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Asymmetric synthesis of chiral macrocyclic ligands

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Abstract: Chirality is a fundamental property of biological molecules, and the recognition phenomena associated with these compounds. In order to better understand the energetics and dynamics of such recognition processes at atomic resolution, one needs to be able to separate the electrostatic and dipolar interactions from the stereoelectronic contributions. In this lecture, I shall discuss some of the different strategies adopted for the design and synthesis of chiral ligands for the study of complexation phenomena. The design of highly functionalised ligands capable of multi-point recognition is also presented along with the synthetic route adopted.

INTRODUCTION

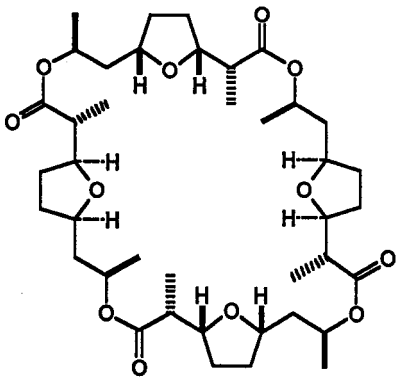
Chirality is a fundamental property of biological molecules and the recognition phenomena associated with these compounds. In order to better understand the energetics and dynamics of such recognition processes at atomic resolution, one needs to be able to separate the various three-dimensional contributions from each other (*i.e.* electrostatic, dipolar and stereoelectronic contributions). This can be achieved either by studying the naturally occurring chiral entities participating in recognition processes, or by careful design of mimics of natural compounds. The latter approach is the intellectually more rewarding and challenging one; at least in principle it allows the possibility of designing selective model systems which can be used to separate the different contributions. Experiments and test compounds can be designed in such a manner that one can ask, and expect to get answers, detailed questions on the energetic contributions of various structural changes using the well established methods of, say, calorimetry. One can take a snapshot of the interacting species by X-ray crystallography and study the structural parameters directly. With modern high-resolution and high-field NMR methods, one can not only study the static but also the dynamic aspects of the binding event. However, one should bear in mind that since the energy contributions of the individual structural changes are often very small, great care must be exercised in designing the experiments and the probe molecules.

In this lecture, I shall first discuss some of the different strategies adopted for the design of chiral ligands for the study of recognition phenomena, starting from models provided by nature, and then moving on to man-designed chiral structures. I shall then discuss the strategies of asymmetric synthesis in general, especially as related to target design (as opposed to synthesis design). The strategic approaches will be exemplified by a few case studies involving the design and synthesis of small-molecule probes for both direct recognition studies and receptor recognition.

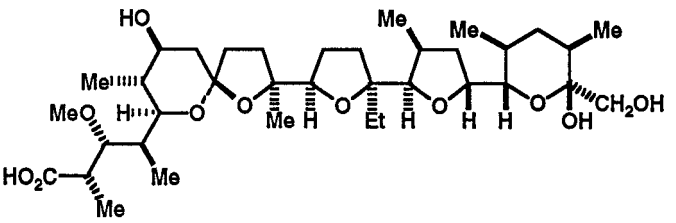
1. NATURAL COMPOUNDS

Nature uses various structural types for binding metal cations and small molecules in a chiral environment. Cyclopeptides provide a well known example of natural chiral ligands capable of binding various mono- and divalent metal atoms. A steadily growing number of relatively small size peptides and cyclopeptides are emerging, which are capable of three dimensional, *i.e.* chiral, recognition. These structures include the glycopeptide antibiotics (e.g. valinomycin) which inhibit bacterial cell wall synthesis often targeting a very short peptide sequence.[1] Similar principles guide the recognition by the immunophilin proteins of the immunosuppressant cyclosporin A, which is another compound whose binding mode to the receptor has been studied recently, using crystallographic, NMR and molecular modeling methods.[2]

Polyether antibiotics, also known as the ionophore antibiotics, are capable of selectively binding alkali metal cations. Their selectivity arises from the size differences of the cavities lined with the oxygen atoms. The oxygen atoms themselves are held rigidly in their spatial positions because of the structural constraints in the molecules. Nonactin is a cyclic macrolide antibiotic, whereas monensin belongs to the broad group of acyclic polyether antibiotics.

