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REVIEW

Strained cyclophane natural products: Macrocyclization at its limits

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Cyclophane natural products comprise an intriguing class of structurally diverse compounds. As inherent for all cyclic compounds regardless of their origin, macrocyclization is naturally the most decisive step, which defines the overall efficiency of the synthetic pathway. Especially in small cyclophane molecules, this key step constitutes an even greater challenge. Due to the strain imparted by the macrocyclic system, free rotation of the benzene ring(s) is often restricted depending on both the constitution of the tether and the aromatic portions. Not surprisingly, the synthesis of natural cyclophanes with their often outstanding pharmaceutical activities and the inherent issues associated with their preparation has attracted much attention among the synthetic community. In particular, it stimulated the development of new strategies for the ring-closing step, as often otherwise well established and robust reactions fail to perform effectively. In this review, we describe the challenges synthetic chemists are facing during the synthesis of this small, but structurally and biologically fascinating class of natural products, concentrating on the representatives exhibiting configurational stability. The main focus will be on the different concepts for the installation of the macrocyclic system, in most cases the central problem in assembling these extremely rigid molecules.

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1 Introduction

Molecular strain has intrigued organic chemists over the past century and has thus been an inspiration for the development of new chemical reactions as well as for the exploration of novel reactivities and physical properties. Cyclophanes constitute an intriguing class of rigid molecules. These bridged aromatic compounds exhibit extraordinary physical and chemical properties that can be attributed to their unusual molecular architecture and the immense strain caused by their cyclic frameworks. Although the first cyclophane molecule, [2.2]metacyclophane (**1**), was already synthesized at the end of the 19th century,[1] the development of cyclophane chemistry began to flourish after the serendipitous discovery of [2.2]paracyclophane (**2**) by Brown and Farthing in 1949[2] followed by the directed construction of **2** by Cram and Steinberg two years later (Fig. 1a).[3] This latter work truly set the basis for the entry of a new group of aromatic compounds onto the stage of chemistry and helped to evolve them from a chemical curiosity to an attractive and intensively studied branch of modern organic chemistry.[4–8]

Within the last 60 years, the focus of cyclophane chemistry has shifted dramatically. At the beginning, the main emphasis was on exploring the chemical space of this compound class and on

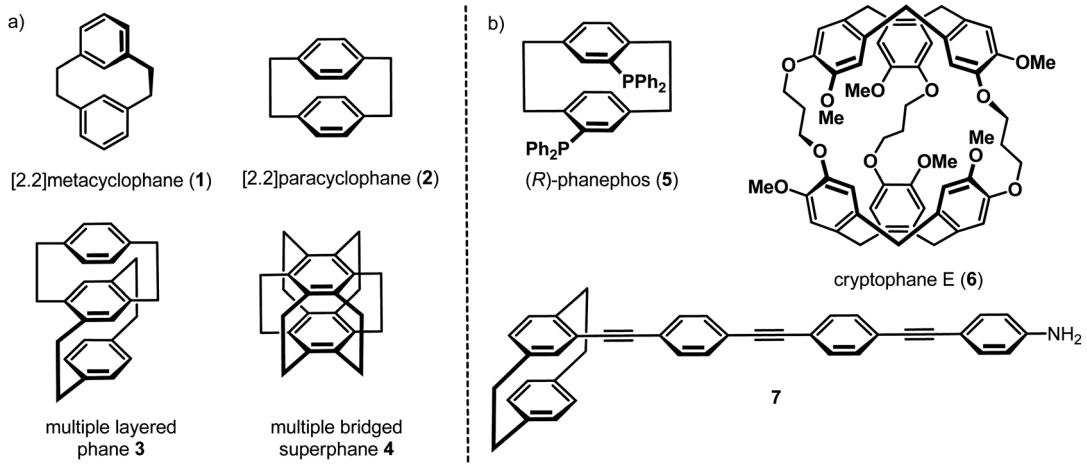


Fig. 1 a) The first cyclophane representatives [2.2]metacyclophane (**1**) and [2.2]paracyclophane (**2**), as well as the more complex multilayered and multibridged representatives **3** and **4**; b) selected examples of cyclophanes applied to asymmetric synthesis,[12–14] supramolecular chemistry,[15,16] or material science.[17]

tackling the synthetic challenge these structures represent. This started a race for the preparation of a series of analogs of **1** and **2** with more and more 'exotic' frameworks showing, *e.g.*, multiple layers (like in **3**)[9] and bridges, as in the superphane **4** (Fig. 1a).[10] With the development of reliable, efficient, and high yielding synthetic methods to cyclophane derivatives over the decades, extensive findings emerged on novel and often surprising structural, spectroscopic, and chemical properties arising from their stiff structure and the often "bent and battered benzene"[11] rings contained in these layered compounds.

Due to their configurational as well as chemical robustness, planar chiral cyclophanes are applied in different fields of stereoselective synthesis.[12–14] In this context they either serve as chiral auxiliaries[14,18] in, *e.g.*, Diels–Alder cycloadditions[19–21] and aldol condensations,[22,23] or as ligands in catalytic systems, such as PHANEPHOS (**5**),[24] which is used in Ru-catalyzed asymmetric hydrogenations (Fig. 1b). The formation of precise cavities by functionalized cyclophanes, such as the cation receptor cryptophane E (**6**), makes them also an interesting supramolecular host for small molecules.[25–29] Furthermore, these carbocyclic substrates can be found in polymer chemistry,[17] *e.g.* in the Gorham process,[30] or as key building blocks in materials science,[17,31,32] such as the [2.2]paracyclophane **7**.[33–37]

Despite intensive studies on artificial cyclophanes, naturally occurring representatives were added to the repertoire of this class of compounds not before 1990 when Moore *et al.*[38,39] reported the isolation of the [7.7]paracyclophanes cylindrocyclophane A (**8**) from the terrestrial blue-green algae *Cylindrospermum licheniforme* Kuetzing (Fig. 2). Due to the unprecedented C_2 symmetric structure along with the high *in vitro* cytotoxicity, **8** and its natural analogs cylindrocyclophanes B–F (not shown) constitute an attractive target for synthetic chemists, which has culminated in several elegant total syntheses by the groups of Smith, Hoye, Iwabuchi, and Nicolaou over the years.[40–45]

Tanja Gulder

Tanja Gulder studied chemistry at the University of Würzburg where she received her diploma in 2004. After earning her Ph.D. with distinction under the supervision of Prof. G. Bringmann in 2008, she pursued postdoctoral studies with Prof. P. S. Baran at The Scripps Research Institute (La Jolla, CA) focusing on the synthesis of strained natural products. In late 2010 she started her independent career supported by a Liebig fellowship of the Fonds der Chemischen Industrie at RWTH Aachen university, where her group is focusing on the development of new catalytic methods guided by natural product synthesis.

Phil S. Baran

Prof. Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from NYU with Professor David I. Schuster in 1997. After earning his Ph.D. with Professor K. C. Nicolaou at Scripps in 2001, he pursued postdoctoral studies with Professor E. J. Corey at Harvard until 2003, at which point he began his independent career at Scripps, rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.

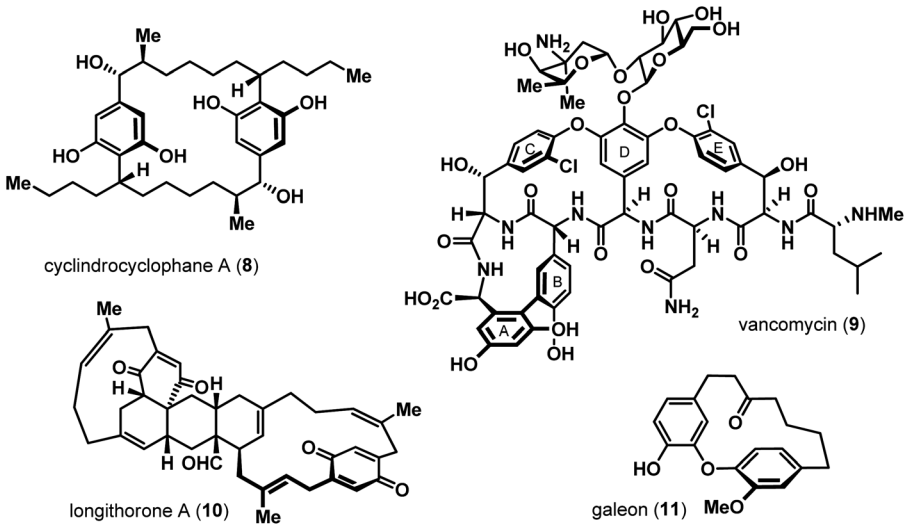


Fig. 2 Naturally occurring cyclophanes: cylindrocyclophane A (**8**), the first cyclophane isolated, vancomycin (**9**), longithorone A (**10**), and galeon (**11**).

Meanwhile, a huge number of cyclophane-containing secondary metabolites of different biosynthetic origins and with fascinating biological activities have been found in diverse living organisms. These macrocycles, albeit extending over a broad structural spectrum reaching from 'simple' cyclophane-containing substrates, such as the diarylheptanoid galeon (**11**),[46] to more complex molecules, like longithorone A (**10**)[47–49] and the glycopeptide vancomycin (**9**),[50] all exhibit an intrinsic three-dimensional structure which has a significant impact on their properties, such as their distinguished bioactivities.[51–54] Although the focus in preparation of the majority of structurally complex natural products has shifted from feasibility to elegance and efficiency (*e.g.* step, atom, and redox economy, chemo- regio-, and stereoselectivity, protecting-group free, *etc.*) over the last years,[55–66] the main problem in the synthesis of macrocyclic structures still remains in the strategy of tying up both ends of the linear precursor. For the macrocyclization of cyclophane natural products the synthetic bar is raised due to the rigidity of the ring structure to be formed, in many cases accompanied by the introduction of axial, planar and/or helical chirality into the cyclic framework.

In this review we describe the challenges associated with the synthesis of members of the structurally intriguing class of cyclophane natural products, concentrating on the most strained representatives that show configurational stability at the aromatic ring(s). Our main focus lies on evaluating the different concepts for the installation of the highly strained macrocyclic carbon skeleton, which in most cases is the key step in assembling these extremely rigid molecules that affects the efficiency of the complete synthetic pathway.

The group of cyclophane natural products comprises a huge variety of most diverse compounds with unprecedented structures and outstanding biological activities. Regardless of their overall constitution, including the size of the macrocycle, ring closure is certainly the central issue faced in the preparation of these targets and determines the efficacy of the overall synthetic strategy. In general, the outcome of this key step highly depends on both the choice of the strategic bond formation and the method selected for this reaction. Not surprisingly, this problem has attracted tremendous attention from synthetic chemists and provided impetus for the alteration of existing and the development of new synthetic methodologies in this field.

2 Strain in cyclophane natural products

In general, the name *cyclophane* is composed of three words *cyclo*, *ph*enyl, and alk*ane*.[67] It was originally introduced for molecules with two *para* phenylene moieties held together face-to-face by an aliphatic chain.[3,11] In 1969, Vögtle[68,69] extended this concept to characterize cyclic compounds built up by at least one aromatic portion and a $(CH_2)_n$-handle with $n \geq 1$. Today the name cyclophane is classified by more complex rules. According to IUPAC, substrates belong to this group of compounds if they bear (1) a cyclic or a system of cyclic units having (formally) the maximum number of noncumulative double bonds (mancude-ring system) and (2) atoms and/or saturated or unsaturated chains, with or without heteroatoms, as alternate components of a macrocycle.[70] This very general definition meets the structural properties of a wide range of compounds. However, aromatic units present in cyclophanes are mostly carbocyclic rings, such as benzene or naphthalene derivatives. In principle, cyclophanes can be divided into two categories, which differ fundamentally in their chemical properties and behavior: the 'small' cyclophanes and their macrocyclic analogs. While the main interest in the latter group arises from a supramolecular point of view originating from their ability of being interesting vehicles for host–guest chemistry,[5,6,8,25,29] the 'small' phanes, with [n]cyclophanes as the archetype of this group, constitute a model for studies on fundamental aspects of strain and aromaticity.[11,71–80] The short bridges in such cyclophanes often prohibit free rotation of the rings and thus place these molecular portions into unusual and thermodynamically often disfavored orientations to each other, which would never be observed in open-chain systems. The cyclic core can even impart such strain on the whole system that the benzene ring is twisted out of plane and adopts a boat- or chairlike configuration, depending on the type of cyclophane.

Even if the existence of such bent aromatic rings in nature was deemed unlikely due to the strain energy required for the distortion of bond angles, such deformations of benzene rings are not restricted to artificial cyclophanes, but can also be found in natural representatives (Fig. 3), such as the alkaloid haouamine B (**12**)[81] or the fungal metabolite hirsutellone A (**13**).[82,83]

The rigidity of these molecules, and consequently the restricted rotation of the benzene ring(s), highly depends on the length and the constitution of the bridge. The tremendous influence of small variations in the constitution of the handle in small cyclophanes is clearly visible, *e.g.*, within the family of acerogenine-type compounds (Fig. 4).[84] Although all members comprise a 15-membered macrocyclic framework, the hydrogen atoms in the *para* disubstituted phenyl ring (ring A) show different splitting patterns in acerogenin A (**14**) and C (**15**).[85] While only two sets of protons (AB quartet) are observed in the ^{1}H-NMR spectrum of **15**, the same H atoms in **14** resonate as four distinct doublets of doublets. This observation might indicate that the rotational barrier of the *endo* diaryl ether moiety is higher in **14** than in **15**. The only structural difference between the two molecules is located within their tethers, which in **14** bears only sp^3 carbon atoms, in contrast to the occurrence of a sp^2 center (carbonyl group) in **15**. Because of the smaller bond angle of sp^3 compared to sp^2 hybridized carbons, the angle strain as well as the van der Waals hydrogen–hydrogen interactions are increased, leading to a more biased and thus rotationally restricted ring system in acerogenin A (**14**).

The point of attachment of the aliphatic bridge to the aryl moiety also plays an important role for the strain exhibited by the macrocycle. While in paracyclophanes the shortest unstrained handle possible consists of eleven sp^3-hybridized atoms, the respective *meta ansa* compounds can contain one atom less to guarantee rotational freedom of the aromatic portion.[86] For that reason, cyclopeptide alkaloids of the frangulanine class, such as mauritine A (**16**), which contain a 14-membered macrocycle, show significant rigidity of their scaffold, whereas the handle in their *meta*-bridged congeners (zizyphine-A type), like, *e.g.*, zizyphine A (**17**), is flexible (Fig. 4).[87,88] X-ray analysis of **16**[89,90] showed the extent of strain within this natural product. A high degree of distortion of the styrylamide system was obvious, which avoids the overlap of the π-orbitals and thus conjugation of the π-systems of the olefin and the endocyclic aromatic ring. Furthermore, this benzene moiety is slightly bent and the atoms at the benzylic position are thus considerably twisted out of the aromatic plane.

The described phenomena can result in the formation of configurationally stable isomers if the aryl moiety is sufficiently substituted, leading to strain-induced, geometrically chiral compounds, even in the absence of any traditional chiral element, like, *e.g.*, stereocenters. Such structures might thus be considered as a 'special form of planar and axial-chirality'.[91] Cyclic bisbibenzyl natural products are such asymmetric compounds, as any of their non-planar conformations possess a mirror-imaged partner.[92,93] These secondary metabolites are exclusively found in bryophytes and originate biosynthetically from two lunularine units (**18**) connected by biaryl and/or biaryl ether bonds formed in phenol oxidative coupling processes (Fig. 5a). The coupling reactions can occur *ortho* or *para* to the phenol functions and thus give rise to various sub-groups of compounds in which all members are devoid of any stereogenic center and equipped with biaryl axes appearing to be configurationally unstable. This renders them achiral molecules at first sight. Nevertheless, optical rotation was found among isolated cyclic bisbibenzyls. The rotational barriers of these compounds are, however, distributed over a wide range and thus their macrocyclic scaffolds vary from configurationally stable to slowly interconverting stereoisomers at room temperature. Studies on the origin of chirality of these compounds showed that, in principle, all macrocyclic bisbibenzyls are restricted in their conformational flexibility and thus are chiral at sufficiently low temperatures.[94–99]

One well studied example of this class of natural compounds is isoplagiochin C (**19**, Fig. 5a), which has been obtained from nature in different enantiomeric ratios depending on the plant source and the isolation protocol.[100–104] Experimental as well as computational investigations by Bringmann *et al.*[95] revealed that the chirality of **19** does not arise from isolated stereogenic elements as such, but from the combination of two biaryl axes and one helical stilbene unit disposed in a rigid macrocyclic framework, which largely decreases the configurational freedom of the entire molecule. Determination of the rotational barriers of the different stereogenic elements identified the axis between ring C and D as the only rotationally restricted structural scaffold in **19** with 102–115 kJ mol^{-1} needed for isomerization. The energy required to cause atropisomerization of the other biaryl axis (ring A and B) and of the double bond, however, can be easily overcome at room temperature. These stereochemical features in **19** lead to a mixture of rapidly interconverting diastereomers for each of the two enantiomeric series of *P*- and *M*-isoplagiochin C (**19**).

