as by a thia-zip cascade,[19,20] generally leaving at least one thiol unit in the final product.

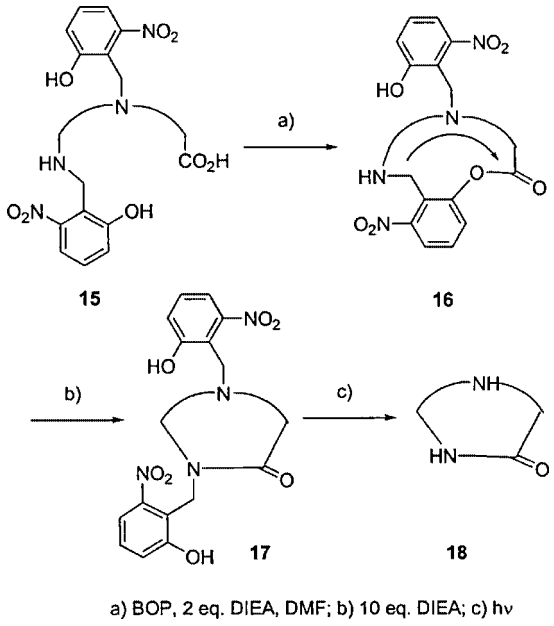
An elegant procedure that employs the S→N acyl rearrangement involves the use of the oxyethanethiol moiety as an auxiliary (Scheme 3), which obviates the need to use cysteine as the N-terminal residue. Introduction of a *N*-(oxyethanethiol)amine group as a terminal sequence, as in **11**, leads to the intermediate thioester **12**, which rearranges to the *N*-oxyethanethiol-substituted macrocyclic lactam **13**. The oxyethanethiol auxiliary is then removed by reduction with zinc dust to give the macrolactam ring **14** without a residual thiol group (traceless approach).[21]



Scheme 3.

Cyclic peptides are generally synthesized through amide-bond-forming reactions of the C and N termini under conditions of high dilution. The efficiency of such processes is sequence-dependent and is particularly low for the synthesis of cyclotetrapeptides and cyclopentapeptides.[22] Originally starting from a thioester, Meutermans, Smythe and coworkers have developed a neat cyclization protocol in which a photolabile nitrobenzyl aldehyde was used as the N-activating and pre-organizing group in order to obtain cyclic peptides that are otherwise difficult to access.[23] By *N*-alkylation of the backbone amide, the linear peptide is prone to adopt a turn conformation owing to its higher propensity to form the *cis*-amide configuration which facilitates the cyclization process. By following this route, the all-L cyclic tetrapeptide cyclo[Tyr-Arg-Phe-Ala] was successfully synthesized (Scheme 4).[24]

Another interesting method using Staudinger ligation, which involves S→N acyl transfer, has recently been developed for the synthesis of seven- to ten-membered cyclic lactams in moderate-to-good yields.[25,26] All three strategies facilitate the end-to-end cyclization of peptidic systems by a traceless approach and might be worth considering when difficulties are encountered in the more classical pathways.



Scheme 4.

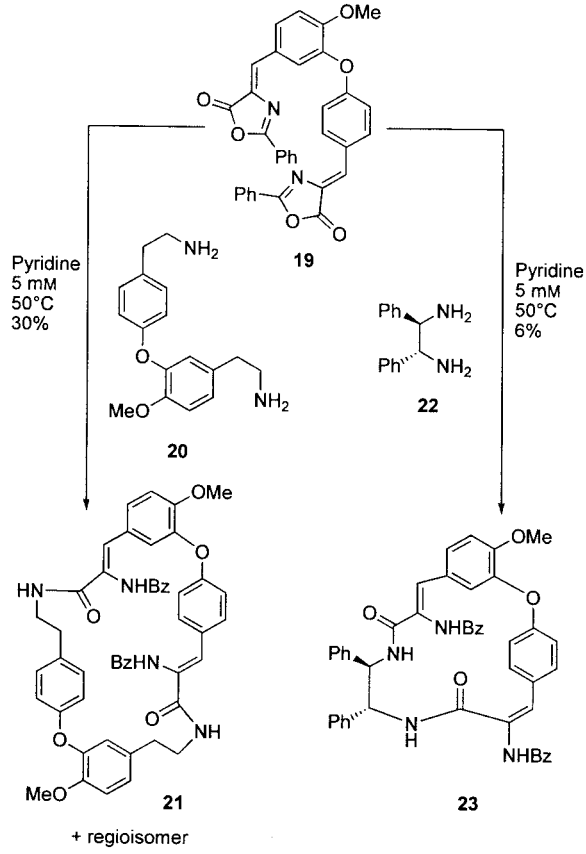
3.3 Templates

Another highly elaborate method to facilitate the formation of macrocycles involves the use of templates that may be cationic,[27] uncharged organic[28,29] or anionic[30] in character. Templates are characterized by their ability to organize "*an assembly of participating molecules geometrically in order to enable the reaction to proceed in a way it would not pursue (or at least less efficiently) in its absence*" whilst not being one of the reactants itself.[31] Since in template-mediated reactions the conformation is directed by an "external" force we do not consider these fascinating systems in this article. Moreover, template-mediated macrocyclization reactions have already been reviewed extensively.[32,33]

3.4 Substrate Tailoring

Sometimes the exact chemical structure of a cyclic compound is not the prime target of the synthesis. On the contrary, the focus is on the formation of a general cyclic structure in order to obtain certain three-dimensional properties, as is often the case for peptidomimetics or the construction of compound libraries. The possibility of incorporating various structural elements into these macrocycles allows the reaction partners to be tailored to give an optimized cyclization step. Therefore, these examples may provide evidence of the factors that tend to facilitate macrocyclization reactions.

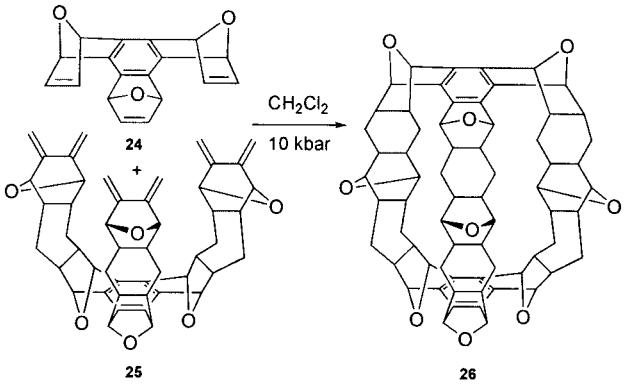
The importance of substrate tailoring is illustrated by the reaction of diamines and bis-oxazolones (Scheme 5). The heating of bis-oxazolone **19** and diamine **20** in pyridine gave the regioisomeric 28-membered macrolactam **21** in about 30% yield by a tandem Erlenmeyer condensation–macrolactamization process.[34] However, the reaction of the same bis-oxazolone **19** with (1*R*,2*R*)-1,2-diphenyl-1,2-diaminoethane **22** under identical conditions provided the corresponding macrocycle **23** in only 6% yield. Molecular modeling indicated that the interatomic distance between the two amino groups in the extended conformation of **20** (9 Å) closely matches the intercarbonyl distance in **19**, thus allowing facile cyclization. In the case of vicinal diamine **22**, significant torsional strain would have to be introduced in order to achieve the right orientation of the two reactive functional groups in the intermediate en route to **23**.