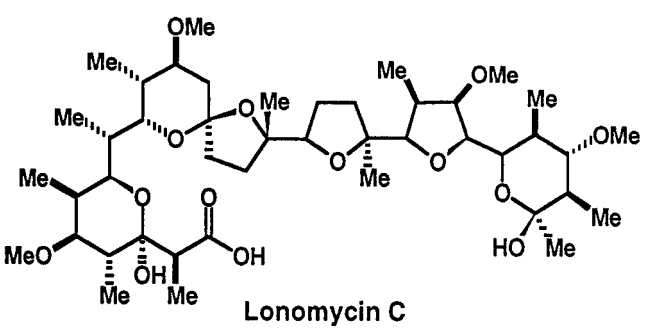


Nonactin

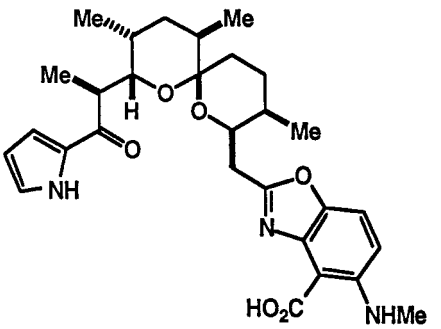


Monensin

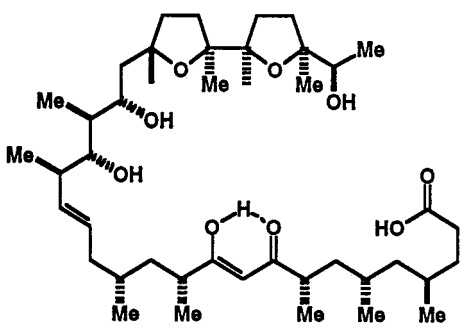
The number of known polyether antibiotics is large and steadily growing, and their physiological activities cover a wide spectrum of biochemically and clinically important areas. All of the ionophore antibiotics bind metal cations in their physiological environment, and the structures of some of these complexes have been elucidated using standard methods.



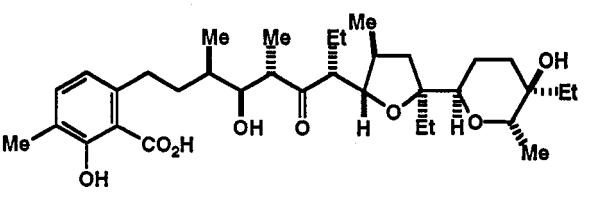
Lonomycin C



Calcimycin (A-23187)



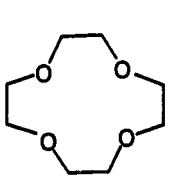
Ionomycin



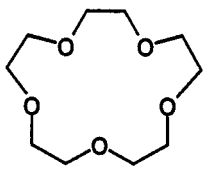
Lasalocid A

2. SYNTHETIC ANALOGUES

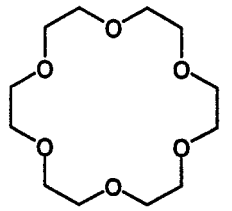
Natural products have been an inspiration in the design of most man-made molecules, and it is no surprise that the synthetic ligands designed for various purposes also find their precedents in Nature. Crown ethers can be viewed as simple models of polyether antibiotics. Again, we know a great deal about the cation binding specificities, energetics of complex formation and structural features of these compounds and their analogues. The selectivity follows the size complementarity between the cavity size and the ionic radius of the cation in question.