An example within the bisbibenzyl family that impressively demonstrates the influence of small structural alterations onto the ring strain of the whole molecular framework, and, as a consequence, their impact on the configurational stability as well as on the distortion of the aryl portion, are the members of the riccardin subgroup (Fig. 5b). While all isolated samples of riccardin C (**20**), regardless of their natural source, display no optical activity,[105–108] its regioisomer riccardin D (**21**) has been isolated recently in *enantio*-enriched form from *Reboulia hemisphaerica*.[109] NMR spectroscopic studies by Harrowven[94] showed that the cyclic array of **20** has sufficient conformational freedom at ambient conditions that fast interconversion of the different enantiomeric forms occurs on the NMR time scale, thus making **20** an achiral molecule at room temperature. Only by cooling the NMR sample of **20** to 243 K, do the signals of the aromatic protons start to resolve as expected for increasingly

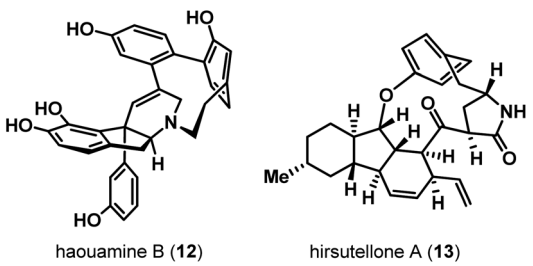


Fig. 3 Natural cyclophanes with bent benzene rings.

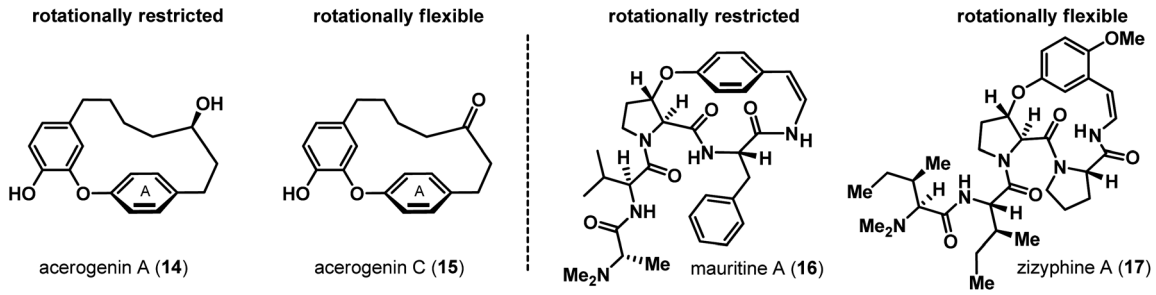


Fig. 4 Examples of the influence of the substitution pattern of the *ansa* bridge and its points of attachment to the benzene ring(s) on the rigidity of the cyclophane skeleton.

hampered rotation of the biaryl portion. By varying solely the position of the hydroxy function in ring B from *para* in riccardin C (**20**) to *ortho* in riccardin D (**21**), the atropisomerization barrier of the biaryl axis rises significantly. Thus, at room temperature riccardin D (**21**) displays two separable, configurationally stable atropenantiomers. It is noteworthy that this single, minimal structural change, that does not change the constitution of atoms within the macrocyclic system itself, has such a dramatic influence on the flexibility and, as a consequence, on the chirality of these cyclophane natural products. The only macrocyclic bisbibenzyl compound obtained as a single enantiomer so far also belongs to the riccardins and is named cavicularin (**22**). This structurally intriguing molecule is derived from the liverwort *Cavicularia densa* Steph.[91] and shows the overall riccardin C architecture with an additional biaryl linkage between *C*-10′ (ring A) and *C*-3′ (ring D), altogether resulting in dibenzyl and dihydrophenanthrene units connected by aryl–aryl bonds and a diaryl ether bridge. This contraction of the flexible riccardin C skeleton induces such a strain on the system of cavicularin (**22**) that one of the benzene rings (C) is twisted out of plane by as much as 15° in the solid state and thus adopts a boatlike configuration. The atropisomerization barrier of the biaryl axis between the phenyl moieties A and B guarantees the configurational stability of **22**, locking its configuration as a single enantiomer. Although the occurrence of strain-induced chirality is one of the most fascinating aspects of cyclophane natural products, its exploration has often been neglected during the structure elucidation process in the past. Predictions of whether a compound is geometrically chiral, based only on the overall constitution of the molecule, is very difficult if not impossible.

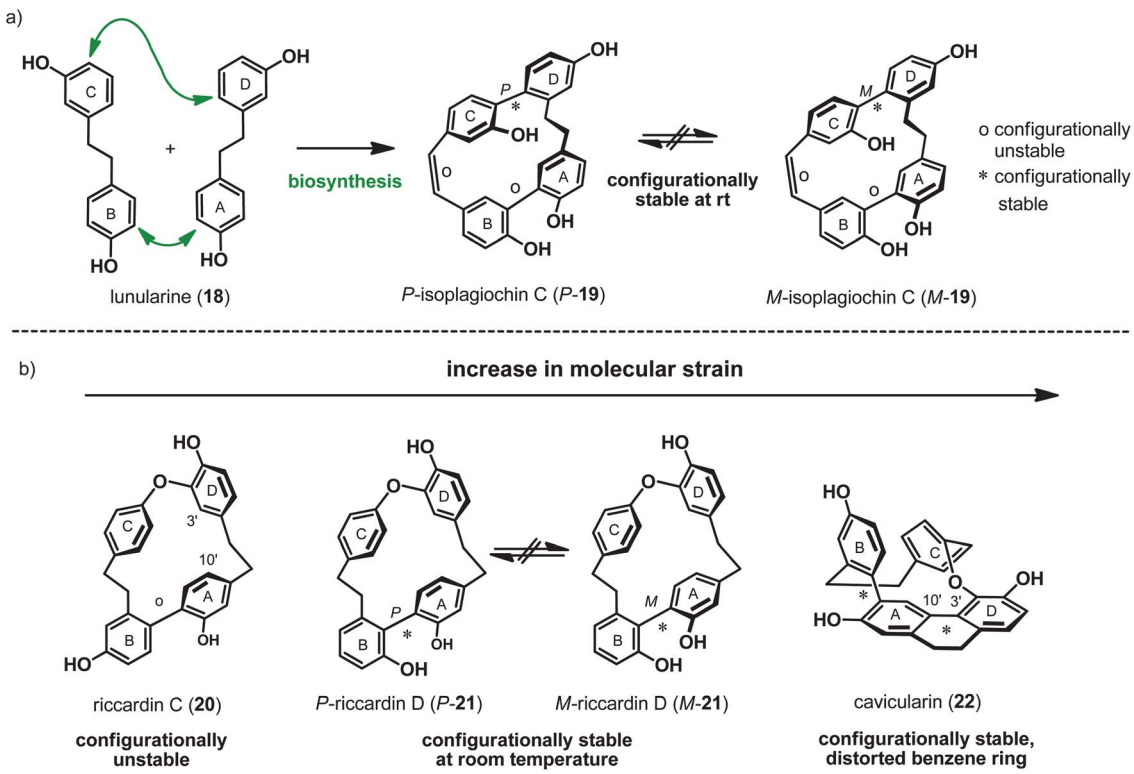


Fig. 5 a) The biosynthetic precursor lunularine (**18**) and the atropisomers of isoplagiochin C (*P*-**19**) and (*M*-**19**), which are configurationally stable at room temperature; b) influence of structural alterations on the ring strain of the cyclophane core and thus on the geometrical chirality as well as on the conformation of the aryl portions as exemplified by members of the riccardin subclass.

Detailed studies on the conformational and configurational properties are needed to unambiguously determine the strain-induced chirality of cyclophanes, which comprises extended experimental as well as theoretical investigations. Because of the lack of such studies we assume that many more cyclophane natural products, which are drawn with a 'flat' macrocyclic structure in the literature, are indeed configurationally stable, but were not described as such as they were obtained as racemates or their optical activity was attributed to other, more obvious stereoelements, like *e.g.* stereocenters, appearing in the overall structure of the compound. Due to the complexity of this aspect in small cyclophane chemistry, only natural products that were described as configurationally stable in the literature are included in this review.

The rigidity of the skeleton of these often chiral target compounds makes their preparation even more challenging compared to configurationally flexible macrocycles: Here, not only the kinetic barrier has to be overcome during the cyclization event, but simultaneously chirality has to be introduced into the system. Not surprisingly, the synthesis of natural cyclophanes with their often outstanding biological activities and the inherent challenges associated with their synthesis has attracted much attention among the synthetic community for decades and has encouraged the development of new strategies for the macrocyclization step as often otherwise well established and robust reactions fail to perform effectively.

3 Synthesis of natural cyclophanes with rotationally restricted aryl moieties

3.1 Diaryl heptanoids

Among cyclophane natural products the diarylheptanoids are the structurally simplest sub-class with their scaffold consisting of two benzene rings tethered by an oxygenated aliphatic heptyl chain.[84,110] These secondary metabolites are mainly found in plants of the genera *Alpinia*, *Zingiber*, *Curcuma*, and *Alnus* and count more than 300 representatives.[84,110] The diaryl heptanoids have caught attention over the last 25 years due to their outstanding anticancer, antiemetic, estrogenic, anti-Alzheimer, antimicrobial, and antioxidant properties.[111–123] The cyclic members of the diaryl heptanoid family can be classified into biphenyls ([7.0]-metacyclophanes), such as alnusdiol (**24**),[124] and diphenyl ethers (14-oxa-[7.1]-metaparacyclophanes) like maximowicziol (**25**, Fig. 6).[125] Because of the high ring strain caused by the short carbon bridge, rotation of the biaryl and biaryl ether bond is prohibited or at least restricted in certain macrocycles. This phenomenon, resulting in axially and/or planar chiral diarylheptanoids, however, has only been described for a few compounds,[85,110,126–129] but we assume that several additional diarylheptanoids are showing strain-induced chirality. In principle, two retrosynthetic disconnections for closing the macrocycle have been invoked for both types of diarylheptanoids. As depicted in Fig. 6, this can either proceed by linking the two aryl portions in the linear biphenyl **23** or by forming the seven-membered handle starting with biaryl **26**. Both approaches have been probed and led to numerous synthetic protocols.[110]

The first synthetic approach to a diarylheptanoid was conducted by Semmelhack and co-workers[130,131] in 1975 applying their zerovalent nickel-promoted biaryl coupling procedure.[131] The pseudo-symmetry of metacyclophane alnusone (**29**), which can be found in the wood of *Alnus japonica* Steud. along with its close analogs alnusonol and alnusoxide,[132] indicated that a straightforward strategy involving intramolecular coupling of the arylhalide units in **27** should be possible (Scheme 1a). In this key step a solution of diiodide **27** in DMF was treated with superstoichiometric amounts (1.5 equiv.) of tetrakis-(triphenylphosphine)nickel(0) resulting in the formation of the desired 13-membered macrocycle **28** in 46% yield. Subsequent acidic hydrolysis of the MOM-ethers gave the natural product **29** in overall seven linear steps.

Semmelhack's Ullmann-type reductive coupling method was later also utilized by Whiting *et al.* in the synthesis of other *meta*-bridged biphenyls,[133,134] like *e.g.*, myricanol (**33**), which has been isolated from the bark of different Myricaceae species.[126–128,135–137] Heating of precursor **30** in the presence of the zero-valent nickel species gave macrocycle **32**, but only in 7% yield (Scheme 1b, top). During ring-closure, de-iodination of the linear diaryl heptanoid **30** occurred as the major side reaction and led to degradation of starting material. Comparison of the outcome of the cyclization in the synthesis of alnusone (**29**) and myricanol (**33**) showed tremendous erosion in efficacy using the same Ni(0) reagent, which can be traced back to the presence of three sp^2 instead of sp^3 carbon atoms in the bridge of alnusone (**29**). Like already described for the acerogenins A (**14**) and C (**15**, *cf.* chapter 2), these differently hybridized carbon atoms result in less distinct H–H steric interactions as well as reduced bond angle strain in **29**. Furthermore, steric hindrance at the coupling site is dramatically increased in myricanol-type compounds due to the buttressing effect of the substituents at the trisubsituted aryl portion. All these effects together build up so much strain in myricanol (**33**) that the biphenyl unit is even twisted out of plane

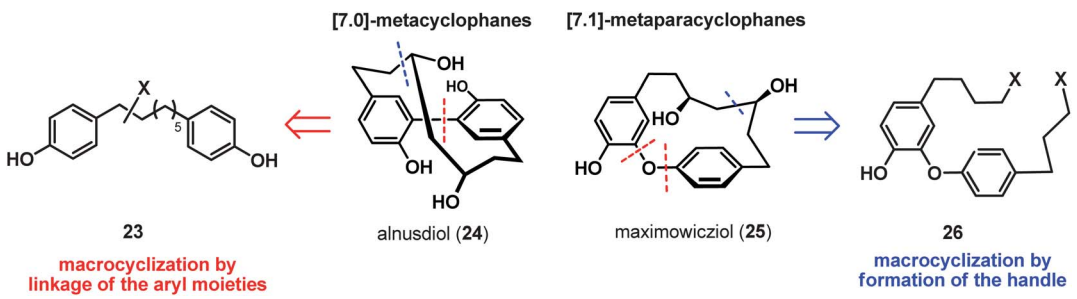
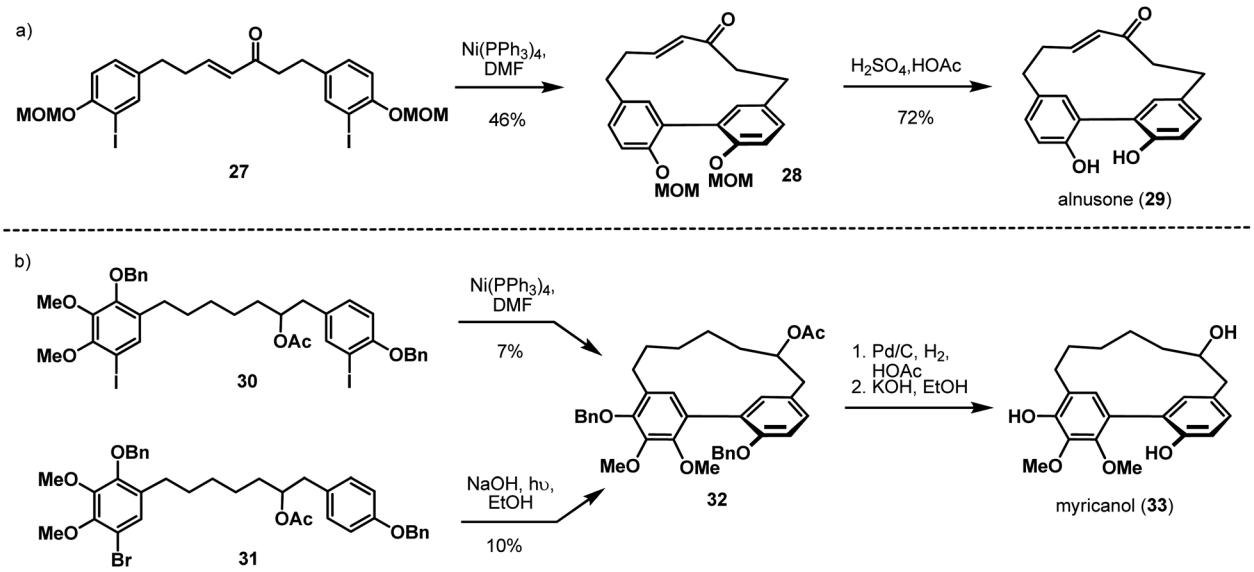


Fig. 6 General retrosynthetic analysis for the macrocyclization step of both types of diaryl heptanoids.