Scheme 5.

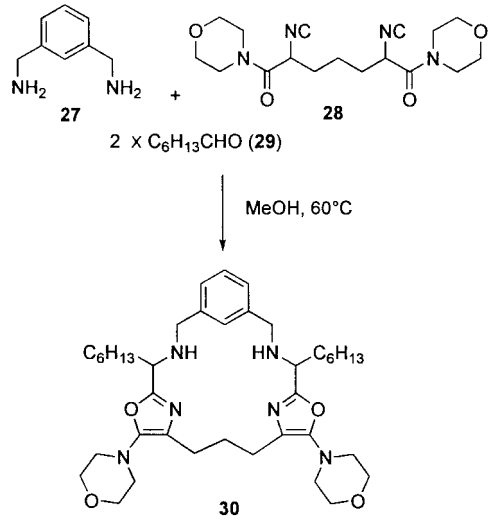
This LEGO®-like matching of the building blocks can suppress unwanted side-reactions and facilitate macrocyclization, but sure enough, it is important to stay within reasonable limits when choosing the reactants. Another sophisticated example is shown in Scheme 6.[35] The reaction of tridienophile **24** and tridiene **25** under high pressure produced cage compound trinacrene **26** by a remarkable sequence involving one inter- and two intramolecular Diels–Alder cycloaddition reactions.

The outcome of multicomponent reactions depends strongly on the choice of precursors, even more so when they are designed to yield macrocyclic structures. A new macrocyclization strategy displaying the power of substrate tailoring was developed by our group which allowed a one-



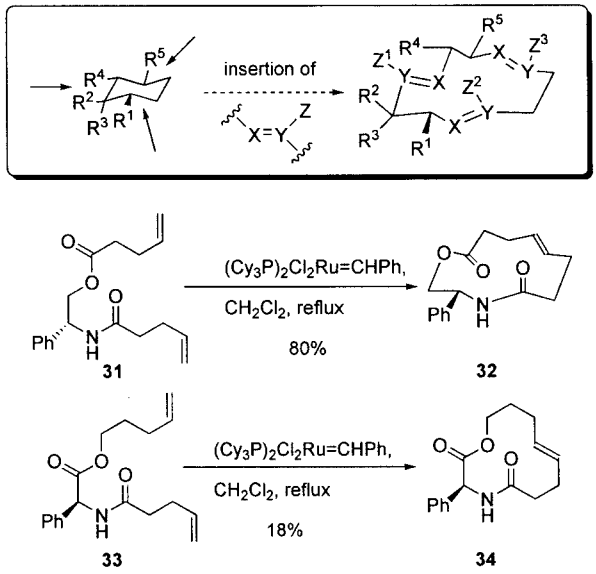
Scheme 6.

step synthesis of the cyclophane **30** from readily accessible starting materials (Scheme 7).[36]



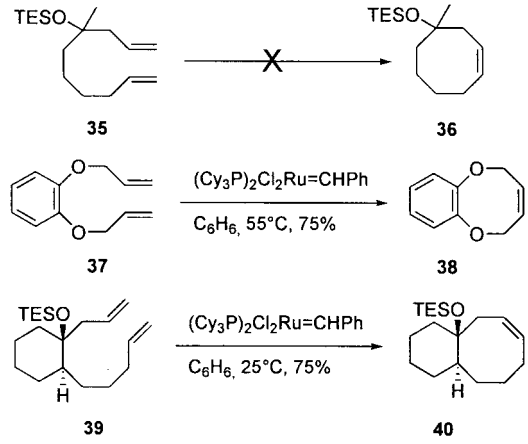
Scheme 7.

Generally six-membered rings are formed with high effective molecularities. This is the result of favorable conformational organization that lowers the entropic as well as the enthalpic barriers to cyclization. The conversion of six-membered cycles into larger systems involves expansion of the structure, while at the same time conserving its geometric pattern. By careful conformational analysis, Schreiber[37] elucidated that by inserting planar, sp^2-hybridized atoms with *trans* geometry into the appropriate positions of a saturated six-membered ring, an hexagonally shaped 12-membered macrocycle free of transannular and torsional strain should be obtained (Scheme 8). In fact, ring-closing metathesis (RCM) of conformationally tailored precursor **31** in the presence of Grubbs' catalyst[38] provided the macrocycle **32** in 80% yield. In contrast, cyclization of nonidealized substrate **33**, in which only the structure of the ester is inverted, afforded the macrocycle **34** in only 18% yield under identical conditions. These examples convincingly demonstrate the power of conformational design in the development of efficient macrocyclization processes.



Scheme 8.

Some other successful examples of conformation-directed cyclization reactions are shown in Scheme 9.[39,40] While precursor **35** failed to cyclize under various RCM conditions, the catechol derivative **37**, as well as the *trans*-substituted cyclohexane **39**, underwent rapid RCM to form the eight-membered rings **38** and **40** in 75% yields (Scheme 9). Evidently, the presence of the the cyclic backbone in the linear precursor pre-organized the molecule into a productive conformation, thus facilitating end-to-end cyclization. In addition to the conformational effect, note that introduction of a trigonal carbon atom into a linear substrate can increase the effective molecularities of the ring-forming process by decreasing ring strain and transannular interactions.



Scheme 9.

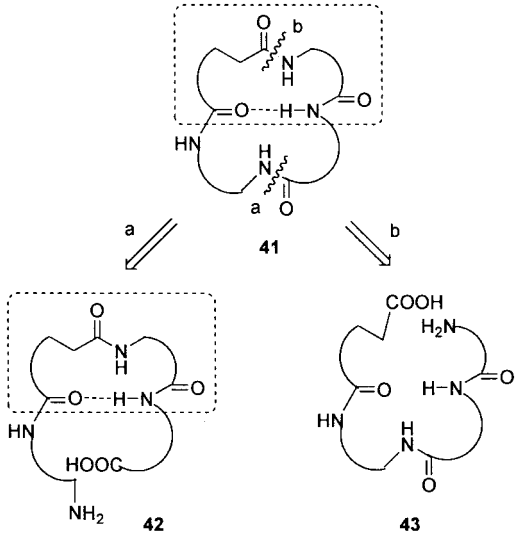
These examples show nicely that the desired cyclic structures can be obtained by fine tuning the reactants, regardless of the chemical method employed for the cyclization

step. While the LEGO-like matching of the building blocks is an obvious approach, the conformational analysis of Schreiber and co-workers[38] and the fixation of linear precursors to a cyclic backbone represent concepts that are transferable to other syntheses.