12-Crown-4

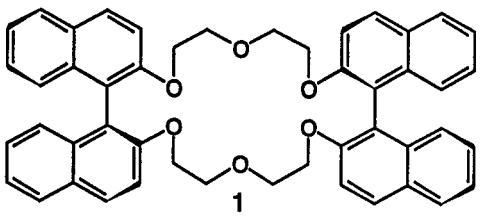


15-crown-5

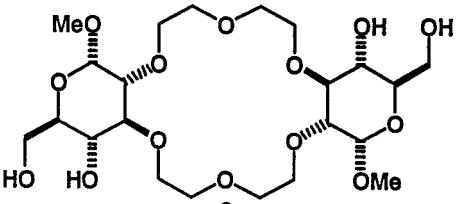


18-crown-6

Crown ethers have been used as the starting point for the consideration of chiral hosts for various practical purposes. In principle a chiral crown ether could be used to extract one enantiomer of a suitable co-ordinating compound from a racemic mixture. Several chiral crown ethers have been synthesized and tested for this purpose, most notably by Cram and his group, but the final goal has remained somewhat elusive. One of the earliest well characterised crown ethers **1** was that derived from binaphthol, which itself has gained an important role as a chirality mediator in a number of asymmetric catalytic processes.[3] The carbohydrate based crown ether analogues **2**, developed most notably by Stoddard, were designed to mimic the functions of natural chiral receptors.[4] Both of these compound types have found commercial applications in e.g. the development of chiral columns, which are currently commercially available.

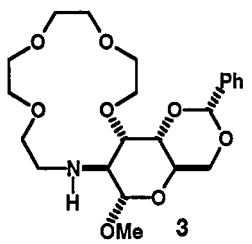


1



2

Crown ethers provide the binding mode only through the participation of the lone pairs on the ether oxygens, in other words as hydrogen bond acceptors. Replacement of one or more of the oxygens by nitrogen gives rise to azacrown ethers (ACE), or cryptands, which can participate in binding also as hydrogen bond donors as well as through Coulombic interactions. Azacrown ethers **3**[5] and diazacrowns **4** with the chirality originating from carbohydrates,[6] as well as more symmetrical compounds **5** derived from tartaric acid[7] have been studied. The tricyclic functionalized **6** crown ethers designed by Lehn have given important structural insight into the binding of these compounds with ammonium ions.[8]



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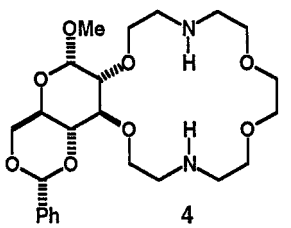

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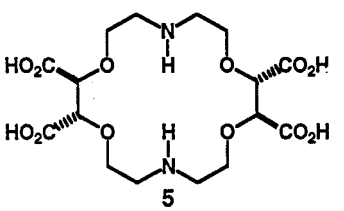

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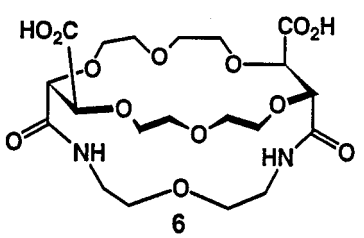

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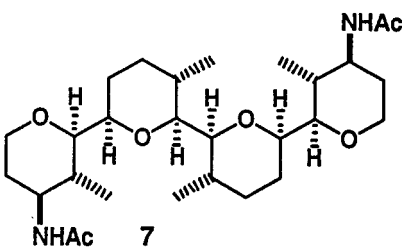


7

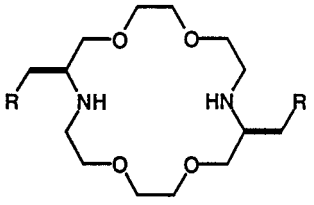
In the above examples, the shape of the binding cavity is fixed through the network of covalent bonds in the molecule. Recently Still has developed a series of tetrahydropyran derived podands (*e.g.* **7**) capable of highly stereoselective binding with a number of chiral amines, including amino acids and their esters.[9] The conformation of the podand is held rigid by careful adjustment of the stereochemistry in the podand tetrahydropyran ring: the methyl groups tend to direct the conformational equilibrium

towards one predominantly favored conformation of not only the rings but also the inter-ring linkages, leading to a strongly biased molecular topology.