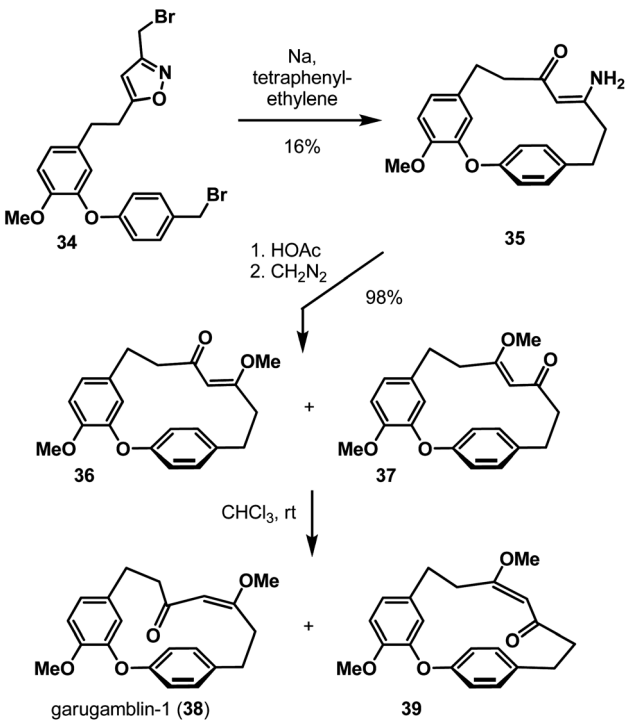
Scheme 1 Synthesis of [7.0]metacyclophane natural products a) alnusone (**29**) by Semmelhack[130,131] and b) myricanol (**33**) by Whiting.[133,134]

and its biaryl bond is distorted from linearity in both directions.[126–128]

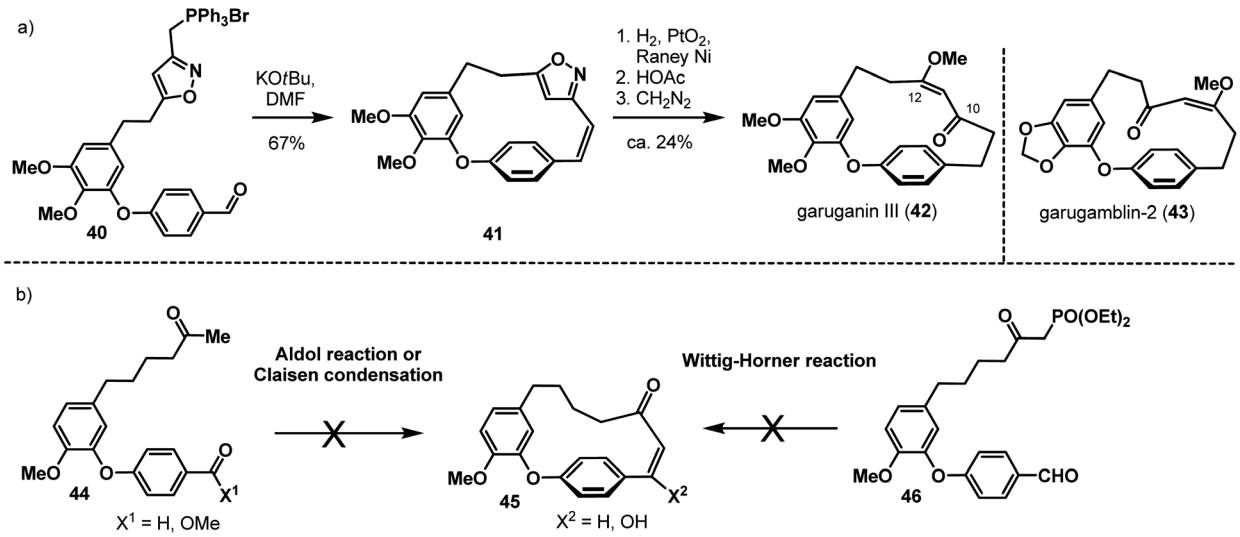
As an alternative to the transition metal-mediated ring-closure described above, Whiting also attempted to apply a photochemically induced radical cyclization (Scheme 1b, bottom).[133,134] Irradiation of arylbromide **31** with UV light (254 nm) in basic medium gave **32** in only a slightly better yield (10%), once more reflecting the rigidity of the ring closed product. Further manipulations of the aryl substituents in **32** yielded the natural product myricanol (**33**) after hydrogenolytic removal of the *O*-benzyl groups followed by saponification of the ester function.

For the preparation of the first metaparacyclophane diarylheptanoid, Nógrádi targeted garugambline-1 (**38**),[138] a compound originating from the Indian plant *Garuga gamblei*,[139] featuring a Wurtz coupling in the key step (Scheme 2). In order to generate the radical carbanion, the biaryl ether **34** was treated with sodium in tetraphenylethylene. This ring closing procedure accompanied with reductive cleavage of the isoxazole ring afforded the enaminoketone **35** in low yield (16%), but due to hydrogen bonding, exclusively in form of the *Z*-isomer. Hydrolysis of the enamine functionality followed by *O*-methylation of the enol using diazomethane gave the corresponding enolether as a mixture of the two regioisomers **36** and **37**. The synthesis of garugambline-1 (**38**) was finalized by isomerization of the double bond in the tether to the desired *E*-enolether upon standing of **36** and **37** in chloroform at room temperature for two weeks. This spontaneous inversion was not expected as the *E* form should lead to higher ring strain in the macrocycle.

Because of the unsatisfying outcome of the cyclization step using a Wurtz coupling, Nógrádi and co-workers envisaged a Wittig reaction to perform ring closure by building the C_7 tether in the synthesis of garuganin III (**42**).[140] Therefore, cyclization precursor **40**, equipped with a phosphonium salt moiety and an aldehyde function, was prepared (Scheme 3a). Treatment of a dilute solution of **40** with KO*t*Bu produced the 15-membered macrocycle **41** in surprisingly high yield (67%). It is important to note that the isoxazoline fragment may play an important role during the macrocyclization event. It can be speculated that the heterocycle causes a bent conformation and thus helps to preorganize **40** in such a way that the entropically disfavored intramolecular reaction is indeed facile and can compete with intermolecular pathways.[110] Although no conformational analysis of **40** has been conducted, this hypothesis is supported as cyclizations by an aldol reaction, Claisen condensation, or Wittig–Horner olefination with starting materials **44** and **46**, which are devoid of the isoxazole, failed during the attempted synthesis of acerogenins (Scheme 3b).[141]



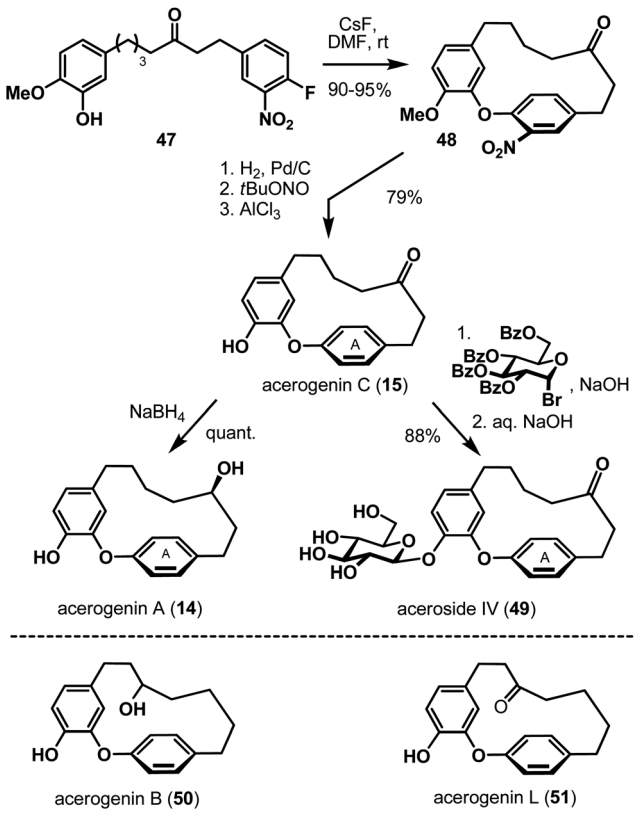
Scheme 2 Formation of garugamblin-1 (**38**) featuring an intramolecular Wurtz coupling.[138]



Scheme 3 a) Construction of the macrocycle **41** in the synthesis of garuganin III (**42**)[140] by Wittig reaction and b) macrocyclization attempts using precursors **44** and **46** without the isoxazole moiety.[141]

Garuganin III (**42**) was finally obtained from the cyclization product **41** in three further steps (Scheme 3a). Hydrogenation of **41** over PtO_2 doped with RANEY® Ni reduced the olefin and cleaved the isoxazole ring. Subsequent acidic hydrolysis of the resulting enaminoketone followed by *O*-methylation afforded four different products identified as the *Z* and *E* isomer as well as the *C*-10- and *C*-12-keto regioisomers of **42**. As already observed for garugamblin-1 (**38**, see Scheme 2),[138] isomerization of the kinetically more favored *Z* enolether to the more strained *E* form occurred spontaneously enhancing the yield of the natural product **42** to *ca.* 24%. Another diarylheptanoid, namely garugamblin-2 (**43**), was obtained by Nógrádi's group following the same procedure.[142]

The bark of *Acer nikoense* Maxim, which has been used in traditional medicine against liver diseases and as an eyewash,[143] contains several acerogenin-type biaryl ethers.[144–148] Although acerogenin A (**14**) was isolated by Nagai *et al.* as the first representative of this class of compounds in 1976,[149] it took over twenty years until the first total synthesis of acerogenins was reported, most likely owing to a lack of suitable macrocyclization methods.[150] With the development of a mild, intramolecular S_NAr reaction, an efficient protocol for the facile construction of *endo* aryl–aryl ether bonds became available, which was employed in the preparation of different natural products,[85,110,150–152] *i.a.* the diarylheptanoids acerogenin A (**14**), C (**15**), and aceroside IV (**49**) by Zhu.[85,150] By stirring the linear compound **47** in DMF in the presence of CsF, ring closure to the metaparacyclophane **48** occurred in excellent 90–95% yield (Scheme 4). Even at higher concentrations ($c = 1.0$ M), at which intermolecular reaction pathways should dominate, **48** was still obtained in 50%. The surprising tendency of **47** for macrocyclization was attributed to the fact that the tether in the cyclization precursor **47** does not predominately exist in an extended conformation,[153] but preferentially adopts a turn structure that is stabilized by interactions of the electron-rich with the electron-poor aromatic ring. This preorganization[154] brings the two ends of **47**, in particular the phenolic hydroxy function and the carbon bearing the fluoro atom, in close proximity and thus accounts significantly for the success of this conformationally directed[155] macrocyclization. From the central building block **48**, acerogenin C (**15**) was accessible after reductive removal of the nitro substituent followed by *O*-demethylation in 79% yield. Reduction of the carbonyl function of **15** gave



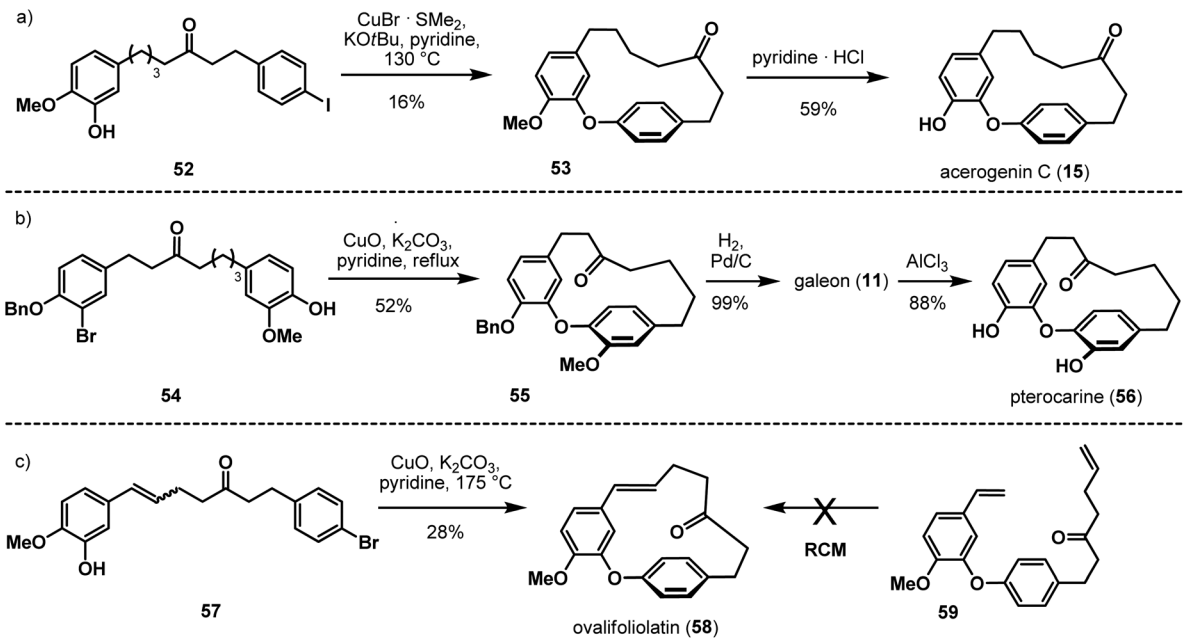
Scheme 4 Conformation-directed[155] biaryl ether bond formation by Zhu and co-workers in the synthesis of acerogenins **14**, **15**, and **49–51**.[85,150]

acerogenin A (**14**) quantitatively, while glycosidation of **15** afforded aceroside IV (**49**) in 88%. It is noteworthy that this slight structural alteration (**15** → **49**) in the periphery of the cyclophane scaffold causes a change in the overall strain of the systems and thus on the rotational freedom of the macrocycle. With the conversion of acerogenin C (**15**) into its glycosylated analogue aceroside IV (**49**) all aromatic protons become chemically and magnetically distinguishable. This can be explained by the presence of a now buttressed substituent next to the biaryl linkage in **49** resulting in a configurationally hampered diaryl ether bond.[85] Other diarylheptanoids, acerogenine B (**50**) and L (**51**, Scheme 4), were synthesized by the same group likewise applying the conformation-directed strategy described here.[85]

In parallel to Zhu's work, Nógrádi also reported on the synthesis of acerogenin A (**14**) and C (**15**). In this case, macrocyclization was carried out by biaryl ether formation featuring a modified Ullmann coupling (Scheme 5a).[156] Applying Boger's protocol (*cf.* chapter 3.2),[157–161] aryl iodide **52** in pyridine was heated with $CuBr \cdot SMe_2$ in the presence of KO*t*Bu. This method gave the diarylheptanoid scaffold **53** in low yield (16%), which was transformed to acerogenin C (**15**) by removal of the *O*-methyl group. The use of classical Ullmann conditions for the formation of the cyclophane skeleton proved to be very efficient in the preparation of galeon (**11**) by Jahng *et al.* (Scheme 5b).[162,163] The copper oxide promoted ring closure of **54** yielded *O*-benzyl galeon (**55**) in 52% yield. *O*-Debenzylation under hydrogenolytic conditions furnished galeon (**11**). Subsequent Lewis-acid mediated *O*-demethylation of **11** yielded another diarylheptanoid, pterocarine (**56**). This reaction sequence was used by the same group to target acerogenins A–C (**14**, **15**, and **50**) and L (**51**).[163] Another example for the application of a classical Ullmann reaction for the formation of a diaryl ether linkage constitutes the synthesis of ovalifoliolatin (**58**) by Natarajan (Scheme 5c).[164] Treatment of ketone **57** with CuO and K_2CO_3 in refluxing pyridine afforded the natural product **58** in only 28% yield and as a 13 : 1 mixture of its *E*/*Z*-isomers in favor of the desired product. The poor yield for the macrocyclization of **57** can be attributed to the high ring strain in **58** originating from the *trans* configured double bond in its aliphatic bridge. Applying the same reaction conditions to compounds missing this olefin moiety (not shown) resulted in increased yields for the saturated system (50% *vs.* 28%), which should possess less ring strain compared to the *trans*-configured **58**.[164] The rigidity of the macrocycle was also evident as other methods, like, *e.g.* ring-closing metathesis (RCM) of compound **59**, were unsuccessful under several conditions using diverse catalysts.

3.2 Cyclic peptides

This class of natural products comprises a gigantic and steadily growing number of members present in all types of organisms. These compounds, which are exclusively composed of proteinogenic and non-proteinogenic amino acid building blocks, span a huge range of different molecular shapes and sizes, varying from just a few amino acids to hundreds. The cyclic congeners are classified by the bond type that holds together the amino acid residues in the ring. This leads, in general, to homodetic and heterodetic peptides, in which the first group exclusively contains peptide bonds. In heterodetic cyclic peptides at least one non-amide bond, like, *e.g.*, an ester functionality, disulfide bridge, *etc.*, links the amino acid building blocks in the cyclic system. A subdivision of cyclic peptides are those showing a cyclophane unit, which can be both conformational flexible and/or restricted. The rotationally fixed derivatives (Fig. 7) can further be distinguished into the *ansa* bridged cyclopeptide alkaloids, such as sanjoinine A (**60**),[165–167] and the dityrosine-containing diaryl ethers, like, *e.g.*, renieramide (**61**),[168] as well as the 4-hydroxyphenylglycine-containing cyclopeptides, such as chloropeptin I (**62**).[169,170] The unique molecular architecture of cyclophane peptides combined with the often stunning biological properties



Scheme 5 Classical and modified Ullmann couplings in the synthesis of diarylheptanoids.

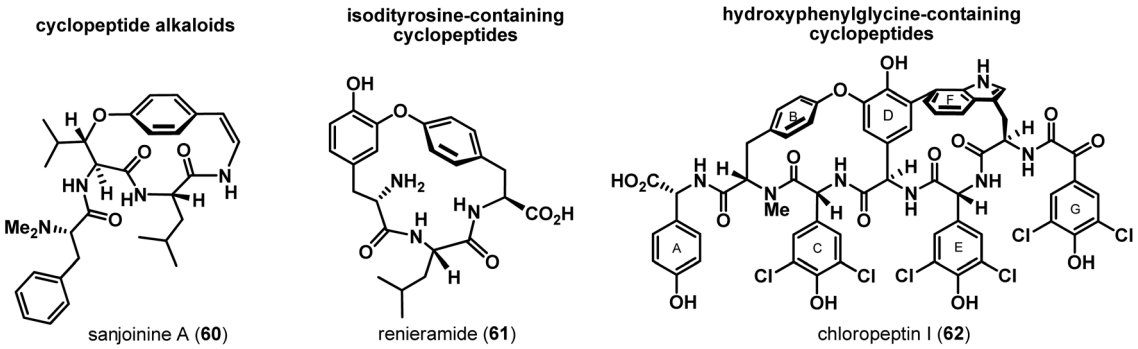


Fig. 7 Different classes of cyclophane-containing peptides: cyclopeptide alkaloids, dityrosine- and hydroxyphenylglycine-containing cyclopeptides.