3.5 Intramolecular Hydrogen Bonding

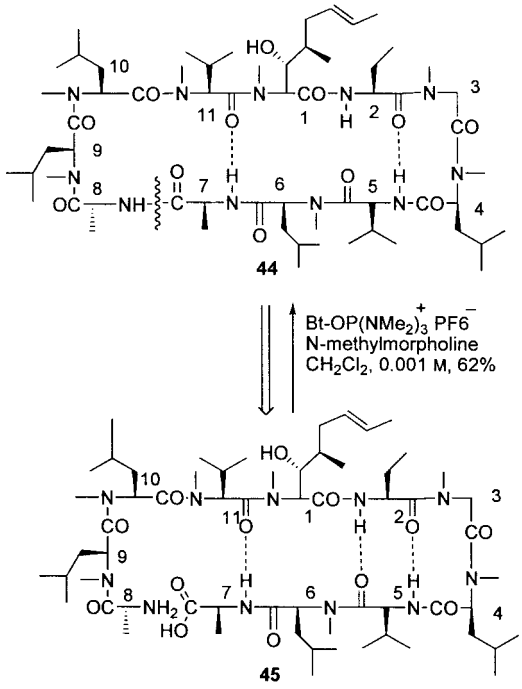
The extraordinary importance of hydrogen-bonding interactions in determining the conformation of molecules is highlighted by the vast diversity of spatial arrangements adopted by peptides and proteins in which hydrogen bonding plays a crucial role. Their secondary structures are induced by a multitude of directional changes and folding patterns stabilized by hydrogen bonds across the chains, the so-called "turn" units.[41,42] Obviously, hydrogen bonding is also of special importance in the context of the design of effective conformation-directed macrocyclization reactions. Intramolecular hydrogen bonding can lead to one conformation being favored over another, thereby enabling or preventing the two cyclization sites to achieve productive proximity.

In the total synthesis of cyclopeptides, ring disconnection carries significant strategic importance having a large impact on the overall efficiency of the synthetic approach. Generally for target molecules displaying hydrogen-bonding interactions, the incorporation of a turn fragment into a linear precursor is the obvious choice in order to obtain a conformation-biased substrate. Consider the general structure **41** with a turn motif in the top part of the molecule, the cyclization of **42** (disconnection a) is more promising than the same process for substrate **43** (disconnection b), evoking the potential of the conformational principle (Scheme 10).



Scheme 10.

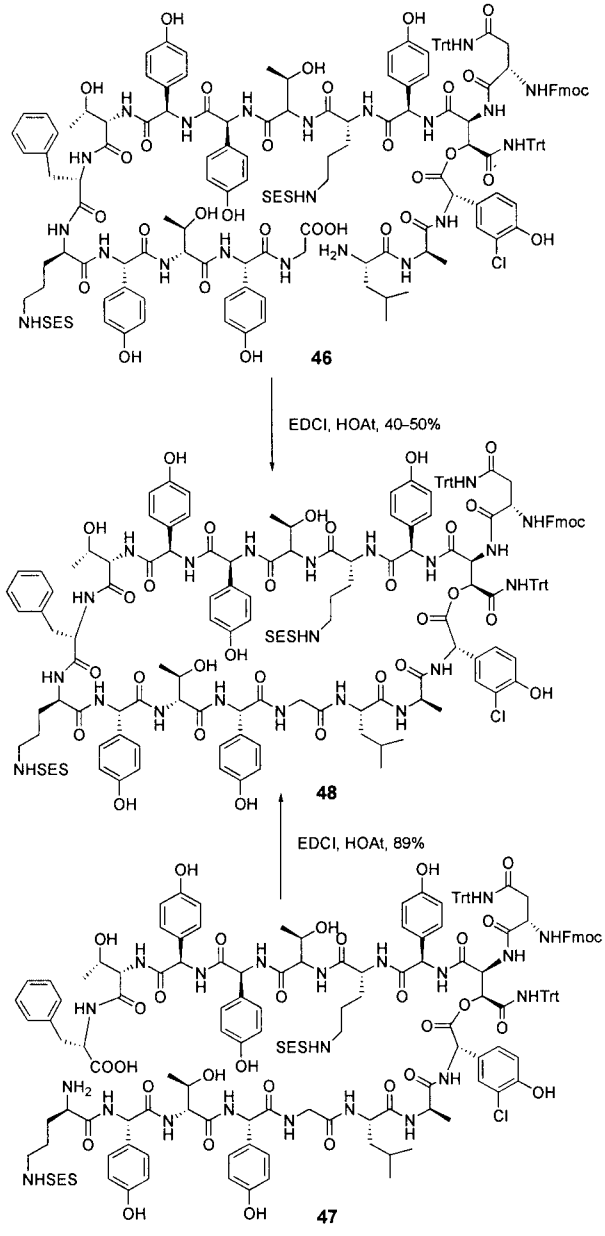
The practical importance of hydrogen-bonding interactions was highlighted by Wenger's total synthesis of cyclosporine, an immunosupressant (Scheme 11).[43] The amino acids 1 to 6 of this cyclic undecapeptide are engaged in an antiparallel β-pleated sheet conformation which contains three transannular hydrogen bonds. The remaining amino acids form an open loop that contains a D-alanine in position 8 and the only *cis*-amide linkage between the two adjacent *N*-methylleucine residues 9 and 10. Wenger selected the peptide bond between the L-alanine (residue 7) and the D-alanine (residue 8) as the strategic bond leading to linear substrate **45**. One of the major reasons for such a strategic choice is as follows: the linear undecapeptide **45** may adopt a folded conformation through the formation of intramolecular hydrogen bonds, as found in the cyclic structure of cyclosporine. Indeed, cyclization of **45** under appropriate conditions provided 33-membered macrocycle **44** in 62% yield. The presumed conformation of the linear precursor as a "cyclosporine"-like, hydrogen-bond-stabilized folded structure was supported by NMR analysis. Additionally, this cyclization reaction may also be facilitated because it has a D-amine terminus (D-Ala) as the nucleophilic moiety and the small side-chains of two alanine residues.[44]



Scheme 11.

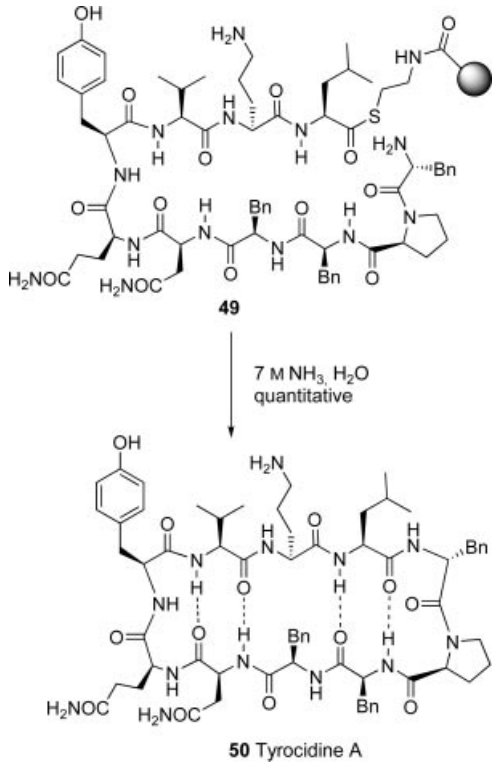
The recent remarkable total synthesis of the antibiotic Ramoplanin A2[45] by the group of Boger is another example of the outstanding importance of hydrogen-bonding interactions in pre-organization.[46] The convergent approach towards the 49-membered cyclodepsipeptide envisaged two different sites for the final cyclization reaction, both of which potentially benefit from pre-organization, although to different degrees. Although the cyclization site between the glycine (14th AA) and leucine (15th AA) units (**46**) is less sterically hindered, it does not involve ring closure at a

D-amino acid site and is situated at the more flexible loop of the macrocycle. In contrast, the macrolactamization between Phe (9th AA) and D-Orn (10th AA) (**47**) occurs next to the β turn [aThr(8)-Phe(9)], involves a D-amino acid and the linear precursor is stabilized by the antiparallel β strands.[47] As the coupling reaction of the latter proved to be highly successful (up to 89% yield for the purified precursor), no extensive attempts to improve the 50% yield of the former macrocyclization strategy were made. However, both sites are obviously pre-organized by the hydrogen-bonding pattern of the precursors and vary only in the degree of organization (Scheme 12).[48]



Scheme 12.