3. NOVEL SYNTHETIC ANALOGUES

In connection with a major programme we have recently initiated on developing the chemistry of γ-chiral β-keto phosphonates, we had the opportunity to apply this chemistry to the design and synthesis of novel diazacrown ethers which can be equipped with varied functionality. This is of interest to us also because the functional compounds can be so designed that the spatial positioning of the interacting groups can be fine tuned, and therefore used to give insight on the energetic effects of relatively small structural changes in the host molecule.

The diazacrown derivatives **8-10** can be derived from β-amino alcohols, which themselves are accessible from amino acids. Compounds **8**, upon consideration of conformational effects using molecular dynamics simulations, prove to be structurally too much biased towards a conformation with the side chains pointing away from the binding cavity. Although this problem can be relieved to some extent by incorporation of a further substituent at the 'angular' carbon, as in **9**, the conformational space sampled by the side chains is still not favorable. As a conclusion, we have arrived at the Lehn type tricyclic structures **10**. These compounds allow a careful adjustment of the geometric features through a number of structural modifications. The linking bis-amide bridge plays a crucial role in the overall shape of the molecule. Extending of shortening of the link will lead to different 'sizes' of the cavity, as well as differently oriented lone pairs capable of hydrogen bonding. As a consequence of the variation of the shape and size of the diazacrown core, the relative spatial positioning of the R groups varies also. This phenomenon, coupled with the possibility of introducing spacer atoms, heteroatoms (with varying bond lengths, angles and other geometric features) and taking advantage of the conformational effects of changes in hybridization, gives access to a broad family of probe molecules with finely tuned structural variations.



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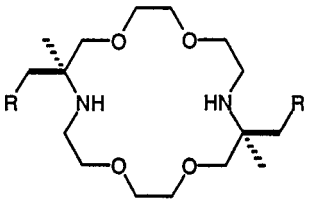

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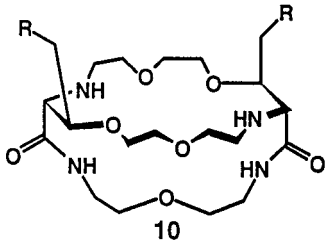
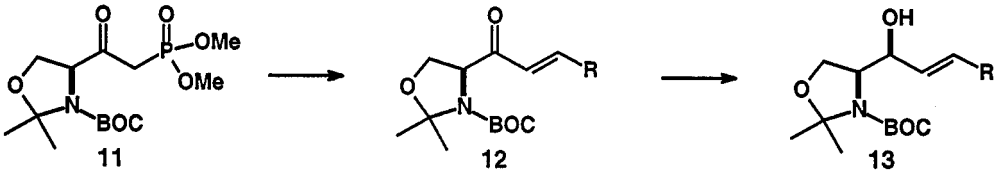


10

The appendage R in compounds **8-10** allows the introduction of various groups which can participate in the recognition process by ionic, hydrogen bonding or van der Waals effects. The synthesis of the β-hydroxy-α-amino acids needed for the construction of compounds **10** follows a route developed in our laboratory starting from naturally occurring L-serine. Serine is converted in high yield in four steps to the phosphonate **11**.[10] Reaction of the phosphonate with a number of aldehydes initially proved to be problematic. We were prompted to develop a new variation of the Wittig-Horner type olefination in order to achieve a practical reliable access to the α'-chiral enones **12**. Creation of the secondary alcohol center with high levels of asymmetric induction from the existing stereogenic center has also been achieved with satisfactory results in one diastereomeric series to give the allyl alcohols **13**.[11]