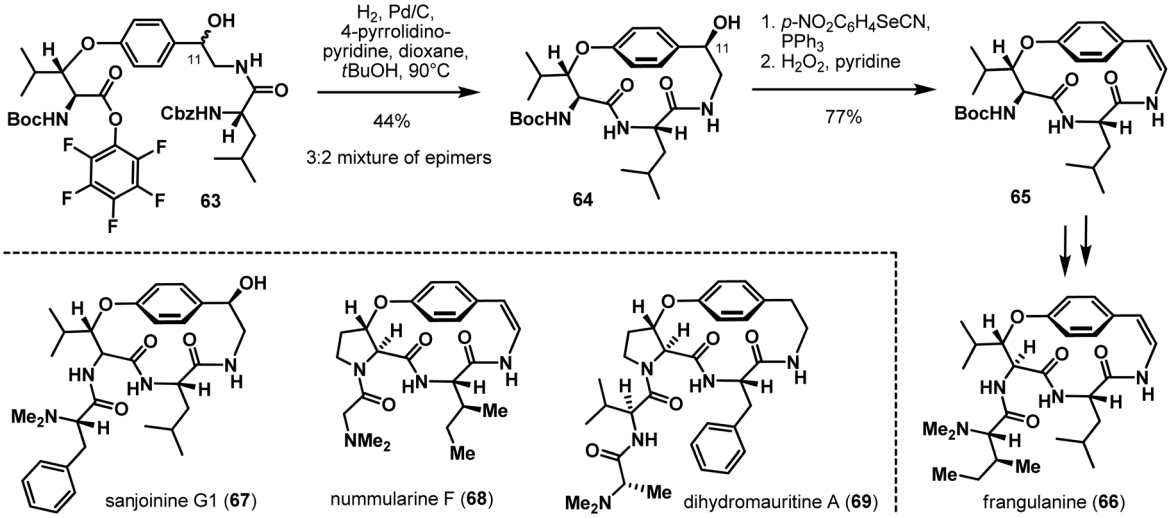
of these natural products sparked the interest of many research groups,[53,171–181] resulting in the development of new methodologies as well as numerous creative total syntheses of these target compounds, which are described below.

3.2.1 Cyclopeptide alkaloids. With over 200 isolated members, the cyclopeptide alkaloids[171,176–181] are a group of steadily growing, closely related polyamide bases mostly originating from plants of the Rhamnacea family, where they are usually present as complex mixtures. As Rhamnacea plant extracts have been used as remedies in folk medicine, in particular for the treatment of insomnia,[182] the bioactivity of these *ansa* peptides has been subject of extensive studies,[176–179,181,183] which, however, have been often hampered by the lack of availability of these minor constituents from natural sources. Cyclopeptide alkaloids can be found as 13, 14, and 15-atoms containing macrocycles with a benzene ring embedded in a 1,3 or a 1,4-orientation within the peptidic ring system. Among these three categories, only the 14-membered *p-ansa* representatives (frangulanine-type) show restricted motion of the aromatic portion due to the huge ring strain exhibited by the framework (*cf.* mauritine A (**16**), chapter 2, Fig. 4), which makes their synthesis more challenging when compared to their *meta*-bridged analogs. However, not only the macrocyclization turned out to be the major difficulty in this endeavor, but the formation of the characteristic alkyl–aryl-ether bond and the introduction of the styrylamine unit also had to be solved during the synthesis.[177]

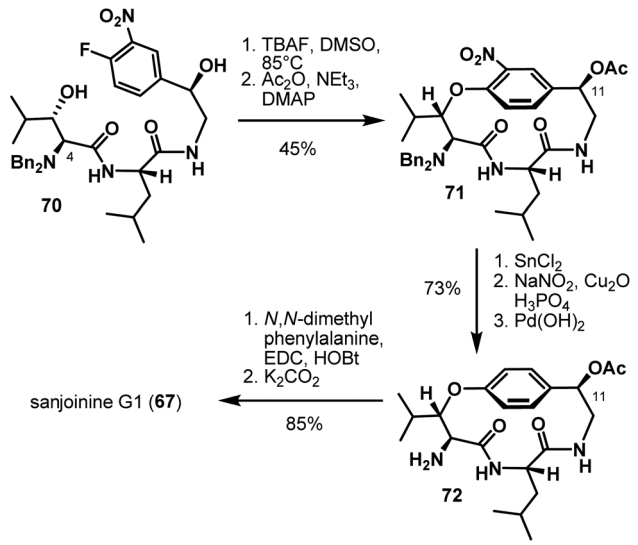
Pioneering work, especially for the ring closure of 14-membered compounds, was done by the group of Schmidt,[184,185] which advanced the field of cyclopeptide alkaloid preparation substantially. In the synthesis of frangulanine (**66**), Schmidt activated the carboxyl group of cyclization precursor **63** as its pentafluorophenyl ester (Scheme 6).[185] Upon hydrogenolytic removal of the *N*-Cbz-protecting group at the other end of **63**, formation of the amide bond occurred spontaneously, affording the macrocycle **64** in moderate yield (44%) as a mixture of *C*-11 epimers (3 : 2) separable by HPLC. Conversion of the hydroxy functionality into the desired enamide unit turned out to be challenging, which may be due to an increase of ring strain in product **65**. Standard procedures, *e.g.* using Martin sulfurane or Burgess' reagent, did not lead to dehydration of compound **64**.[186] The *cis* double bond was finally established by Grieco elimination yielding **65** in 77% if the *R*-epimer was used as the starting material. Subjecting the corresponding epimer (*C*-11 *S*) to Grieco conditions also resulted in **65**, but in a diminished yield (11%) along with numerous by-products. Attachment of the *N*,*N*-dimethylisoleucine moiety to **65** in two further steps finalized frangulanine (**66**). Influenced by Schmidt's macrocyclization strategy, the groups of Han[187] and Joullié[186,188–191] accomplished the synthesis of other frangulanine-type alkaloids, namely sanjoinine A (**60**, Fig. 7) and G1 (**67**), nummularine F (**68**), as well as the synthetic derivative **69** of mauritine A (**16**).

In the synthesis of sanjoinine G1 (**67**) by Zhu and co-workers, macrocyclization was achieved using a S_NAr reaction in the key step.[192–195] Intermediate **70** underwent cycloetherification smoothly upon heating in DMSO in the presence of TBAF (Scheme 7). This aryl–alkyl-ether bond forming procedure worked equally well as the corresponding *endo* aryl–aryl ether formations towards diarylheptanoids (*cf.* Scheme 4), giving the *ansa* compound **71** after *in situ O*-acetylation in 45% yield and as a single atropdiastereomer. As with the diaryl cyclization precursor **47** (see Scheme 4), used in the preparation of acerogenine C (**15**), the intramolecular preorganization of **70** favoring a bent conformer supported the ring-closure reaction. The moderate yield of the cyclization of the sanjoinine G1 building block **70**, however, may be explained by the high steric hindrance at the secondary alcohol in **70**, since its adjacent carbon atoms are equipped with a bulky *i*-propyl and a *N*,*N*-dibenzylamino group. Attempts to change the residue at the *C*-4 amine in **70** and thus to reduce the steric demand at the reactive site showed that the *N*-protecting group is crucial for the feasibility of the S_NAr-based cyclization reaction. Installation of an *N*-Boc group, for example, resulted in complete decomposition of the material. Having cyclophane **71** in hand, the nitro group, which is decisive for the aromatic substitution reaction, had to be removed following a reduction/reductive deamination sequence. Subsequent *N*-debenzylation was carried out by hydrogenolysis using Pearlman's catalyst, giving amine **72** in excellent yield. Interestingly, the benzylic acetoxy group (*C*-11) stayed intact during these transformations. The inherent ring strain associated with the target molecule **67** positions the *C*-11 carbon atom out of plane of the aromatic ring, which results in a decrease in benzylic character of *C*-11 and is therefore responsible for the unusual stability of the carbon–oxygen bond under reductive conditions.

Attachment of the phenylalanine side chain and basic saponification of the acetyl ester function in **72** finalized the natural product sanjoinine G1 (**67**) in eight steps and 21% overall yield.



Scheme 6 Formation of frangulanine-type cyclopeptide alkaloids by macrolactamization of pentafluorophenyl activated esters.



Scheme 7 Total synthesis of sanjoinine G1 (**67**) by Zhu *et al.*[192,195]

The versatility of this straightforward route to cyclopeptide alkaloids was proven in its application to the synthesis of the even more strained mauritine A (**16**, see chapter 2, Fig. 4) and its derivatives mauritine B, C, and F,[196,197] the latter only differing from **16** in their terminal amino acid residues.

3.2.2 Isodityrosine-containing peptides. Isodityrosine is a key fragment in a number of highly bioactive natural products (Fig. 8) whose characteristic structural feature is the presence of two aromatic rings connected by an oxygen atom. The structurally simplest member of this class is the antifungal piperazinomycin (**73**),[198,199] in which the 14-membered macrocycle is equipped with a piperazine moiety. The two tyrosine building blocks involved in the formation of the cycloisodityrosine skeleton can either be directly joined, like in RP-66453 (**74**)[200] and bouvardin (**75**),[201] or be separated by one amino acid resulting in 17-membered macrocycles, such as the protease inhibitor K-13 (**79**)[202,203] and OF4949-III (**80**).[204,205] In both cases, the two possible connection modes can be observed, one having the *N*-terminus at the phenol moiety containing amino acid (compare structure **74** and **80**) and *vice versa* (compounds **75–79**). More complex compounds, *e.g.* showing bicyclic structures, have also been isolated with RP-66453 (**74**), a neurotensin receptor antagonist, and the members of the antitumor antibiotics bouvardin (**75**),[201] deoxybouvardin (**76**),[201]RA-IV (**77**), and RA-VII (**78**).[206,207] In many cases, the formation of an additional ring fused to the cycloisodityrosine moiety contributes to a higher conformational stability and thus has a pronounced influence on the biological activity of the natural products. Among the bouvardin-type molecules **75–78**, the tetrapeptide within the 18-membered cyclic subunit (southern fragment) is responsible for the maintenance of an active, normally inaccessible conformation (*e.g.* s–*cis* amide bond) within the annulated 14-membered cyclic array and thus increases the potency of the pharmacophore, the *N*-methyl cycloisodityrosines (northern fragment).[208–213]

The difficulty in accessing fully synthetic 14-membered cycloisodityrosine compounds has hampered in-depth studies on their medicinal potential and their mode of action for many years.[210,214–225] The severe ring strain in these derivates led to many failures in their attempted preparation, especially in the macrocyclization step.[161,210] The most obvious reaction for ring closure of cyclopeptides would of course be a macrolactamization,[226,227] which has, however, never been achieved for cycloisodityrosine-containing compounds. Other biosynthetically inspired approaches towards these compounds applying phenol oxidative coupling conditions[210,214] also did not result in the elusive macrocycle. The first successful example of the synthesis of a 14-membered cycloisodityrosine compound was reported by Yamamura *et al.* in 1986.[228] In their synthesis of piperazinomycin (**73**) they utilized a thallium(III) nitrate (TTN) induced indirect intramolecular phenol coupling procedure to assemble the cyclic framework (Scheme 8). Treatment of the tetrabromodiphenol **81** with TTN in methanol directly followed by a reductive rearomatization of the over-oxidized intermediate

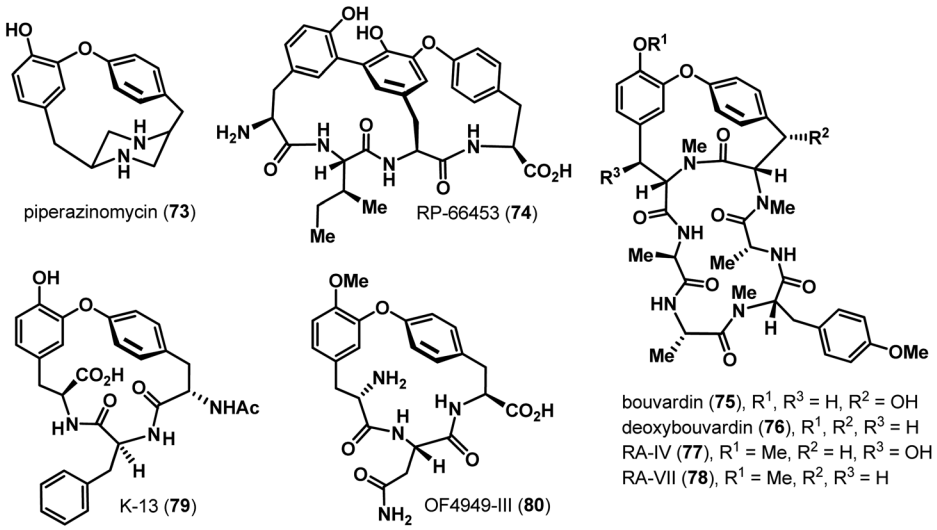
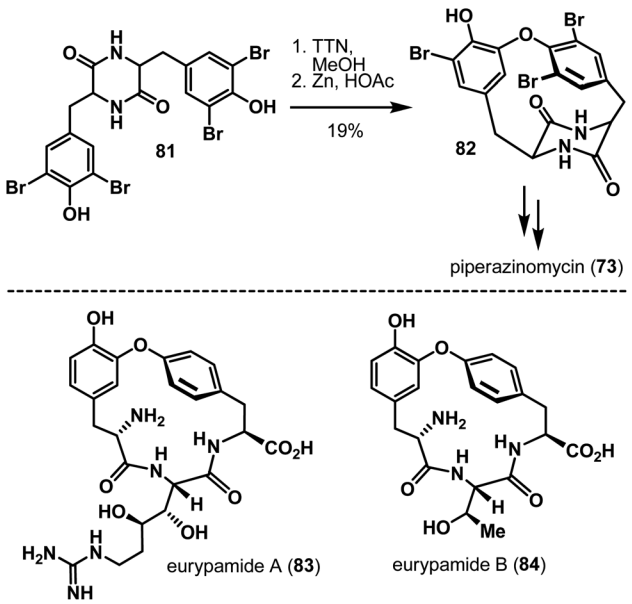


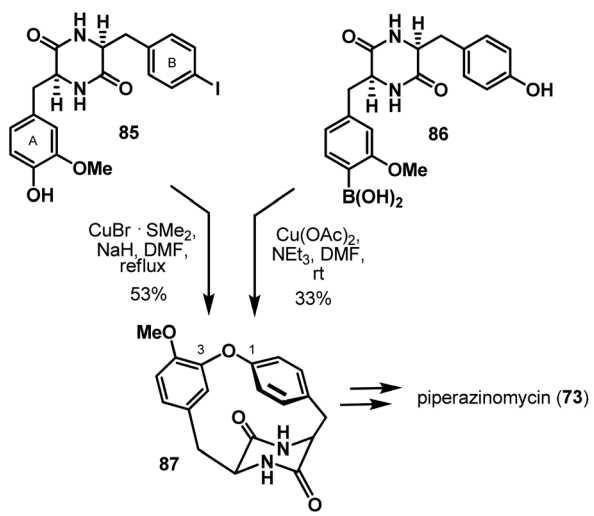
Fig. 8 Cyclopeptides bearing an isodityrosine unit.



Scheme 8 Application of an indirect phenol oxidative coupling reaction in the synthesis of piperazinomycin (**73**).[228]

with zinc powder in acetic acid afforded the diketopiperazine **82** in low yield (19%) and as an inseparable mixture of products. Further transformations *i.a.* dehalogenation and reduction of the amide functions furnished the synthesis of piperazinomycin (**73**) in poor overall yield (2%). Nevertheless, this method was again chosen by Yamamura,[228–230] as well as by the groups of Inoue[231–233] and Evans[234] to access deoxybouvardin (**76**), RA-VII (**78**), K-13 (**79**), OF4949-III (**80**), and eurypamides, like *e.g.*, **83** and **84**.