Another example of the turn-directed synthesis of natural cyclopeptides has been reported by the group of Guo.[49] The linear precursors of tyrocidine A and gramicidin S were synthesized on a solid support and subsequently cyclized in aqueous ammonia solution in quantitative yields. Remarkably, possible side-products resulting from intermolecular aminolysis, hydrolysis of the thioester and the competitive cyclization of the δ-NH_2 group of the ornithine were not observed. Tyrocidine A adopts a rigid antiparallel β-pleated sheet conformation with four intramolecular hydrogen bonds. The linear peptide **49** is likely pre-organized into a tyrocidine A-like conformation that is responsible for the observed high specificity of the desired head-to-tail cyclization reaction. Additionally, this cyclization reaction may also be favored again by the D-amino acid (D-Phe) located at the end of the hydrogen-bonded antiparallel β strands (Scheme 13).

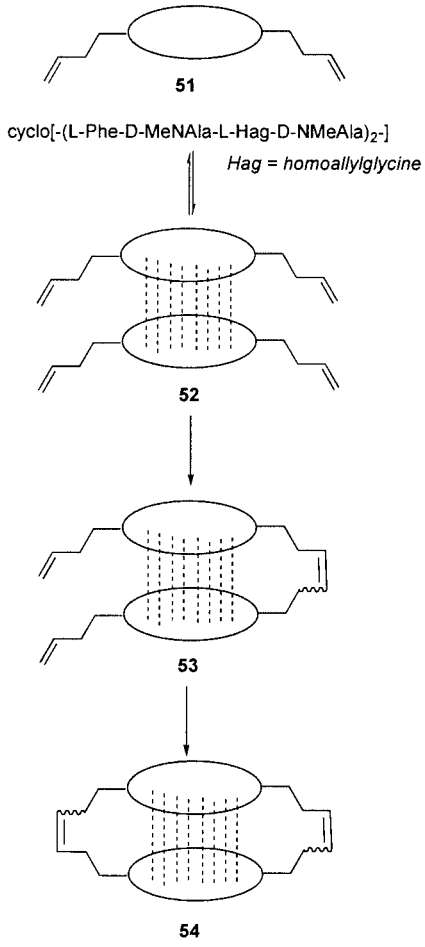


Scheme 13.

While in natural product synthesis the hydrogen-bonding pattern is imposed by the target molecule, a manifold of publications deal with the synthetic introduction of hydrogen bonding via turn units. Indeed, various turn motifs, such as the γ (helical),[50] δ[51] and β turns[52] and others,[53] have been used as structural elements to pre-organize linear substrates into a productive conformation for macrocyclization.

One particularly impressive example is the cyclodimerization of cyclopeptide **51** by way of hydrogen-bond-promoted olefin metathesis (Scheme 14). Ghadiri and coworkers[54] found that cyclooctapeptide **51** self-assembles via eight interstrand hydrogen bonds to form two slow-exchanging antiparallel β-sheet-like hydrogen-bonded cylinders **52** in a nonpolar organic solvent. By simply adding Grubbs' catalyst to the chloroform solution of **51** the tricy-

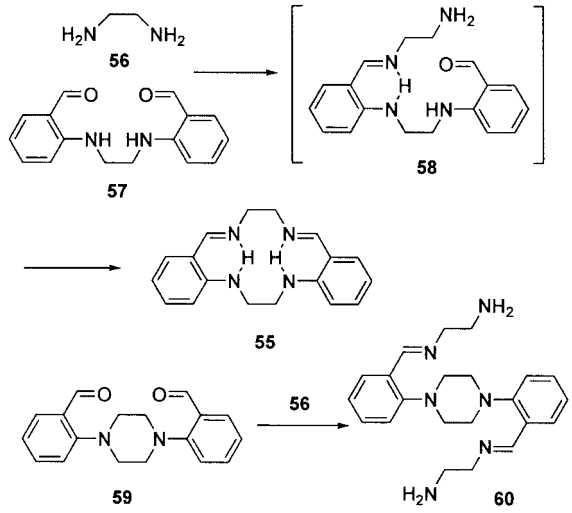
clic structure **54** was obtained via intermediate **53** in 65% yield. Evidently, both inter- and intramolecular metatheses were facilitated by hydrogen-bond-assisted conformational pre-organization of the starting cyclopeptide.



Scheme 14.

Hydrogen-bond-assisted conformation-directed macrocyclization is not restricted to the peptide domain. The highly successful synthesis of macrocycle **55** by condensation of diamine **56** and dialdehyde **57** can be explained on the basis of the stabilization of the imine bond by intramolecular hydrogen bonding that favors the folded conformation. In the absence of this structural element, no cyclization occurred as shown by the reaction between **56** and dialdehyde **59**; instead of the macrocycle, only the linear condensation product **60** was isolated (Scheme 15).[55]

By reacting diamine **61** with a central 2,6-disubstituted pyridyl unit and diacyl chloride **62,** Hunter and co-workers obtained the corresponding macrocycle **63** in 88% yield. However, when a similar reaction was carried out with diamine **64**, which contains a central isophthaloyl diamide subunit, macrocycle **65** was obtained in a much lower yield (37%) (Scheme 16).[56] Hunter and co-workers proposed that in the 2,6-disubstituted pyridyl derivative **61**, intramolecular hydrogen bonding between the pyridine lone pair



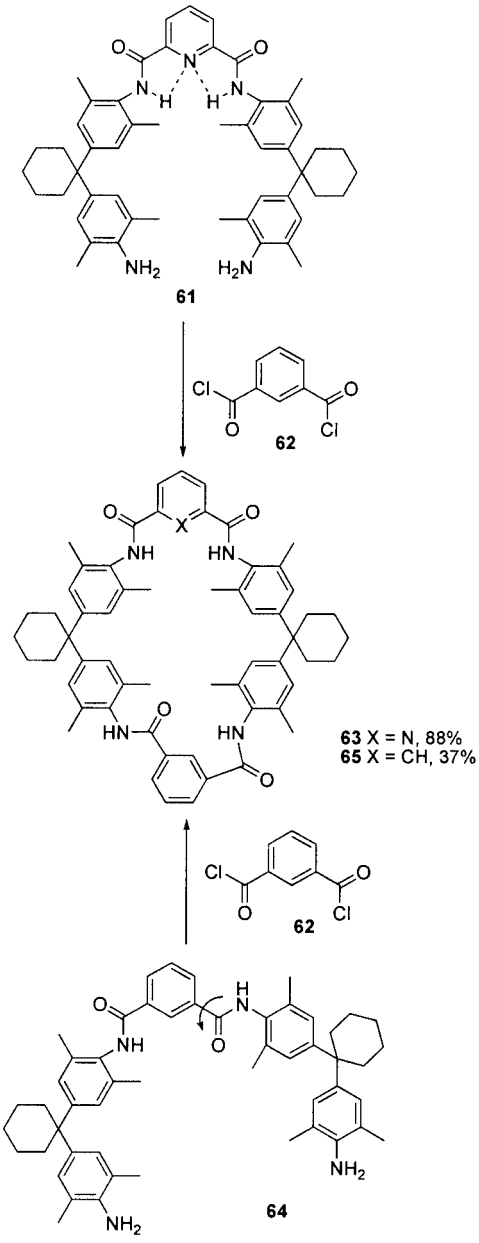
Scheme 15.

and the amide protons locks the diamides into the *cis* conformation, thus holding the acid chloride and amine in close proximity for cyclization. In contrast, the diamide units in the isophthaloyl derivative **64** adopt a *trans* conformation in order to minimize the amide–amide interactions. Hence, the diamide must flip into the high energy *cis*-NH conformation before macrocyclization can take place.