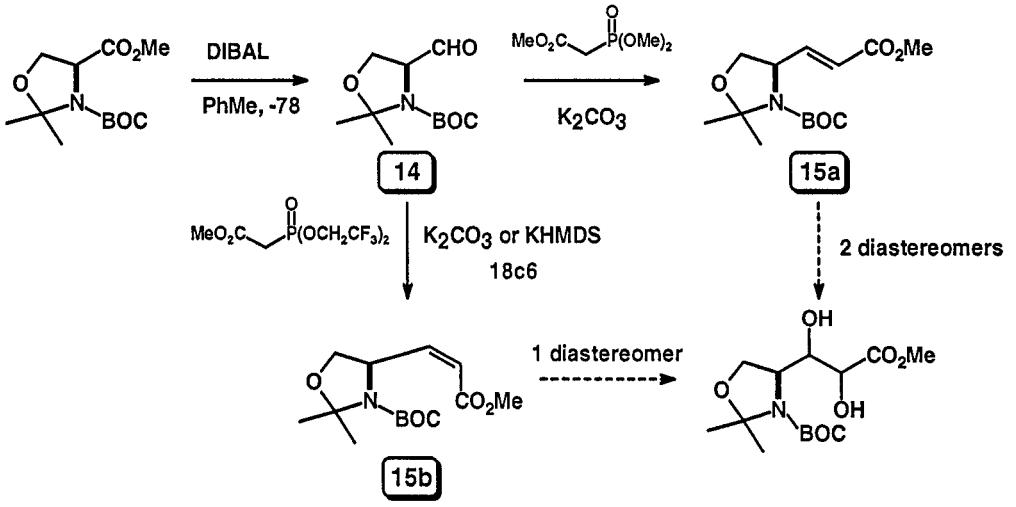
11 12 13

The stereoselective formation of the secondary alcohol chiral center proved to be somewhat problematic, especially in trying to achieve an efficient entry to one diastereomeric series (**13'**). Upon closer inspection, utilizing molecular modeling (MarcoModel v. 3.5X),[12] we found that the lowest energy conformer of the starting compound **12** is accompanied by several other conformers falling within 12 kJ/mol. Most notably the four clusters of lowest energy conformers (0, 0.5, 2.1 and 3.3 kJ/mol, respectively) exhibit some noteworthy properties as far as stereoselectivity is concerned. The

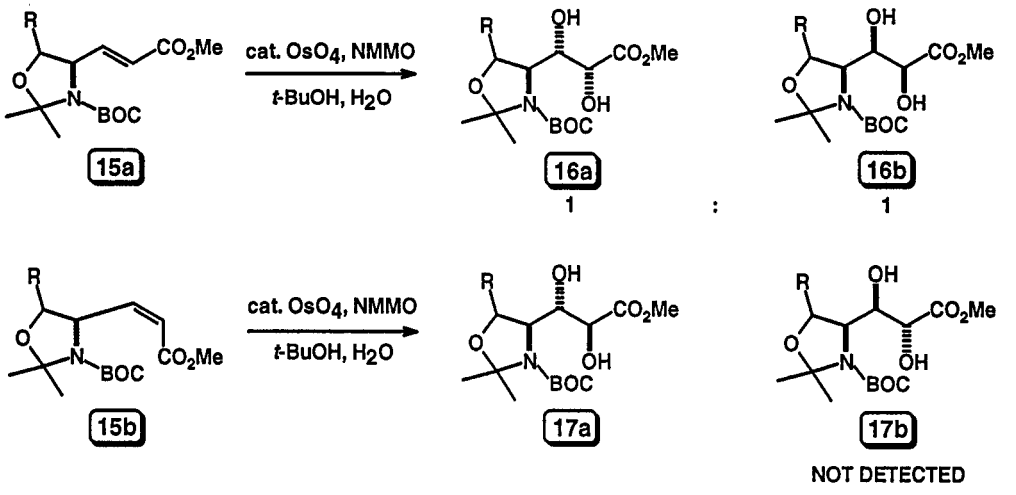
BOC group adopts two distinct conformations, with the O*t*Bu grouping either *syn* or *anti* to the acyl side chain. The second, and even more important, conclusion is that the acyl side chain occupies the conformation predicted by the established Felkin-Anh generalizations in the lowest energy conformation, but rotation of the side chain by approximately 60 ° gives rise to only about 0.5 kJ/mol in energy. The consequence is diminished diastereomeric induction in the hydride reduction.