In the search for an alternative ring closure procedure towards natural product **73**, Boger's group developed a method to obtain the cyclic diketopiperazine **87** featuring a modified Ullmann synthesis (Scheme 9, left).[160] It turned out that the success of this diaryl ether formation is highly dependent on which arene the carbon–oxygen bond is formed (*C*–1–*O vs. C*–3–*O*). The reaction proceeded smoothly when the hydroxy function is located at ring A and the iodide substituent at ring B, as realized in the cyclization precursor **85**, while the optional macrocyclization with inverse location of the phenol and halogen functions did not provide the cyclic compound at all.[210,235] Macrocyclization to establish the 14-membered ring was conducted by adding $CuBr \cdot SMe_2$ and NaH as the base to phenol **85** in refluxing DMF. The product **87** was obtained in good yield (53%). The major drawbacks of this reaction were, in general, the harsh conditions, which makes it not applicable for substrates bearing sensitive substituents, combined with the use of a huge excess of copper reagent (10 equiv.) and base (4 equiv.), both necessary for a satisfying conversion of **85** to **87**. This intramolecular Ullmann ether synthesis was further extended by employing it in the preparation of other cycloisodityrosine compounds, such as bouvardin (**75**),[159] deoxybouvardin (**76**)[210,236] and RA-VII (**78**)[210,236] as well as a number of synthetic derivates thereof.[212,213,237]

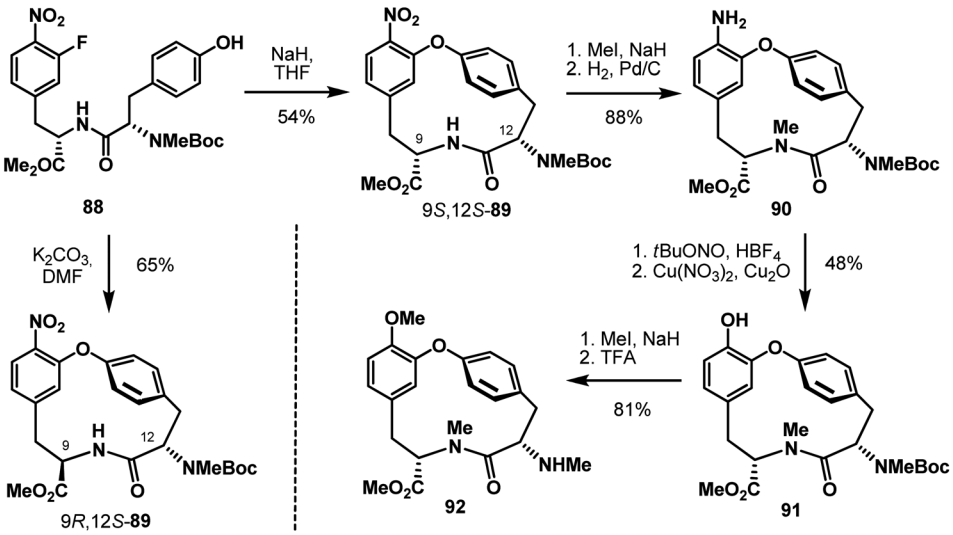


Scheme 9 Copper-mediated macrocyclization reactions used in the preparation of **73**.[160,238]

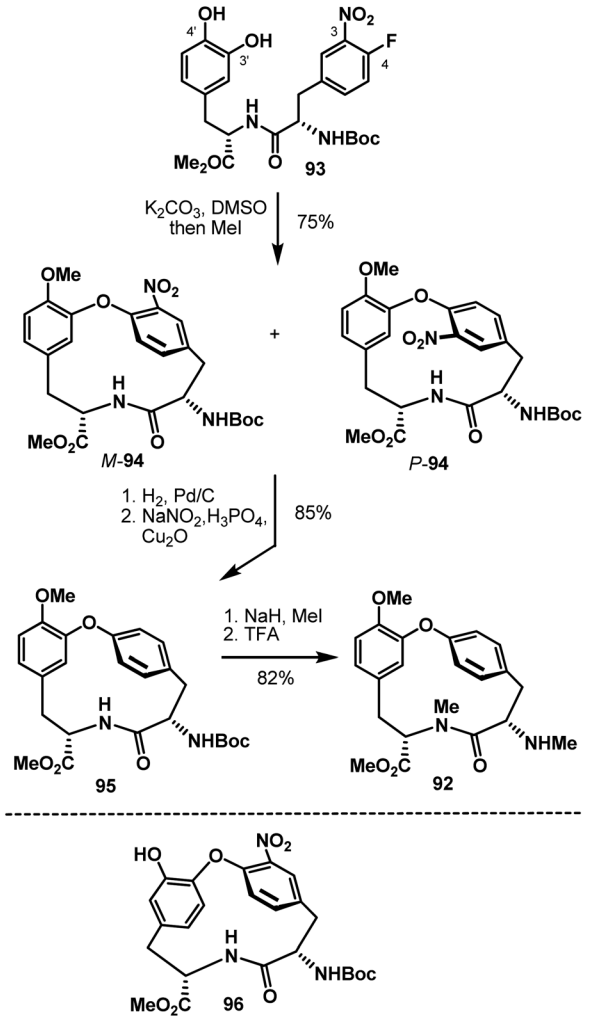
Another copper-induced macrocyclization applied for the formation of the aryl–aryl ether bond was described by Sen in 2009 (Scheme 9, right).[238] Here, the Chan–Lam–Evans procedure was used,[239–241] producing the cyclic intermediate **87** from the boronic acid **86**. This reaction proceeded at room temperature, but gave the constrained diketopiperazine **87** only in 33% yield.

The antitumor compounds bouvardin (**75**), deoxybouvardin (**76**) and their analogs belonging to the family of RA antibiotics, like *e.g.*, RA-IV (**77**) and RA-VII (**78**, Fig. 8), have drawn significant attention among the synthetic community due to their potential as chemotherapeutics, and their unique bicyclic structure, which comprises an unprecedented, strain-induced conformation. Especially the preparation of the very rigid *S*,*S*-cyclodiisotyrosine ring **92**, the pharmacophore of this class of natural products,[206,212,213,232,242–250] has fueled research towards new macrocyclization strategies. Despite the methods described above,[159,210,212,213,231,232,236,249,250] Zhu and co-workers applied their intramolecular nucleophilic aromatic substitution reaction to forge the 14-membered ring scaffold of *N*,*N*-dimethylcyclodiisotyrosine methyl ester (**92**, Scheme 10), the key building block towards **76** and **78**.[251,252] Within this synthetic pathway, the linear starting material **88** bearing an electron-poor nitro-fluoro aryl and an electron-rich phenol moiety as the two reaction partners was readily transformed to the cyclic compound **89** in good yield (65%) under standard conditions using K_2CO_2 at room temperature. Investigations on the stereochemistry of **89** by Zhu and Boger showed that epimerization at the *C*-9 carbon atom occurred readily under these mild conditions.[251–255] The inversion of the *C*-9 and not the *C*-12 stereogenic center, leading to the unnatural, but thermodynamically more favored 9*R*,12*S*-diastereomer of **89**, was very surprising as in general *N*-methyl amino acids[256] are more prone to racemization, thus rendering *C*-12 normally as the more stereochemically labile center. Switching to more basic conditions accompanied with a shorter reaction time reduced the amount of epimerized 9*R*,12*S*-**89**. The desired diastereomer 9*S*,12*S*-**89** was obtained in 54% by treatment of cyclization precursor **88** with NaH in THF for four hours. Subsequent *N*-methylation of the amide function followed by reduction of the nitro group afforded aniline **90** in 88% yield and without any further loss of stereochemical integrity. Formal exchange of the aromatic amino by a hydroxy group was realized in a two-step sequence delivering phenol **91** in moderate yield (48%). *O*-Methylation and final deprotection of the terminal *N*-methyl amine at *C*-12 gave the 14-membered ring of deoxybouvardin (**76**) and RA-VII (**78**) in the form of their methyl ester **92**. A similar route was used to gain access to the tripeptidic ionophore K-13 (**79**). This time no epimerization during macrocyclization was observed.[257]

An improved route to cycloisodityrosine **92** was published by Zhu again featuring a S_NAr reaction in the *endo* aryl–aryl ether forming step (Scheme 11).[252,258] In this second-generation approach, the electrophilic partner in the cyclization reaction was changed from 3-fluoro-4-nitrophenylalanine used in the synthesis described above (*c.f.* compound **88**, Scheme 10), into the corresponding 4-fluoro-3-nitrophenylalanine **93** in order to prevent the undesired epimerization, which might be facilitated by the *p*-nitro substituent in **88**.[251] In addition, the cumbersome transformation of the nitro group into a methoxy function within the synthesis of **92** from **88** can be replaced in this case by reductive removal of the nitro substituent in **94**, which can be achieved more easily. With catechol **93**, ring closure proceeded smoothly with K_2CO_3 in polar aprotic solvents like DMSO or DMF at rt followed directly by *in situ* *O*-methylation. The two atropisomers of the metaparacyclophane *M*-**94** and *P*-**94** were exclusively obtained in high yield (75%). The likewise possible cyclization involving the *C*-4′ OH-group, which should be almost equally reactive as the hydroxy function at *C*-3′, was not observed. This phenomenon may be attributed to the high ring strain appearing in the regioisomeric paraparacyclophane product **96**, which would be formed if C-4′ is the reaction partner. The synthesis of **92** was continued by removal of the nitro group in a reduction/diazotation/reduction sequence yielding compound **95**. *N*-Methylation and acid-mediated deprotection of the amino group finalized the second-generation



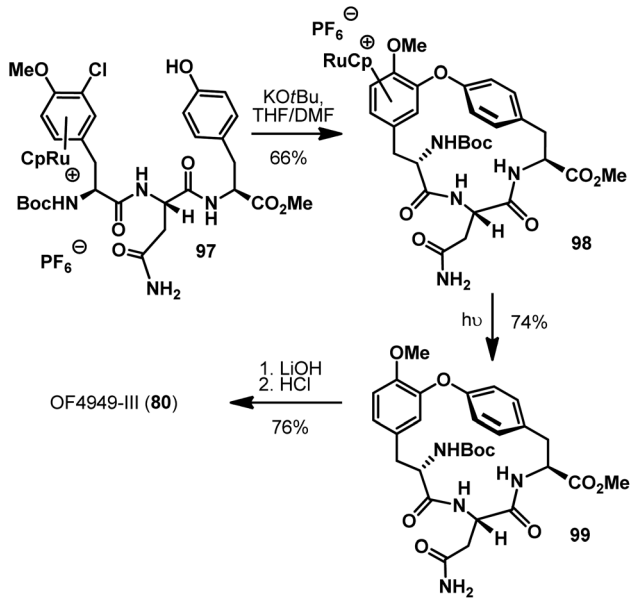
Scheme 10 Formation of the pharmacophore **92** of deoxybouvardin (**76**) and RA-VII (**78**) by S_NAr reaction and epimerization during aryl–aryl ether synthesis of cyclization precursor **88**.[235,251,255]



Scheme 11 Alternative construction of *N*,*N*-dimethylcyclodiisotyrosine **92**, the 14-membered fragment of RA-VII (**78**), by Zhu and co-workers.[252,258]

synthesis of **92** by Zhu *et al.* The same concept was used to stitch together the 14-membered ring fragment of the bacterial metabolite RP-66453 (**74**, see Fig. 8) by Boger[259] and Zhu.[260] In a conceptually similar approach Rich *et al.* accomplished the synthesis of the tripeptide OF4949-III (**80**, Fig. 8).[261]

Since the intermolecular nucleophilic aromatic substitution of amino acid derivatives activated by complexation of a RuCp moiety,[223,262–266] proceeded smoothly under mild conditions forming the linear tripeptide biaryl ether analogs in good yields,[263,266] this method was also tested for the construction of cyclic ether skeletons. Subjecting the transition metal complex **97** to standard S_NAr reaction conditions, here KO*t*Bu in THF/DMF, afforded the cyclic ether **98** in good yield (66%) without any epimerization (Scheme 12). Removal of the ruthenium metal complex occurred photolytically giving the metal-free tripeptide **99** (74%). Saponification of the methyl ester and liberation of the primary amine finalized the short synthesis of OF4949-III (**80**) in only six steps from commercially available amino acid building blocks. The good yields in the macrocyclization can be attributed to a preorganization of the cyclization precursor **97**. In this conformation-directed cyclization reaction[155] the two reacting

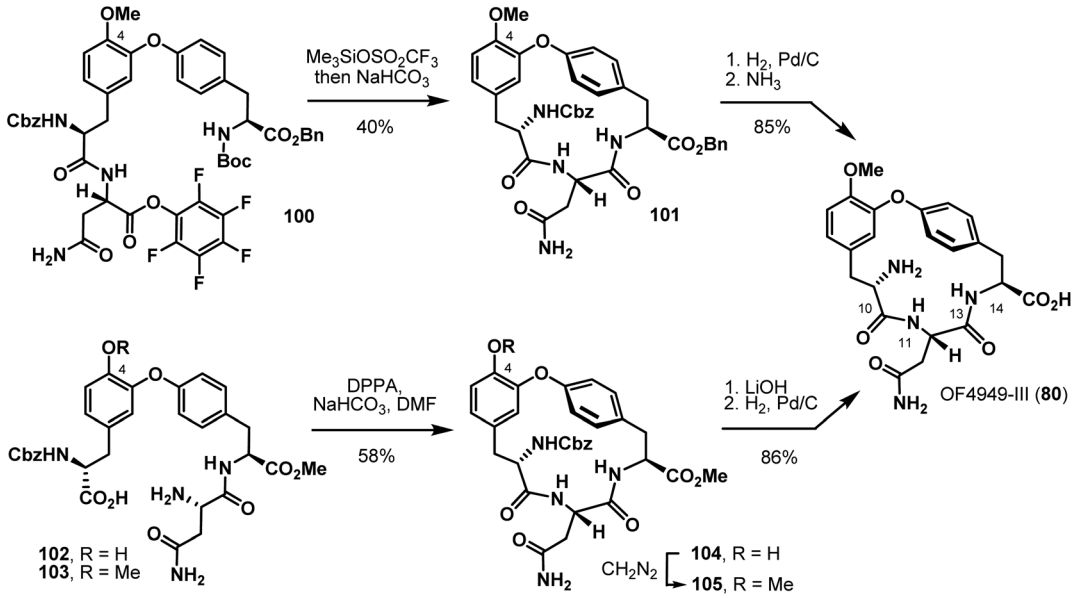


Scheme 12 S_NAr macrocyclization of the π-arene complex **97**.

partners are placed in close proximity by non-covalent interactions, like π,π-stacking, intramolecular hydrogen bonding, and attractive electrostatic interactions of the electron-rich phenol ring with the electron-deficient chlorobenzene–ruthenium complex, thus being conducive for the ring formation to occur. The same strategy was used in the preparation of the para-metacyclophane natural product K-13 (**79**).[261]

Enlargement of the cycloisodityrosine scaffold by one amino acid resulting in the formation of the corresponding tripeptides, such as K-13 (**79**) and OF4949-III (**80**, see Fig. 8), reduces the transannular strain significantly compared to their dipeptide analogs. The less strained, but still conformationally stable cyclic framework in compounds, such as **79** and **80**, allows for the application of more conservative macrocyclization approaches towards these substrates. Even ring closure *via* peptide-bond formation, which could not been realized for the 14-membered systems, was possible, *e.g.* in the synthesis of OF4949-III (**80**). Schmidt accomplished the construction of the peptide ring in natural product **80** in a two-step conversion (Scheme 13, top).[267] After cleavage of the *N*-Boc protecting group of **100** in acidic medium, the amino compound was added into a $NaHCO_3$ solution where the free amino group reacted immediately with the activated carboxyl group of the pentafluorophenyl ester to obtain cyclophane **101** in 40% yield. Subsequent removal of the Cbz-group and saponification of the benzyl ester gave **80** in eleven linear steps.