Proline[57] and glycine units are often found in sequences associated with the turn of the peptide chain. Therefore, their deliberate incorporation into linear substrates is believed to enhance the yields of macrocyclization reactions.[58] One example was elucidated by Liskamp et al. who investigated the effects of a proline residue within a polypeptide chain on macrocyclization by olefin metathesis.[59] Small cycles containing a proline residue were formed with higher yields than those with a valine residue at the same place, indicating the *cis* effect of proline.

Backbone *N*-alkylation has been reported as another means to lower the energy difference between the amide *cis*/*trans* isomers, thus facilitating cyclization.[60] Furthermore, as indicated before, the incorporation of D-amino acids into a peptide backbone has been recognized to generally facilitate head-to-tail cyclization reactions.[61]

These examples show that careful examination of a desired target molecule or its precursors for possible pre-organizing elements is a worthwhile exercise to ensure the cyclization step occurs. Using the intrinsic hydrogen-bonding pattern and looking out for D-amino acid subunits and proline residues to determine the ideal macrocyclization site are the most obvious starting points for a retrosynthetic approach. When the conformation of the target molecular structure is known, the incorporation of a key turn unit into the linear precursor is naturally a useful step in the search for a successful cyclization reaction. But even when the conformation of the target molecule is not known exactly or its structure does not allow the use of turn units, macrocyclization reactions may still take place by employing carefully chosen protecting groups, as shown in the following section.



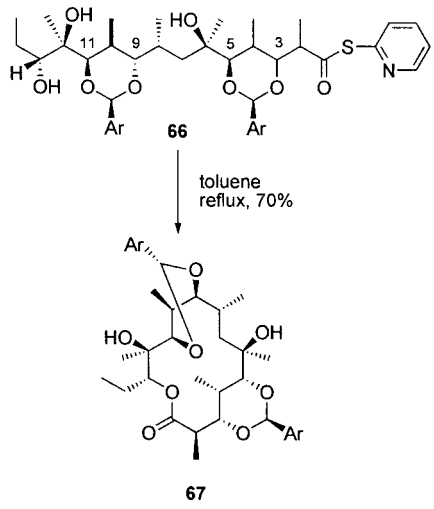
Scheme 16.

3.6 Protecting-Group Tuning

The importance of employing the "right" protecting groups in a molecule for an attempted transformation is evident, not just in total synthesis. Numerous examples of tedious searches for "the" protecting group can be extracted from the literature. In this section we will highlight some examples for which there is evidence that the protecting group influences the pre-organization thus leading to successful cyclization.

Regardless of the complexity of the attempted macrocyclization reaction, cyclic protecting groups like acetals, carbonates and oxazolidines have been widely used to assist conformational steering and to promote cyclization reactions. In planning the synthesis of a macrocycle it seems worthwhile to consider them as the protecting groups of first choice, as the following examples show.

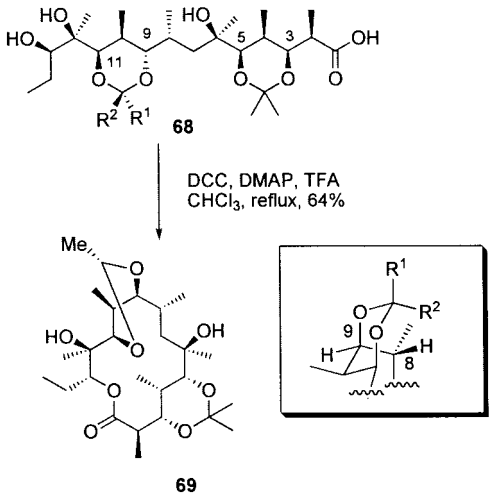
In the total synthesis of erythromycin, Woodward et al.[62] demonstrated that to achieve efficient macrolactonization, the 1,3-diols at C-3/C-5 and C-9/C-11 of the seco-acid must be protected as cyclic acetals (Scheme 17). Substrates with other protecting groups either failed to cyclize or produced much lower yields of the macrolactone. Equally important for macrocyclization is the stereochemistry at C-9. Although in this case its chirality will be destroyed upon oxidation at the end of the synthesis it is imperative that it has the *S* configuration in order to allow the cyclization to take place.



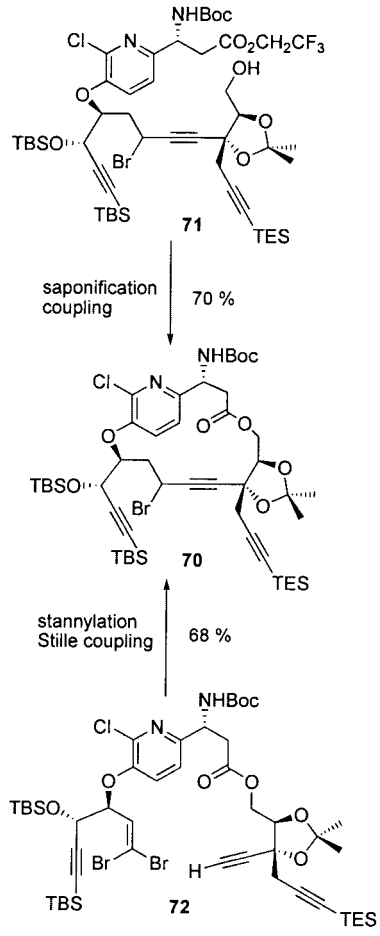
Scheme 17.

In a more detailed conformational analysis, Stork and Rychnovsky[63] revealed the nature of the 1,3-diaxial interaction in the substrate backbone. Conformational analysis of the fragment in solution revealed the close proximity of R^2 to the methyl group on C-8, which results in a strong *syn*-pentane interaction making this conformation,[64] and consequently the macrolactonization process, highly unfavorable (Scheme 18). In accord with this analysis, it was found that the C-9/C-11 acetonide (R^1 = R^2 = Me) and the related acetal (with R^1 = H, R^2 = Me) failed to cyclize under comparable conditions. On the other hand, compound **68** (R^1 = Me, R^2 = H) cyclizes efficiently under Keck's conditions to provide the macrolactone **69** in 64% yield. The same conclusion was drawn by Yonemitsu,[65] Paterson[66] and Evans[67] and their co-workers in their independent total synthesis of 6-deoxyerythronolide B and oleanfolide.

Myers et al. reported another very interesting example of protecting-group-directed macrocyclization.[68] The acetonide protecting group proved to be crucial for two substantially different approaches to macrocycle **70** (Scheme 19). Both reactions, macrolactonization of **71** and palladium-mediated Stille coupling of **72**, were found to be slower and lower yielding when noncyclic protecting groups were used.