The macrocycle synthesis from **13** is straightforward: protection of the secondary alcohol group followed by liberation of the ketal and coupling with the linker chloroethoxyethyl unit is followed by standard operations to give the desired compounds **10**.

Incorporation of further functionalities in the R groups can be also be achieved. As our next generation compounds, we have elected the tricyclic compounds bearing a further hydroxyl group at the γ-position of the original amino alcohol. These compounds can be readily prepared using the route we have developed for the synthesis of some potential glycosidase inhibitors.[13] The serine derived amino aldehyde **14** is coupled (in a Wittig-Horner sense) with a phosphonate to give either the *E* or *Z* enoate **15a/b**.



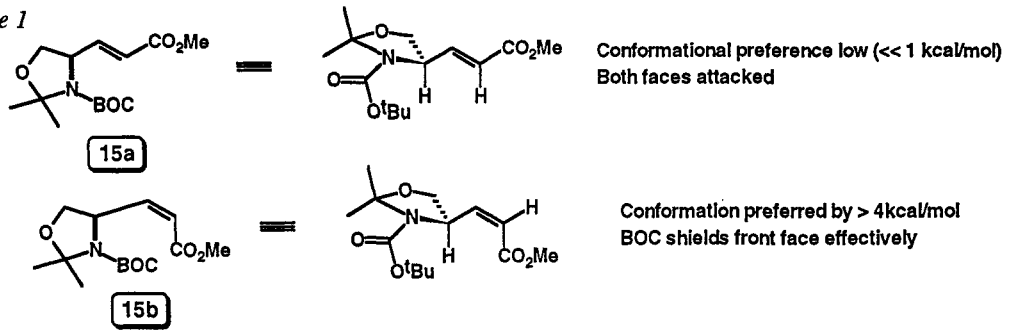
cis-Hydroxylation of the thus formed enoates gives rise to the diols, in varying diastereomeric ratios. The *E*-enoate **15a** is oxidized to an approximately 1:1 mixture of the two diastereomers **16a/b** of the diols, whereas the *Z*-enoate **15b** undergoes dihydroxylation to give practically a single diastereomer **17a**.



The reasons for this rather remarkable conformational bias might be explained by considerations not unlike those developed for the above enone reduction, involving the utilization of the concept of allylic strain *(see Scheme 1)*. In the *trans* enoate **15a**, the conformational bias is very low indeed (estimated to be *ca.* 1 kJ/mol), whereas in the *cis* enoate **15b** the the lowest energy ground state

conformation is at least 10 kJ/mol more stable than the ones leading to the antipodal stereogenicity. However, conclusive studies including careful modeling experiments remain to be performed.

Scheme 1



The tricyclic diazacrown ethers synthesized by the routes described are hoped to give new insight into the structural requirements of various aspects of binding, or host-guest interaction. We realize that the models **10** are still conformationally not optimal; the side chains still retain too much conformational mobility, and the lowest energy conformations still contain the undesired effect of placing the R groups pointing too much away from the binding cavity. It is this latter reason which has prompted us to look at the more highly functionalized compounds derived *via* dihydroxylation. This will allow further bridging of the bicyclic system to adopt a more rigid conformation and the possibility of guiding the R groups more directly to the desired site of interactions.

The ultimate goal for many of the research groups working in the field is to be able to use studies such as this one, or those performed by other groups, to derive new important three-dimensional information on the various types of binding interactions prevalent in the living systems, and to utilize this information to develop new ways of attacking the intricate factors of highly stereocontrolled recognition events to aid us in the design of new compounds for medicinal and materials sciences applications. This line of research is only taking the first steps towards unravelling this vast and complex body of information, but one can already foresee major impact on understanding the intricacies of stereoselective binding. This will help us to rationalize enzyme-substrate and receptor-effector binding, and the information can also be used to design *e.g.* more selective catalysts and reporter molecules.

Acknowledgements

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