Macrocyclization was performed by construction of the *C*-10–*N*-11 amide bond in the synthesis of OF4949-III (**80**) by Boger's group (Scheme 13, bottom).[158] In this synthesis the carboxyl function in **102** was *in situ* activated by its reaction with DPPA under basic conditions followed by immediate formation of the amide bond giving the cyclic compound **104** in 58% yield. *O*-Methylation of the phenol and subsequent deprotection of the acid and the amino group yielded target compound **80**. During this synthesis of **80** as well as the application of this strategy to access K-13 (**79**) by the same group,[158] it appeared that the ring



Scheme 13 Construction of the macrocycle in OF4949-III (**80**) by formation of the *C*-13–*N*-14 and *C*-10–*N*-11 amide bond, respectively.[158,267]

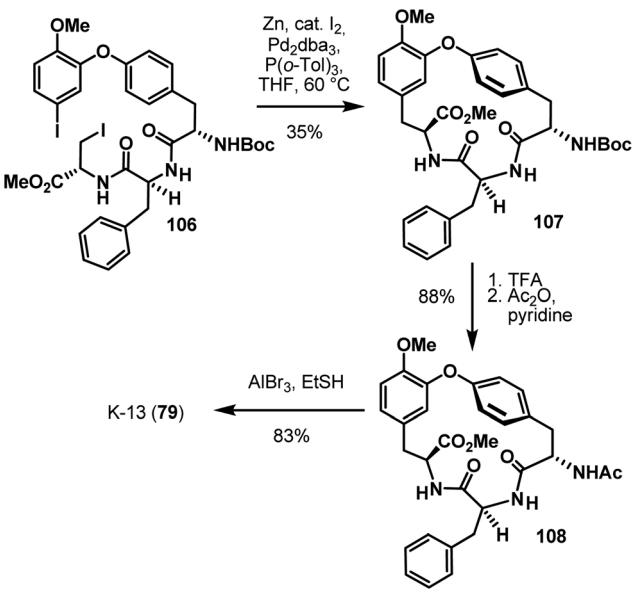
closure event is very sensitive towards the substituent at the *C*-4 oxygen function. Performance of the cyclization with the corresponding *O*-methyl derivative **103** resulted in an unexpected rate deceleration for the formation of **105**. This observation is explained by the fact that the methoxy group enforces the adoption of conformers in the transition state, which disfavors macrolactamization, while the hydroxy function leads to the opposite result, the preferential formation of conformers facilitating ring closure. Giving this example, it is again demonstrated that small structural changes, even at remote sites of the molecule, can have a huge impact for the assembly of the macrocyclic skeleton of cyclophanes. Further approaches to cyclotripeptides following the retrosynthetic scissions of both amide bonds, were reported, *e.g.* for the syntheses of renieramide (**61**, Fig. 7), by the groups of Lygo[268] and Jackson.[269]

A completely new strategy to build up the macrocycle in the preparation of the angiotensin-converting-enzyme (ACE) inhibitor K-13 (**79**) was envisaged by Jackson *et al.* (Scheme 14). In their synthetic entry, macrocyclization was achieved by *de novo* synthesis of the tyrosine amino acid concomitant by closing the tripeptide ring.[269] This sequence was realized by utilizing an intramolecular Negishi alkyl–aryl cross coupling reaction of the diiodo compound **106** using Pd_2dba_3 and P(*o*-Tol)$_3$ as the catalytic system. The cyclic ether **107** was obtained in moderate yield (35%). Functional group manipulations afforded the natural product **79** in three further steps *via* the *N*-acetyl derivative **108**.

3.2.3 4-Hydroxyphenylglycine-containing cyclic natural products. Cyclopeptides containing the non-proteinogenic amino acid 4-hydroxyphenylglycine (**109**, 4-Hpg, Fig. 9) have emerged as a growing class of highly bioactive natural products. Lipohexapeptides,[270,271] such as the arylomycins **110** as well as glycopeptides, like *e.g.*, teicoplanin (**111**),[172,272–275] belong to this class of antibiotics and have been the focus of many excellent research programs dealing with their biological activity, medicinal relevance, and total synthesis.[174,175,276–278]

The synthetic accessibility of many cyclic natural products containing a peptidic *endo* aryl–aryl linkage has, in general, been already restricted by the lack of general and efficient methods for the stereoselective construction of this structural motif due to the inherent strain associated with the small cyclophane core.[279] With a 4-Hpg unit present in the amino acid chain, the methods available for macrocyclization are even further limited, as the stereocenter in 4-Hpg is very prone to racemization. This difficulty has triggered the search for mild strategies towards these target molecules, which have already been summarized in several excellent review articles.[151,172,174,175,276,278–282]

The arylomycin-type lipopetides display only moderate antibacterial activity against several Gram-positive human



Scheme 14 Ring closure by Negishi cross coupling reaction exemplified in the synthesis of the ACE inhibitor K-13 (**79**).[269]

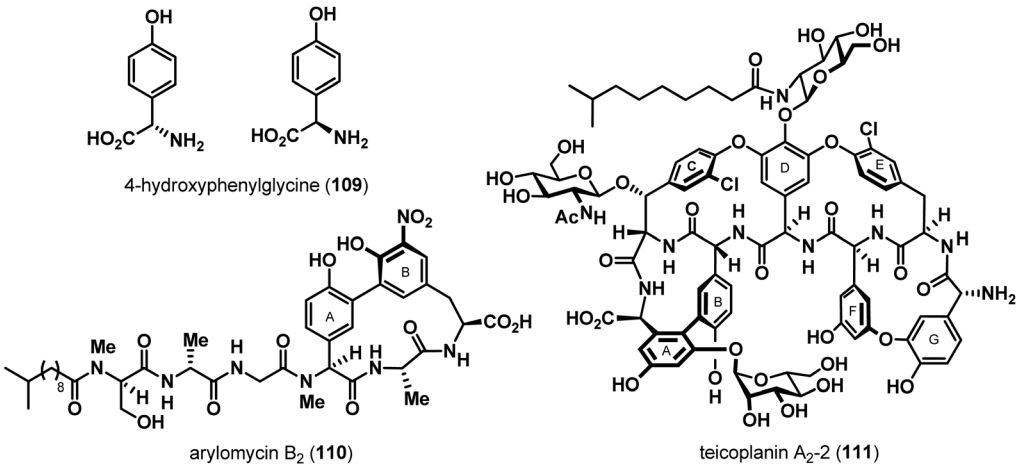
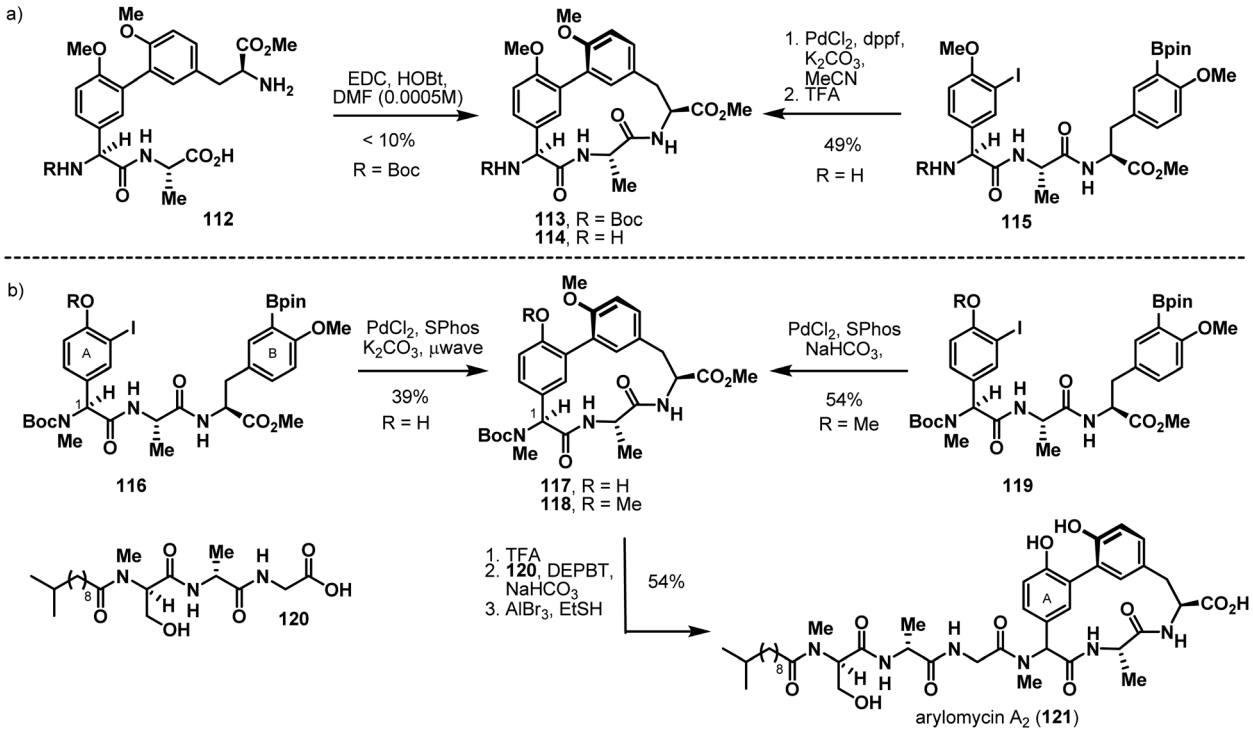


Fig. 9 Both naturally occurring enantiomers of 4-hydroxyphenylglycine (**109**) and a selection of cyclic peptides containing this racemization-prone amino acid: arylomycin B_2 (**110**) and teicoplanin A_2-2 (**111**).

pathogens,[270,271,283–285] but investigations on their mode of action showed that they are potent inhibitors of bacterial signal peptidase I (SPase I), an enzyme responsible for bacterial vitality and growth.[286–288] This novel mechanism of action, however, makes them excellent lead compounds for the development of new drugs, especially against multi-resistant, fatal bacterial strains. From a structural point of view, the 4-Hpg fragment in lipohexapeptides of the arylomycin-type forms, together with one tyrosine and one alanine building block, a metametacyclophane. Because of the high ring strain in the 14-membered macrocycle, rotation of the biaryl axis is restricted, for which reason arylomycins appear as a mixture of two atropdiastereomers in NMR. Interestingly, X-ray structure analysis of a SPase-arylomycin A_2 complex showed that only the *P* atropisomer can bind to this enzyme and is therefore the active species. The groups of Romesberg[283] and Zhu[289,290] consecutively reported on the synthesis of arylomycin A_2 (**121**) using a similar strategy in the key step (Scheme 15). First attempts by Romesberg and coworkers to achieve macrocyclization by peptide bond formation were not successful. Under already optimized conditions (EDC, HOBt, Scheme 15a, left) a mixture of different cyclic compounds was obtained with the desired product present in <10%. Furthermore, the reaction had to be conducted under very high dilution (0.0005 M), which prevented the application of this strategy on large scale. Since ring closure by macrolactamization turned out to be a problem in the preparation of cyclophane **113**, attention was shifted to use a Suzuki–Miyaura reaction for the linkage of the two ends in compound **115**. Therefore, pinacol boronic acid ester **115** was subjected to cross coupling conditions with $PdCl_2$ and dppf as the catalytic system and K_2CO_3 as the base, giving the key intermediate **114** in 49% yield (Scheme 15a, right). In this case, the yield was independent from the concentration of the reaction mixture, which points at a conformational preorganization of starting material **115** conducive for the intramolecular reaction.[155]

Following Romesberg's work, who employed the same strategy later to access analogs of arylomycin A_2 (**121**) for studies of the structure–activity relationship and mode of action of these compounds,[288,291,292] Zhu prepared arylomycin A_2 (**121**, Scheme 15b)[289,290] and B_2 (**110**) at the same time.[290] In the macrocyclization step, they initially used boronic acid ester **116** bearing an unprotected hydroxy substituent at ring A as the cyclization precursor, as it was assumed that the presence of a phenol moiety would minimize the risk of epimerization caused by the base needed during the cross coupling reaction. The best yields (39%) of macrocycle **117** without any observable epimerization were obtained applying Pd(II) with SPhos as the ligand and K_2CO_3 as the base under microwave irradiation. Parallel attempts to perform the Suzuki–Miyaura reaction with the corresponding *O*-methyl ester **119** as starting material indeed resulted in better chemical yields, but always along with the diastereomer having the opposite absolute configuration at *C*-1. The amount of this epimer was minimized to 9% by switching to a weaker base, thus giving compound **118** in 54% when $NaHCO_3$ was used. It is noteworthy that the ring-closing event occurred under complete substrate-control thus delivering solely the *P*-configured atropdiastereomer of **117** and **118**. After removal of the Boc-protecting group the lipopeptidic side chain was installed under standard peptide coupling conditions. Final *O*-demethylation under Lewis acidic conditions yielded the natural product arylomycin A_2 (**121**).

With vancomycin (**9**, see chapter 1, Fig. 2) being the most prominent member, the glycopeptides have been one of the most intensely studied family of natural products in the last decades.[174,175,276–278] As the antibiotic of last resort, **9** is applied clinically to treat *i.a.* methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[173,175,278,293] Recently described resistances of *Enterococci* (VRE) and *S. aureus* (VRSA) against this drug,[173,175,294–296] however, has urged the development of a new generation of active agents based on the cyclopeptidic structure in industry as well as in academia.[278] The assembly of the heptapeptidic backbone in several highly strained rings, *e.g.* three in vancomycin (**9**) and four in teicoplanin (**111**, Fig. 9), results in a very rigid central, axial and planar chiral three-dimensional structure of the glycopeptides, which accounts for their pronounced bioactivity.[297] In principle, the glycopeptides can be divided into three different subfamilies in which the five "western" amino acid modules are aromatic and identical in

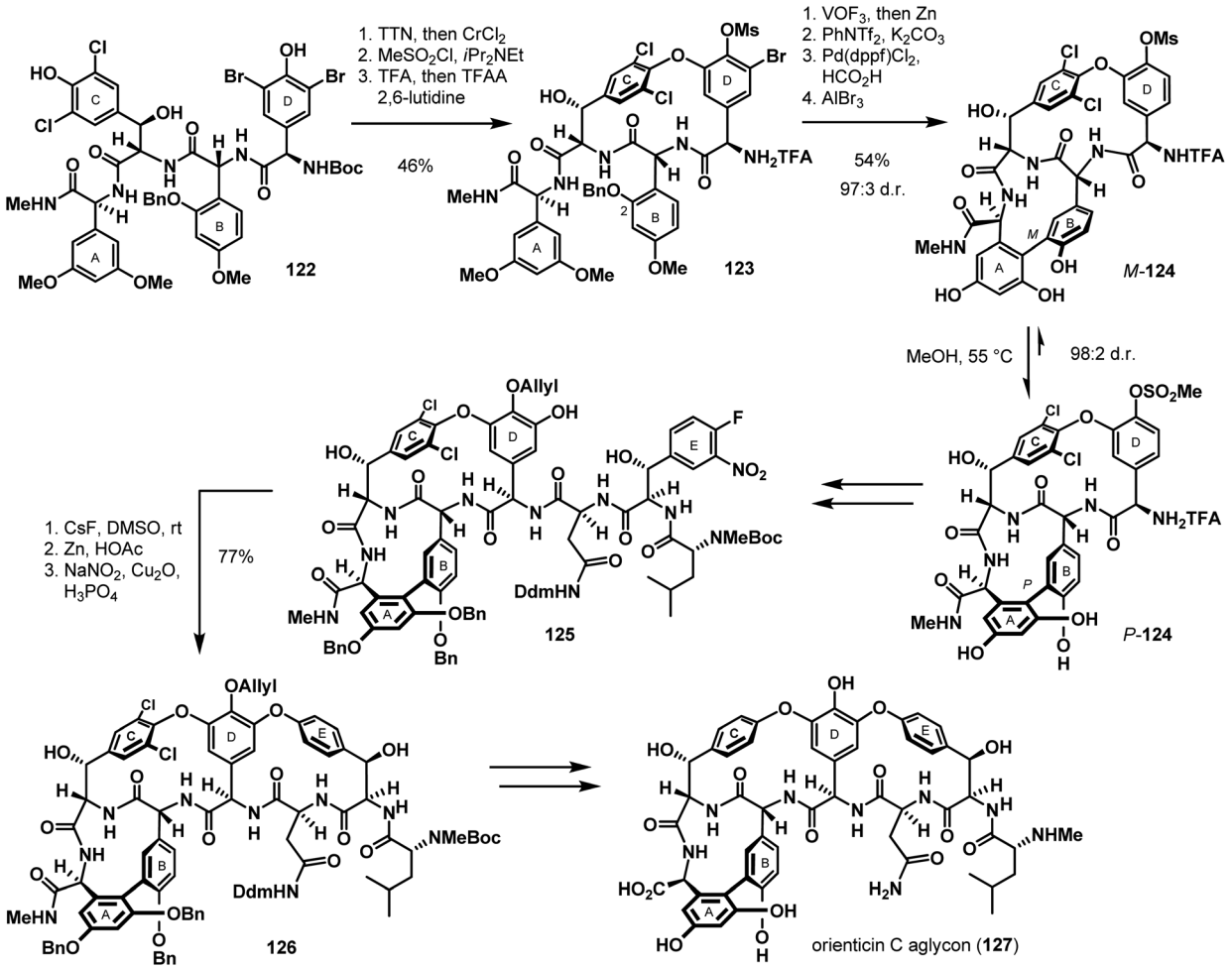


Scheme 15 Total synthesis of arylomycin A_2 (**121**) by a) Romesberg[283] and b) Zhu.[289,290]

almost all substrates. The remaining two "eastern" amino acid building blocks are aliphatic, normally leucine and asparagines, in the vancomycin-type representatives, like *e.g.* leucine and asparagines in vancomycin (**9**), while avoparcin-type metabolites have 4-Hpgs in this position. Teicoplanin (**111**) belongs to the ristocetin subspecies, which bear an additional, but flexible 14-membered macrocycle (metametacyclophane) with another aryl–aryl ether bond (ring FG) together with a fatty acid side chain attached to the sugar moiety. Because of the numerous synthetic efforts towards these natural products and their summary in several review articles[172,174,175,276,278–282] we will concentrate here on the discussion of only one selected example per macrocyclization methodology.