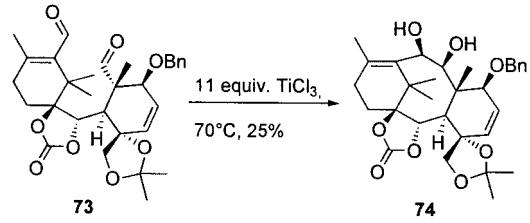


Scheme 18.



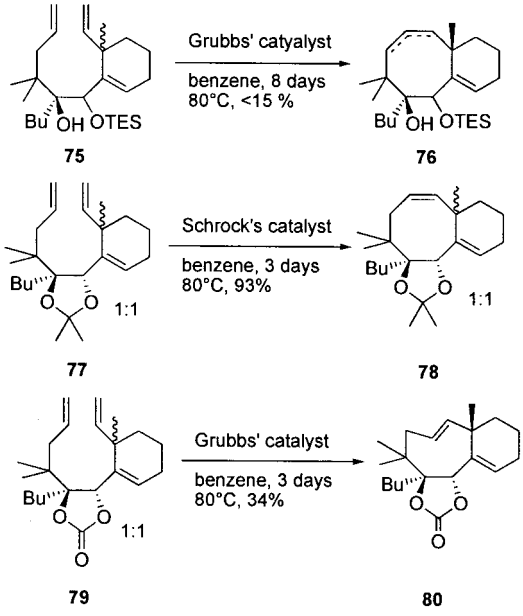
Scheme 19.

The importance of cyclic protecting groups in guiding the desired cyclization reaction has also been demonstrated in Nicolaou and co-worker's total synthesis of taxol.[69] The cyclization of dialdehyde **73** under McMurry conditions provided exclusively the desired 6-8-6 ring-fused taxol skeleton **74** while all other substrates failed to cyclize (Scheme 20). Computational studies suggested that the introduction of both the cyclic carbonate and the acetal protecting group into the backbone was essential to pre-organize the substrate into a productive conformation with the two aldehydes sufficiently close to each other.



Scheme 20.

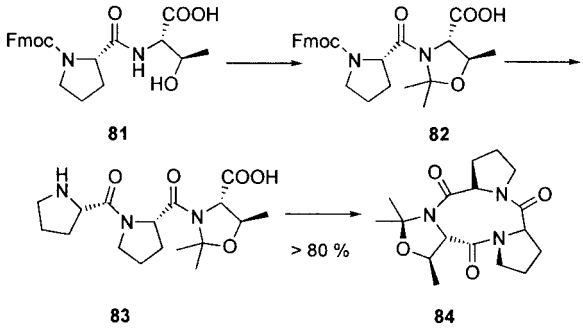
A similar protecting-group directing effect has been observed by Prunet et al.[70] in ring-closing metathesis. Exposure of **75** to Grubbs' catalyst gave the eight-membered ring **76** only in a low yield and after a prolonged reaction time. However, after protection of the diol as an acetonide RCM of compound **77** with Schrock's catalyst provided the corresponding cyclic product **78** in 93% yield. Interestingly, under the action of Grubbs' catalyst, the carbonate derivative **79** provided exclusively *trans*-cyclooctene **80** in 34% yield. Only one diastereomer reacted under these conditions (Scheme 21).



Scheme 21.

The formation of highly substituted cycloheptanes and -octanes from enantiomerically pure sugar derivatives by RCM has attracted some attention and remarkable results have been obtained, again by employing cyclic ethers or carbamates as the principal protecting groups.[71] Note that ring-closing metathesis has become a very prominent tool for cyclization reactions in general and numerous reviews have been published, with one even focused on the formation of macrocyclic natural products.[72]

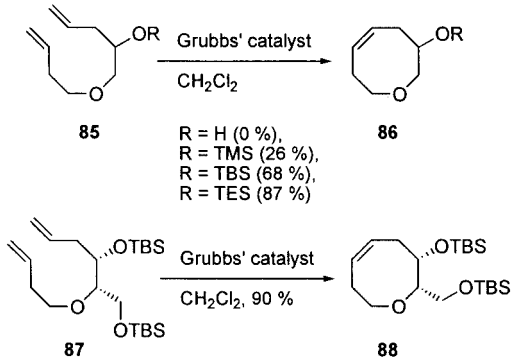
The importance of the *cis*-amide conformation as a turn unit in polypeptides has already been stressed (vide supra). In this context, the finding that polyprolines adopt helical structures depending on whether they have an all-*cis* or an all-*trans* configuration, has been cleverly used.[73] Based on these facts, Mutter and co-workers have developed a strategy in which pseudo-prolines are used as protecting groups with a directing effect in peptide synthesis. Namely, serine, threonine and cysteine can form oxazolidines or thiazolidines with aldehydes or ketones and thus act as pre-organizing pseudo-prolines.[74] Indeed, the oxazolidine of **81** effectively stabilized the *cis*-amide conformation in **83** and excellent yields for the subsequent cyclization reaction were obtained, even at high substrate concentrations (Scheme 22).[75]



Scheme 22.

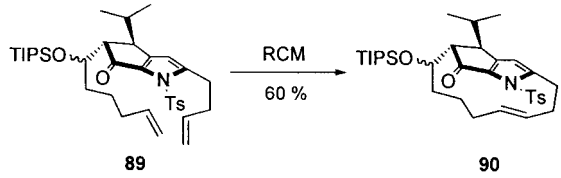
Sure enough, cyclic protecting groups are not the only means to promote pre-organization. Changing the actual conformation of a molecule by modifying its steric interactions is another well-reported method to achieve productive cyclization. Conformational steering by increasing (or decreasing) the size of a protecting group has been documented for both cyclic and acyclic protecting groups. Steric effects are most frequently perceived as a synthetic nuisance, especially when a particular transformation of a given functional group was sought. However, when exploited properly the modification of steric effects by the introduction of substituents, for example, presents an extremely simple way of modulating the conformational properties of a substrate and thus enhancing an otherwise difficult reaction (steric-promoted transformation).[76]

In particular, there are numerous examples of the transformation of hydroxy functions into their large silyl ether homologues. Once again for a RCM reaction, the protection of an alcohol with a bulky silyl group was found to be the key to obtaining eight-membered rings. While the unprotected alcohol did not give any cyclized product, the functionalized eight-membered ring was isolated in 26% yield from the trimethylsilyl-protected alcohol, notably without the introduction of a cyclic backbone (vide infra) (Scheme 23). Successive enlargement of the protecting group up to the large triethylsilyl ether led to successively higher yields of the cyclic product.[77] Furthermore, a remarkable yield for the formation of the eight-membered cycle **88** was obtained with two TBS substituents on its precursor **87**.



Scheme 23.

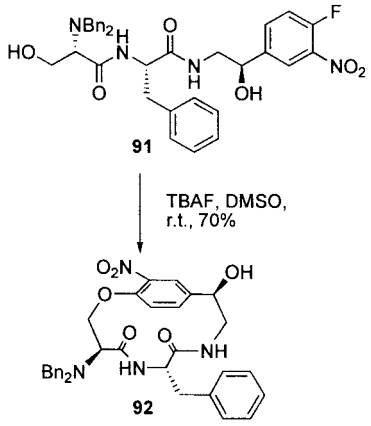
The bulky triisopropylsilyl ether group (TIPSO) was found to be crucial for successful RCM to form the 13-membered ring system of roseophilin (Scheme 24).[78] The steric interactions of the isopropyl group and the TIPS ether in precursor **89** forcing the hexenyl side-chain into the proximity of the butenyl moiety, proved to be the key to the 60% yield of the RCM reaction. Less substituted derivatives failed to give the desired macrocycle and it was deduced that the side-chains were too far apart for the reaction to occur.



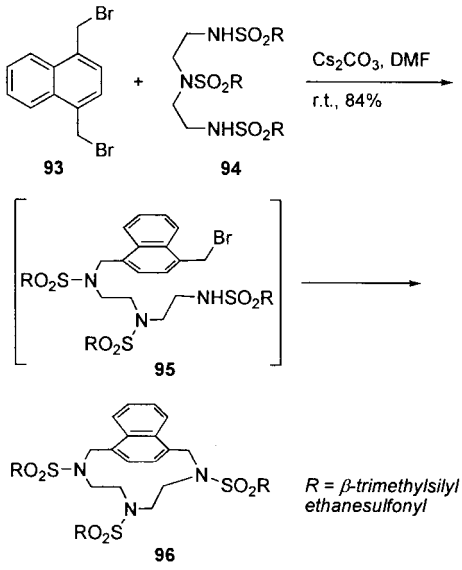
Scheme 24.

In the synthesis of sanjoinine G1, the S_NAr-based cyclization reaction was found to be dependant on the substitution of the terminal amino function.[79] Attempts to obtain the aryl ether failed with a Boc protecting group on the nitrogen, whereas the free amine itself acted as a nucleophile leading to a 13-membered aza-cyclic system. However, the *N*,*N*-dibenzylated substrate readily cyclized to give the aryl ether in good yields (Scheme 25). Molecular modeling of the substrate **91** revealed a close proximity of the reacting sites (4.7 Å), possibly induced by the presence of the two bulky benzyl substituents on the amine. With a Boc-protecting group it has been shown that an elimination process leading to a dehydroamino acid derivative is an important side-reaction.[80]

The Richman–Atkins cyclization reaction is an extremely powerful tool for the synthesis of polyazamacrocycles.[81] The cyclization is generally carried out by the reaction of a bis-sulfonamide salt with a bis-electrophile in a polar solvent. Even for the cyclization to strained cyclophanes conditions of high dilution are generally not required (Scheme 26). It has been proposed that the bulky nature of the sulfonyl group contributes to the pre-organization of the substrate into a folded conformer that is conducive to macrocyclization.[82]



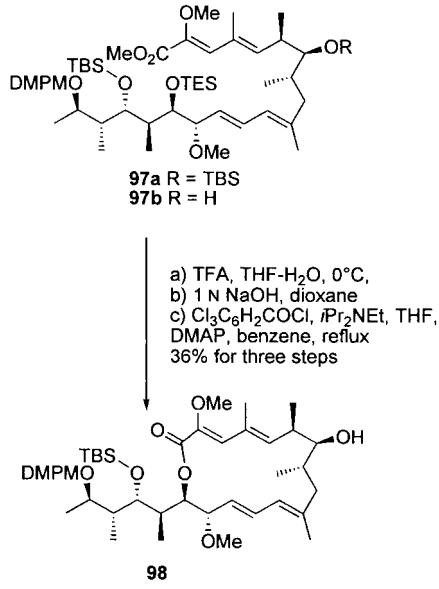
Scheme 25.



Scheme 26.

The importance of size has been highlighted with the series of *O*- and *N*-protecting groups. However, increasing the size is not always the way to promote cyclization reactions. In Roush and co-workers' total synthesis of bafilomycin A_1, attempts to effect a macrolactonization reaction failed when a remote hydroxy group at C-7 in precursor **97a** was protected as the TBS ether (Scheme 27).[83] Examination of the X-ray structure of this compound suggested that an unfavorable interaction of the large silyl group in the axial position might prevent the molecule from obtaining the necessary conformation for cyclization. Indeed with a free hydroxy group at C-7, **97b** is transformed into macrolide **98** after selective TES removal, saponification and macrolactonization in 36% overall yield.

There are surely other examples in the literature of protecting-group-induced pre-organization. However, the general principles seem to appear repeatedly: the use of cyclic protecting groups, if possible, and systematic examination of the steric interactions caused by the introduction of protecting groups in order to obtain substrates with the desired transformation. Molecules containing serine or other similar building blocks, the pseudo-proline approach, is surely worth consideration.



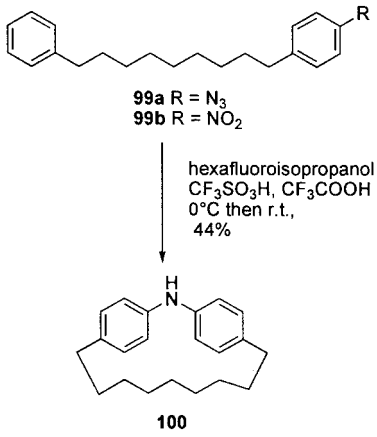
Scheme 27.

3.7 π Interactions

While hydrogen-bonding interactions and the subtle interplay of protecting groups are commonly recognized means of influencing the outcome of reactions, π interactions are less popular with the general organic chemist in terms of day-to-day applications. However, the power of π interactions to organize molecular systems and to selectively steer reactions has been recognized.[84] Even though terms like π-stacking and electron–donor–acceptor interactions are quite frequently used to explain experimental results, the qualitative interpretation and/or the prediction of their directionality is far from simple. In particular, face-to-face interactions of unsaturated systems seem to have been occasionally overestimated.[85,86] Hunter and Sanders have elaborated a set of rules concerning the geometry of π–π interactions, pointing out that mainly π–σ attractions are effective and assuming that maximum π–π overlap is a misleading concept.[87]

There are numerous precedents in the literature for the through-space alignment of two π systems. In particular, in supramolecular chemistry and in the area of foldamers, numerous systems have been elaborated and their π–π interactions studied extensively.[88] Abramovitch and co-workers reported an access to strained macrocycles by way of an intramolecular electrophilic aromatic amination via an arylnitrenium ion intermediate (Scheme 28).[89] Based on molecular modeling, NOE and UV/Vis spectroscopic studies of the nitro derivative **99b** as a model, Abramovitch and coworkers concluded that the arylnitrenium intermediate was pre-organized into a folded conformer that facilitates the otherwise difficult macrocyclization reaction. He suggested an intramolecular attractive interaction between electron-

rich and electron-poor aromatics (a charge-transfer complex in this case) as being responsible for such conformational pre-organization.

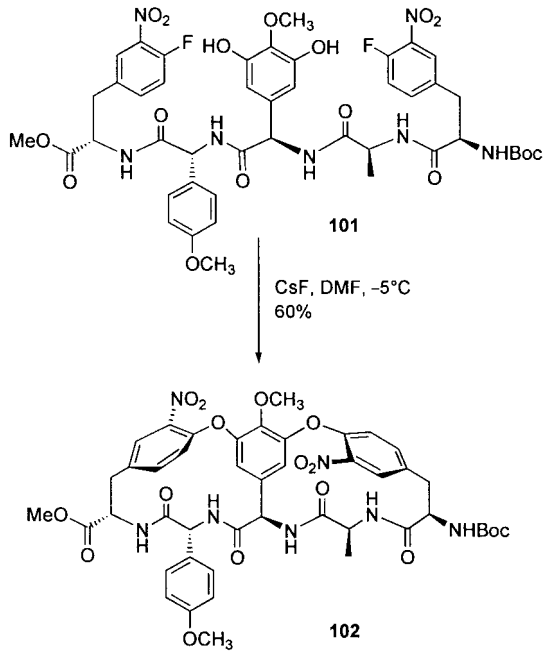


Scheme 28.