The first total synthesis of a glycopeptide was achieved by Evans and co-workers with the preparation of the orienticin C aglycon (**127**), which resembles the overall vancomycin core structure but lacks the chloro substituents at ring C and E. As for the cycloisodityrosine-containing compounds, such as piperazinomycin (**73**, *cf.* chapter 3.2.1) or RA-VII (**78**), ring closure of the 16-membered rings CD and DE was not successful *via* macrolactamization.[223,225] Therefore, Evans made use of another strategy choosing the *endo* aryl–aryl ether as well as the biaryl axis as the sites for macrocyclization (Scheme 16). Since the biaryl-containing cyclic tripeptide (ring AB) by itself exists as a mixture of atropisomers and amide rotamers, which was expected to make the following sequence more complicated, a reaction sequence for the construction of **127** was envisaged in which the macrocycle containing the CD ring was formed prior to the coupling of aryl ring A with B in order to rigidify the whole system.[298] Application of the biomimetic TTN-promoted oxidative cyclization developed by Nishiyama and Yamamura[228] (also *cf.* Scheme 8, chapter 3.2.1) proved to be efficient in the construction of the CD ring starting from the linear dichloro precursor **122**. Subsequent *O*-mesylation of the phenol group to enhance the oxidation potential of ring D in comparison to ring A and B in order to avoid side reactions in the following oxidative biaryl coupling reaction gave the TFA salt **123** in good yield (46%) over three steps. V(v)-induced cyclization of **123** with concomitant cleavage of the *O*-benzyl group gave after reductive work-up the corresponding bicyclic tetrapeptide in a 97 : 3 mixture of diastereomers, unfortunately in favor of the unnatural *M*-atropisomers. The selection for the kinetic product as the dominating epimer is caused by an A(1,3) interaction of the *ortho* oxygen function of ring B (*C*-2) and the proximal stereogenic center.[299] Complete removal of the *C*-2 oxygen substituent in ring B was achieved by triflation followed by Pd-catalyzed hydrogenolysis. Exhaustive *O*-demethylation then afforded the bicyclic tetrapeptide *M*-**124**, which was isomerized by heating a methanolic mixture of *M*-**124** to 55 °C. This thermal equilibration delivered *P*-**124** as the exclusive diastereomer.

As formation of the last macrocycle (ring DE) turned out to be inefficient (<20% yield) using oxidative conditions[300,301] Evans evaluated the use of the S_NAr reaction,[300] which turned out to be efficient in studies towards the preparation of vancomycin (**9**) reported by Zhu[302,303] and Boger.[304,305] The cyclization proceeded smoothly upon treatment of fluorobenzene **125** with CsF in DMSO at room temperature (90% yield). The nitro substituent was removed in a three step reduction/diazotation/reduction sequence to afford the carbon skeleton **126** of orienticin C in 77% yield. Deprotection and dechlorination finalized the total synthesis of the natural product aglycon **127** in five further steps.



Scheme 16 Key steps of the synthesis of orienticin C aglycon (**127**) by Evans *et al.*[298,300]

With this strategy in hand, Evans *et al.* also pursued the total synthesis of vancomycin aglycon (**136**, Scheme 18),[306] which imposes an additional challenge due to the three stereochemical elements of atropisomerism (planar and axial chirality) arising from hindered rotation of each tripeptide ring. After intensive studies on the configurational stability of the macrocyclic fragments by Evans[307] and Boger,[305] Evans readjusted the order of introduction of the macrocycles into the molecule by constructing ring AB first, followed by assembling rings CD and DE (not shown). This new sequential arrangement provided the optimal strategy to achieve good stereoselectivities under substrate control.

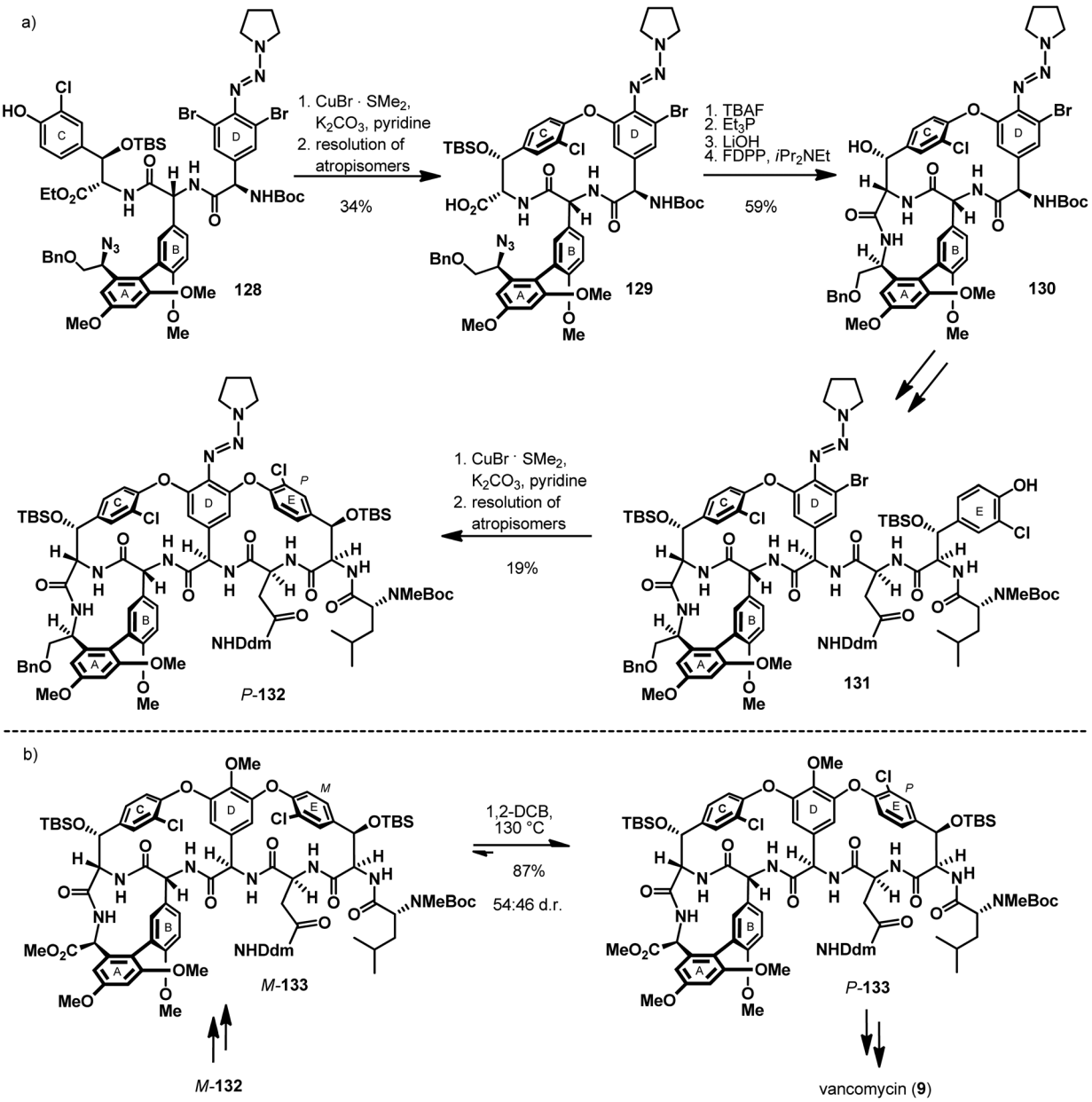
At the same time, Nicolaou and co-workers presented their pathway towards vancomycin (**9**, Scheme 17a).[308–314] Here, the biaryl ether tripeptide fragment (ring CD) was established first by exposure of triazene **128** to copper(I) bromide under basic conditions. This procedure resulted in the formation of the aryl–aryl ether **129**, but unfortunately without any stereocontrol (1 : 1 d.r.). Attempts to convert the unnatural *M*-isomer into the desired *P*-stereoisomer of **129** by thermal isomerization were not successful and thus optically pure **129** had to be gained by chromatographic separation of the two epimers giving **129** in 34% yield. Atroposelective cycloetherifaction of a ring-CD containing derivative, which potentially can be used in an atroposelective route to vancomycin (**9**), was achieved by Nicolaou in 2002 (not shown).[315] There, the Ullman-type reaction shown in Scheme 17 was conducted with a substrate bearing *ortho* to the chlorine substituent at aryl C a bulky OTBS group. This reaction gave the corresponding cyclic ether in excellent yield (94%) and as a single atropisomer. Removal of the silyl-protecting group and subsequent reduction of the azide as well as hydrolysis of the ethyl ester function in **129** set the stage for the second ring closing event, the preparation of the AB-ring subunit. It is noteworthy that Nicolaou did not utilize the biaryl axis of benzene ring A and B to build the macrocycle. Instead he employed Schmidt's amide bond formation procedure (*cf.* chapter 3.3.1, Scheme 6) to achieve the synthesis of the biaryl containing fragment, which implied an *in situ* activation of the acid function as the corresponding pentafluorobenzene ester towards nucleophilic attack. Upon exposure to Hünig's base, the bicyclic compound **130** was obtained in excellent yield (59%) over four steps. After several functional group manipulations and attachment of the peptide chain containing the ring E fragment, the second *endo* biaryl ether linkage was set up with cyclization precursor **131** again applying modified Ullmann conditions. Also in this case, ring closure occurred in poor stereoselectivity (1 : 3 d.r.) with the undesired *M*-conformation at the newly created planar-chirality element being the dominating species.

Separation of the two epimers was conducted by column chromatography to yield the key intermediate *P*-**132** of the vancomycin synthesis in 19% yield.

While atropisomerization of the 'wrong' diastereomer of **132** failed, the adequate supply of material exhibiting the natural configuration at ring E, was, however, guaranteed by recycling the unnatural epimer at a later stage of the synthetic pathway (Scheme 17b). Heating the advanced substrate *M*-**133** to 130 °C in 1,2-dichlorobenzene (1,2-DCB) transformed the pure *M*-atropisomer into a 54 : 46-mixture of *M*- and *P*-**133** in 87% combined yield. With this isomerization procedure the possibility of converting almost the complete material into the natural atropisomers *P*-**133** became virtually available by an iterative thermal equilibration and chromatographic resolution sequence.

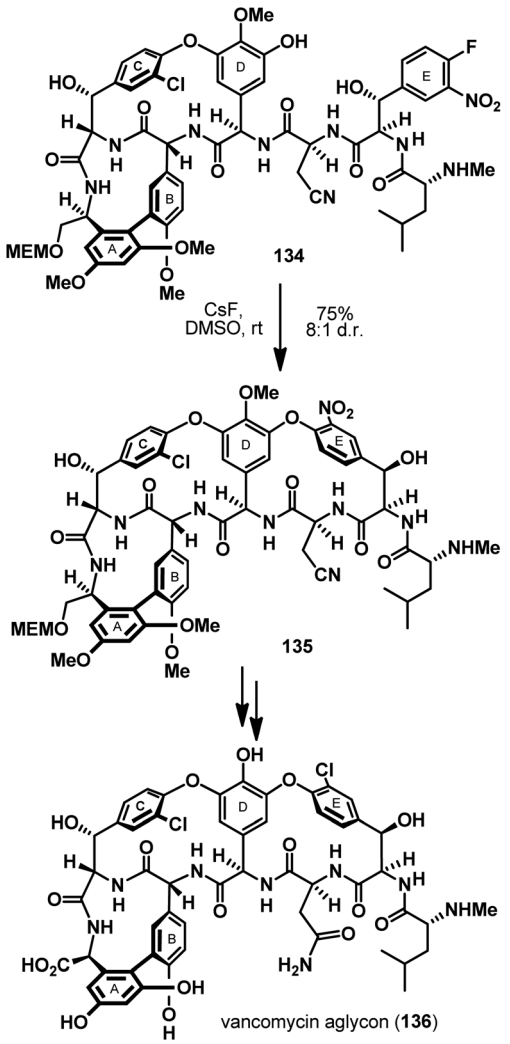
In 1999, Boger's group published the third approach to the vancomycin aglycon (**136**), in which they integrated already successfully applied strategies in their key steps, such as the formation of ring CD and DE *via* nucleophilic substitution and macrolactamization to furnish the biaryl containing AB-subunit.[316,317] Especially the use of the S_NAr reaction, which proceeds under very mild conditions (CsF, rt), to close the last macrocycle from starting material **134** turned out to be beneficial to the stereochemical outcome of the reaction (Scheme 18).

Product **135** was obtained in 76% yield as an 8 : 1-mixture of epimers in favor of the desired *P*-atropisomer. In eleven further steps Boger converted compound **135**, which already shows the complete carbon skeleton of the natural product, to the vancomycin aglycon (**136**).



Scheme 17 a) Macrocyclization steps in the total synthesis of vancomycin (**9**) by Nicolaou and b) atropisomerization of the advanced intermediate **133**.[313]

A small subset of natural products resembling the peptide cores of the glycopeptides are the chloropeptins I (**62**) and II (**137**, complestatin, Scheme 19).[169,170,318–322] These compounds are biosynthetically derived of a heptapeptide chain, featuring a tryptophan, a tyrosine and five heavily modified (*i.e.* chlorinated and/or oxidized) 4-Hpg residues. Two cyclophane ring systems are formed by a biaryl ether bond between the tyrosine and the central 4-Hpg unit (BD ring) and an aryl–aryl bond between the latter and the tryptophan building block (DF ring). However, these compounds are not further functionalized by glycosylation, leading to a significant change in bioactivity from antibacterial to antiviral. Remarkably, this change in activity can be achieved artificially by removing the sugar portions from glycopeptides or, *vice versa*, by attaching such moieties to the chloropeptins.[323] The only structural difference between **62** and **137** is the position of the phenyl-indole junction in the DF ring (Scheme 19). It is interesting to note that the higher ring strain in **137** allows facile acid promoted conversion of this metabolite to the less strained **62** with full retention of the axial *M*-configuration.[324] Compounds **62** and **136** have still been shown to be actual natural products.[318]



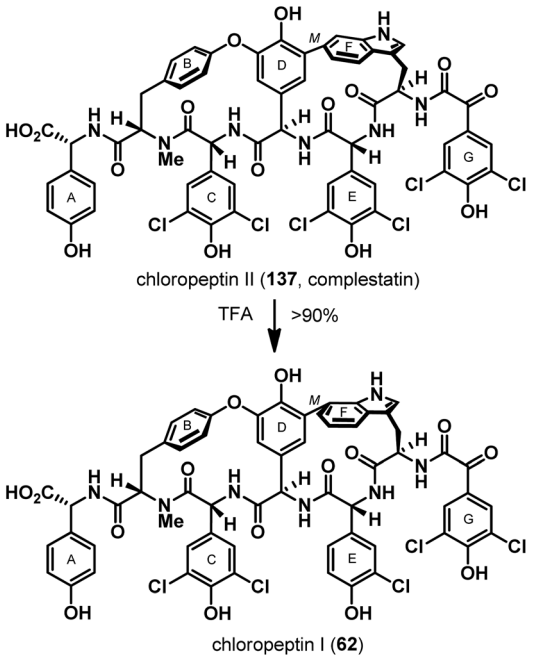
Scheme 18 Formation of the ring DE fragment in Boger's synthesis of vancomycin aglycon (**136**).[316,317]

The first group to successfully tackle the total synthesis of a member of this group of natural products was Hoveyda *et al.*, who completed their route to **62** in 2003.[325] The synthetic strategy was strictly linear and started with the assembly of the BCD ring system (Scheme 20). For formation of the cyclophane unit, tripeptide **138** was first treated with $NaIO_4$ to furnish the respective boronic acid which was further subjected to Cu-mediated synthesis of biaryl ethers following the Chan–Lam–Evans protocol[239–241] to give **139** in 50% overall yield. Optimization of the coupling conditions to this particular substrate was achieved by adding ten equivalents of MeOH to the reaction mixture, thereby potentially forming the boronic dimethyl ester *in situ* and/or enhancing the solubility of the Cu salt. Subsequent stepwise attachment of the amino acid building blocks A, E, and F gave compound **140**, the precursor for DEF-ring formation by Stille cross coupling. The bicyclic product **141** was obtained in 38–42% yield as a single stereoisomer. Important for the success of this coupling reaction was the presence of collidine that most likely stabilized the active Pd species. The total synthesis of **62** was finalized by *N*-deprotection, attachment of building block G and final saponification of the methyl ester (not shown).

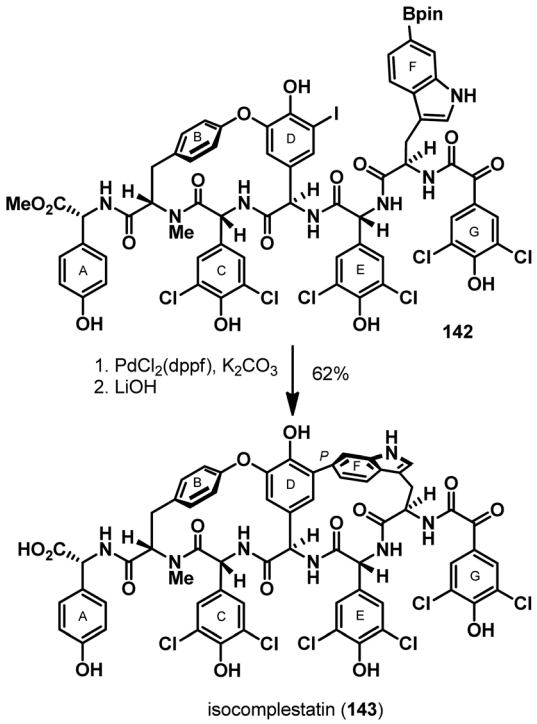
In 2005 Hoveyda *et al.* also reported on the total synthesis and stereochemical revision of isocomplestatin (**143**), thereby providing evidence that this compound has axial *P*-configuration, while the natural product chloropeptin II (**137**) is indeed *M*-configured. The western portion of **143** was prepared following their previous route to **62** (Scheme 20)[325] and was further extended to the full-length monocyclic precursor, boronic ester **142** (Scheme 21).[326] In contrast to their previous Stille protocol, cyclophane formation was this time achieved by intramolecular Suzuki–Miyaura coupling, which upon subsequent saponification furnished target compound **143** as a single diastereomer in 62% yield.