The intramolecular nucleophilic aromatic substitution reaction (S_NAr) developed in this laboratory has been widely recognized as a powerful macrocyclization method for the synthesis of biologically active macrocycles with *endo* aryl ether bonds (Scheme 29).[90] In general, high yields, short reaction times and mild reaction conditions are characteristics of this cyclization reaction in undiluted reaction media. As a matter of course, these extraordinary features raise the question as to the origin of this efficiency. Once more, the source can be found in the pre-organization of the linear precursor. Indeed, molecular modeling of the linear compound **101** revealed the folded conformer to be its lowest-energy conformation. At first glance and in view of the peptidic nature of compound **101**, intramolecular hydrogen bonding and/or π–π interactions, among others, could plausibly assist in the conformational pre-organization of the linear precursor. However, in this case the conformational pre-organization of the linear precursor cannot be attributed precisely to any one of these factors.

However, the synthesis of sanjoinine G1 (Scheme 25, vide infra) offered the possibility of further elucidating this point, the phenol moiety in this molecule having been replaced by a simple secondary alcohol. Therefore, the outcome of the S_NAr reaction should reveal whether the interaction of two π systems is crucial for the pre-organization of the substrate or whether the folding might rather be induced by σ–π or hydrogen-bonding forces. Indeed, at normal concentrations cycloetherification via the formation of an *endo* aryl alkyl ether bond (**91** to **92**) proceeded as efficiently as the formation of the aryl aryl ether bond (**101** to **102**)[91] strongly indicating that the presence of two aromatic systems with different electronic properties, the π–π interaction, is not obligatory for conformational pre-organization in the S_NAr reaction.

The relative importance of the possible intramolecular hydrogen bonds remains to be evaluated. In connection with the total synthesis of acerogenine-type natural products the cyclo-etherification reaction of **103** was investi-

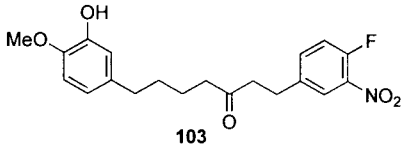


Scheme 29.

gated. This compound lacks a peptide backbone and the two aromatic termini are tethered by a simple hydrocarbon chain.[92] As shown in Scheme 30, the 15-membered *meta-para*-cyclophane can be obtained in high yield even at high concentrations (c = 1 M). In order to exclude the influence of the sp^2-hybridized carbon atom on the conformation, the carbonyl function was removed from **103**. Nevertheless, the excellent yield of the desired cyclophane from the S_NAr reaction was maintained, therefore ruling out hydrogen bonds as the main cause of the pre-folded conformation. Further evidence for the pre-organization of compound **103** was accumulated by the following control experiments. By treating equimolar amounts of **103** and the external nucleophile 4-methoxyphenol with CsF at room temperature, cyclophane **104** was exclusively obtained at the expense of possible cross-coupling products. Similarly, the presence of external nucleophile 4-fluoro-3-nitrotoluene in the reaction mixture did not interfere with the outcome of the intramolecular S_NAr reaction. Molecular modeling as well as spectroscopic studies (NOE experiments) indicated that the bent conformation was indeed the lowest-energy conformer of the linear diarylheptanoid **103**.[93]

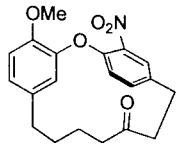
The example shown in Scheme 31 proves further that neither π–π interactions nor backbone hydrogen bonding are required for a successful intramolecular S_NAr reaction and hence nor for the pre-organization of the S_NAr substrate.[94]

These results indicate that the anion–π interaction between electron-deficient fluoro-nitro-arene on the one terminal and a phenoxide (alkoxide, amine) on the other might be responsible for the pre-organization of the S_NAr substrates. While the cation–π interaction is a well-established phenomenon in both biology and chemistry,[95]the anion–π interaction has only recently been the subject of intensive studies and the evidence accumulated argues well for its real



103

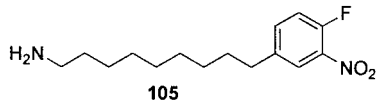
CsF, DMF, r.t.,



104

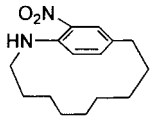
concentration	isolated yield
0.01 M	90–95%
0.05 M	90–95%
0.1 M	75–80%
1 M	45–50%

Scheme 30.



105

K_2CO_3, DMF,
0.01 M, 80%



106

Scheme 31.

existence.[96] However, since the S_NAr reaction has often been performed in polar solvents such as DMF and DMSO, hydrophobic (solvophobic) interactions might also contribute to a certain extent to the folding of the S_NAr substrates.[97]

The above examples demonstrate that the intramolecular S_NAr reaction is a quite general method for the synthesis of macrocycles with an *endo* aryl ether bond.

4 Conclusions and Outlook

Conformational analysis of the targeted structure and pre-organization of the linear precursor are the two key factors that lead to successful macrocyclization reactions. Conformational analysis, pioneered by Sir Derek H. R. Barton, has played a major role in the development of modern organic chemistry. Whenever an unconventional transformation or an unexpected reactivity of a given functional group is observed, chemists tend to turn to conformational analysis and very often, satisfactory explanations can be gained from such an exercise.[98] Furthermore, by deliberately restricting the available conformations of a reaction substrate, specific reactions, including chemo-, regio- and enantioselective transformations, can occur that would otherwise not proceed.[99]

The importance of conformational pre-organization in successful macrocyclization reactions has been recognized ever since Eschenmoser's synthesis of vitamin B12[100] and Woodward's synthesis of erythromycin.[62] However, examples of successful macrocyclization reactions driven by conformational design are, to the best of our knowledge, still rare. This is somehow surprising considering the great success of molecular design in supramolecular chemistry[101] and in the development of chiral selectors[102] in which the same type of weak forces such as noncovalent bonds, π interactions (including cation–π and anion–π), hydrophobic interactions and steric effects are to be considered.

By assembling the present examples we hope to stimulate the use of the pre-organization concept in general synthetic chemistry. Different approaches to productive pre-organization are possible and depend mainly on the degree of freedom in the choice of the structural elements. The pre-organization tool-box contains special reagents and choices of protecting group, proper disconnection and the most successful chemical cyclization methods. In cases in which it is not imperative that the molecular framework has a fixed structure, matching building blocks can be used to assemble a macrocycle. Whenever the molecular architecture leaves no freedom of choice, as in the synthesis of natural products, more subtle methodology has to be employed. In these difficult cases, the choice of the chemical reaction, the protecting group or the introduction of weak interactions can mainly be used to facilitate ring closure.

Careful conformational analysis and strategic pre-organization of linear precursors can be used to overcome the pitfalls often encountered in cyclization reactions. The ongoing accumulation of experimental evidence and the refinement of theoretical interpretations will surely help to further develop conformation-assisted macrocyclization reactions. These types of predesigned reactions may be particularly fruitful in the field of diversity-oriented synthesis.[103]

Acknowledgments

We thank the CNRS for financial support. A post-doctoral fellowship from the Suisse National Science Foundation to J. B. is gratefully acknowledged.

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Received: October 20, 2004
Published Online: April 14, 2005