Interestingly, the cross coupling reaction succeeded with perfect stereocontrol but with opposite stereochemical outcome when compared to the enzymatic biaryl bond formation observed in nature. This phenomenon was investigated in more detail by Zhu and co-workers. In their initial approach to this class of natural products, they first constructed the BCD cyclophane by means of highly regioselective intramolecular S_NAr reaction of **144** to give **145** in 72% yield (Scheme 22).[327] The latter was further elaborated into **147** and its *O*-TBS-protected derivative **146** to test previously observed effects of phenol group protection on the atroposelectivity of the subsequent Suzuki–Miyaura coupling.[328] In this case, however, protection did not have any stereochemical influence on the installation of the biaryl bond, which for both substrates, **146** and **147**, exclusively gave the *P*-configured atropdiastereomer **148** and **149** in 66% and 52% yield, respectively. *O*-Deprotection of **148** furnished **149** in 90% yield. Most interestingly, when altering the configuration of the amino acid building block C from its natural *R*-configuration to *S*, the atroposelectivity of the biaryl bond forming reaction was inverted, thus providing synthetic access to the respective axially *M*-configured *epi*-complestatin methyl ester and *epi*-isocomplestatin methyl ester (not shown).[327]

As a consequence to these studies, Zhu *et al.* altered the order of cyclophane ring formation in their total synthesis of chloropeptin II (**137**).[329] The aryl–aryl bond was thus introduced first into substrate **150** by Suzuki–Miyaura cross coupling in 66%



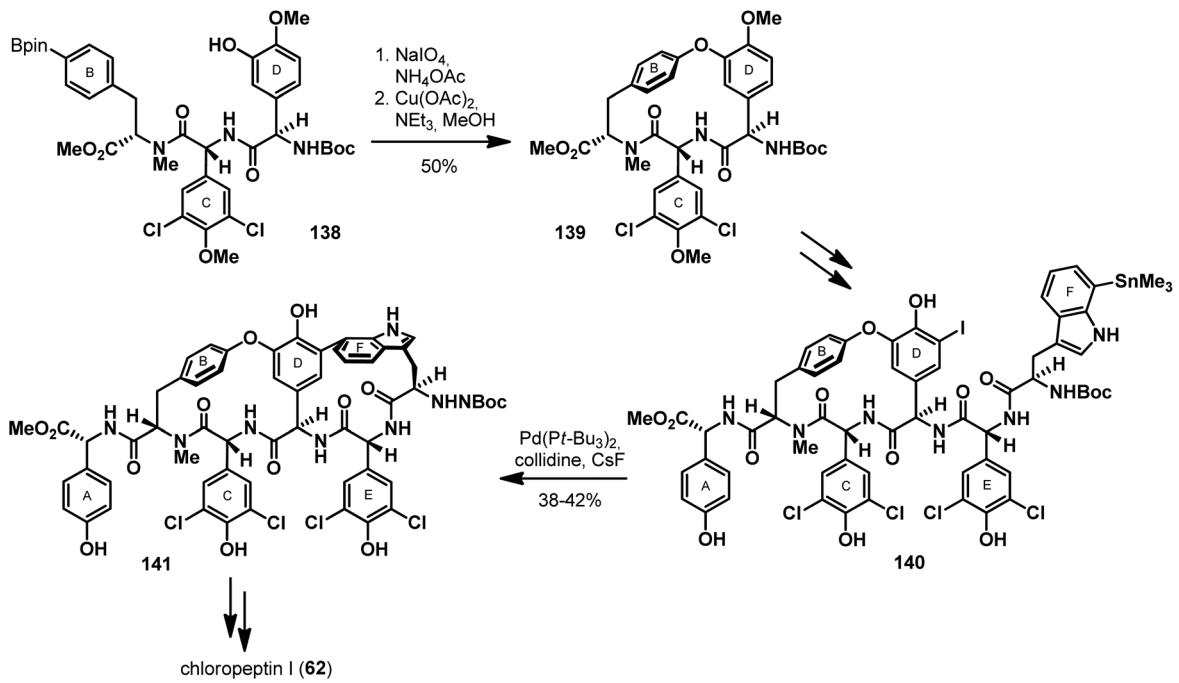
Scheme 19 Acid-catalyzed rearrangement of chloropeptin II (**137**) to chloropeptin I (**62**).



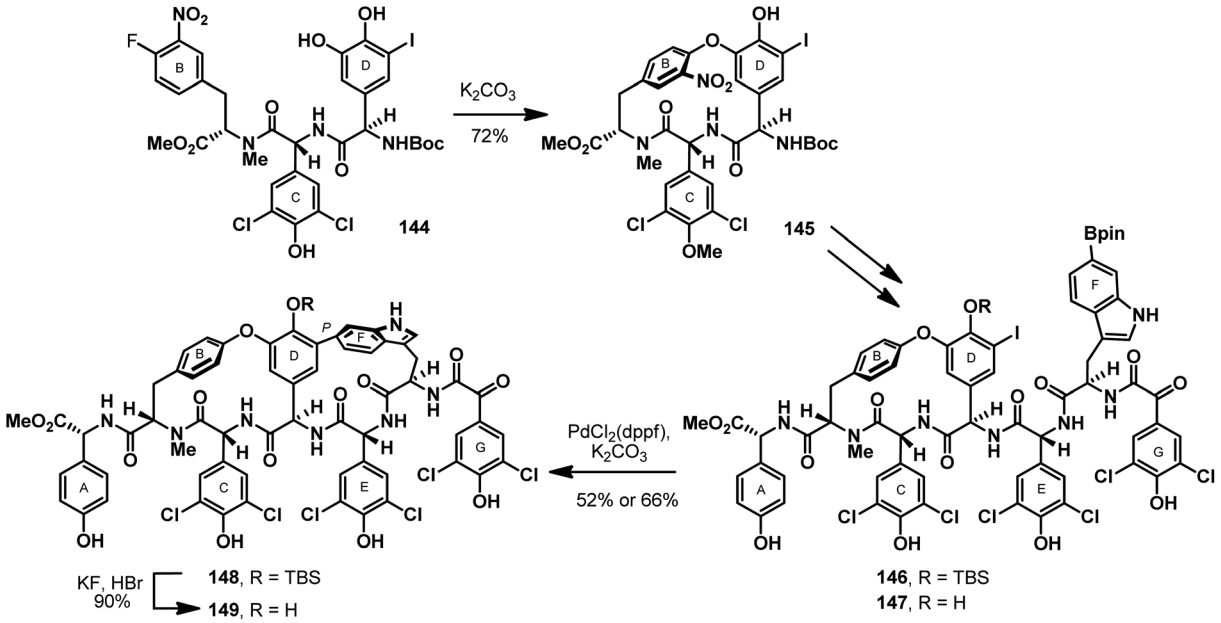
Scheme 21 Suzuki–Miyaura coupling in the synthesis of isocomplestatin (**143**).[326]

yield with exclusive formation of the desired atropdiastereomer **151** (Scheme 23). This compound was converted into **152** by a series of protective group modifications and highly convergent introduction of the still missing three amino acids as the respective tripeptide. **152** was *O*-desilylated and readily cyclized to give the desired **153** in 62% overall yield, which was further transformed into the natural product **137** by a series of functional group conversions and deprotection steps (not shown).

An innovative new approach to the construction of the biaryl bond containing DEF-macrocycle was developed by Boger in the course of the first total synthesis of chloropeptin I (**62**) and II (**137**) that was published in 2009,[330] even before Zhu's work described above. In their synthetic route, the biaryl bond of the eastern fragment was installed very early to give the alkyne



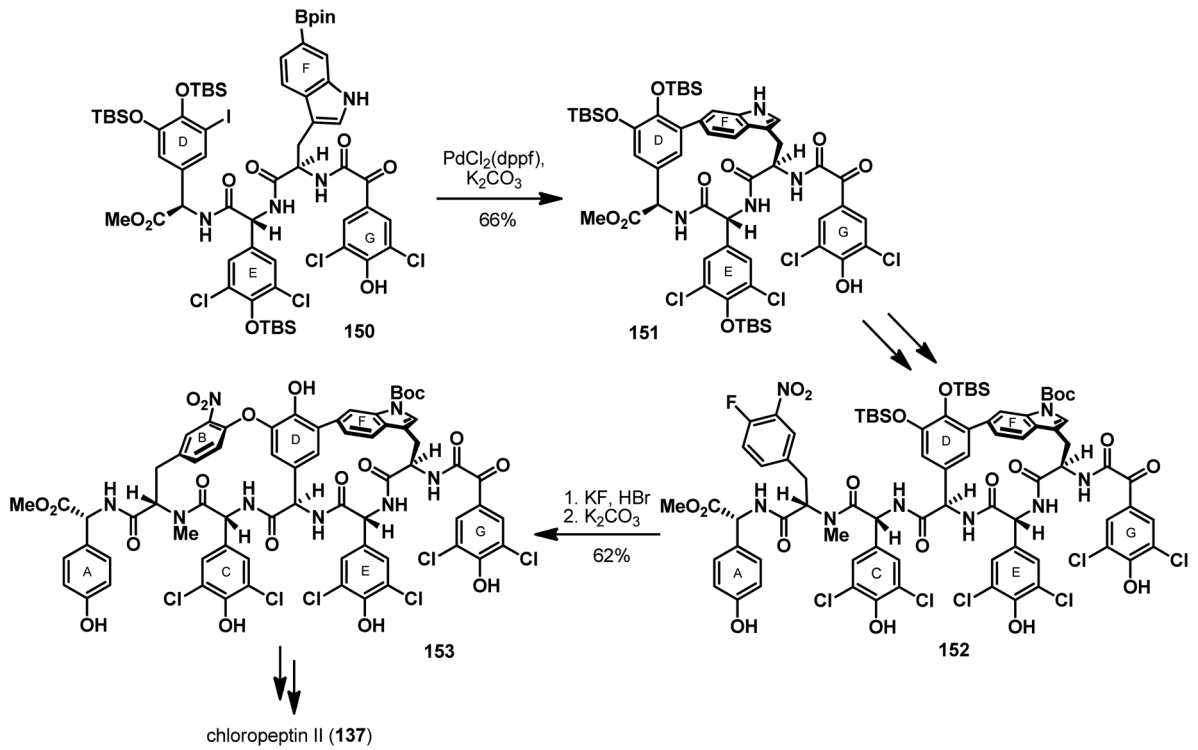
Scheme 20 Cyclophane ring forming key steps in the first total synthesis of chloropeptin I (**62**) by Hoveyda *et al.*[325]



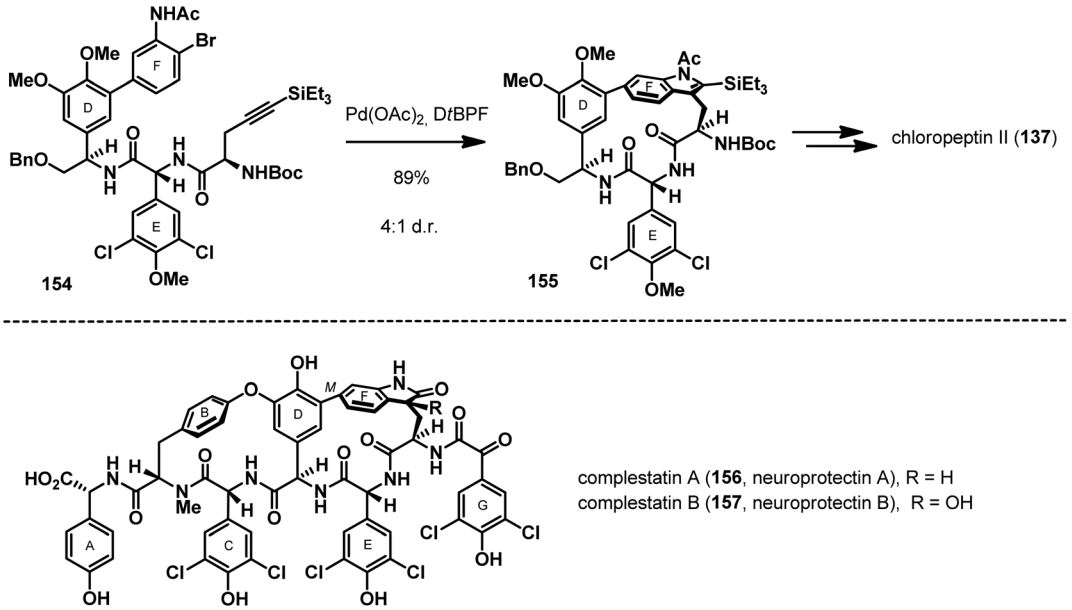
Scheme 22 Synthetic route to isocomplestatin methyl ester (**149**) by Zhu *et al.*[327]

containing biaryl **154**, the direct precursor for cyclophane formation (Scheme 24). Cyclization was achieved by a Larock indole annulation reaction,[331,332] leading to product **155** in 89% yield and in a diastereomeric ratio of 4 : 1 favoring the desired *M*-configured **155**. In the indole-forming cyclization step regioselectivity is thereby controlled by the steric bulk of the large terminal silyl substituent. Cyclophane **155** was transformed into the final product **137** in a series of further transformations involving a S_NAr-cyclization strategy for the construction of the biaryl ether bond.

Only about half a year later, Boger *et al.* reported on an even further improved synthetic access to **137**.[333] In this approach, the order of cyclophane ring formation was reversed. With the biaryl ether bond established prior to performing the Larock macrocyclization reaction, the latter occurred with perfect stereocontrol, exclusively leading to the desired *M*-atropodiastereomer



Scheme 23 Key steps in the total synthesis of chloropeptin II (**137**) by Zhu *et al.*[329]



Scheme 24 Intramolecular Larock annulation for macrocyclization in the total synthesis of chloropeptin II (**137**) by Boger *et al.*[330,333]

in 56% yield. This result is highly remarkable, as the stereochemical outcome of the Larock methodology is thus opposite to that obtained by late-stage construction of the eastern cyclophane unit *via* Stille or Suzuki coupling (see above). By further utilization of the Larock indole formation as the ring closing method, Boger and co-workers accomplished the preparation of the oxoindole analogs of chloropeptine II (**137**), complestatin A (**156**, neuroprotectin A) and B (**157**, neuroprotectin B).[334]

3.3 Pyrrolophanes

The prodigiosin alkaloids are a family of deeply red colored natural products isolated from a wide variety of bacteria, in particular *Streptomyces* and related actinobacteria.[335] These antibiotics have attracted huge interest due to their antimicrobial, cytotoxic, and antimalarial bioactivity[336–338] and their unique architecture.[335] Common to all prodigiosins is the pyrrolylpyrromethen chromophore with structural variations existing between members depending upon different alkyl substituents at one of the pyrrol rings. Of special structural interest are those family members showing an unusual pyrrolophane core, as exemplified by metacycloprodigiosin (**158**) and streptorubin (**159**, Fig.10). Because of their *meta*-bridged heterocyclic core structure, compounds **158** and **159** may also be considered as close structural relatives to the structurally unique alkaloid roseophilin (**160**),[335,339] which has inspired synthetic efforts of several research groups.[340–362] While Laatsch and co-workers already described the conformational stability of the *ansa*-system of **159** in 1991,[363] the stereochemistry of **159** was unambiguously elucidated for the first time simultaneously by Challis[364] and Thomson[365] twenty years later using extensive NMR studies combined with mutasynthesis and total synthesis, respectively. As a result, streptorubin B (**159**) isolated from *Streptomyces coelicolor* was determined to exist as a mixture of diastereomers with the (7'*S*, *anti*) isomer being the major component (88%).[364]

As the formation of the pyrrolylpyrromethen chromophore in general has been well established in the literature,[335,337,366–382] the inherent challenge in the synthesis of *m*-pyrrolophane-type prodigiosin antibiotics is the preparation of the *ansa*-core structure (Scheme 25).[335]

Fürstner and co-workers therefore targeted racemic cyclophane **165** featuring a Pt(II)-promoted cycloisomerization reaction to assemble the *meta*-bridged bicyclic system in a formal enyne metathesis.[383] Upon addition of catalytic amounts of $PtCl_2$ to enyne **161**, a skeletal rearrangement was observed, leading to the ring expanded product **162** in excellent 79% yield. This atom economic method turned out to be very efficient also on larger scale (up to 7.5 g) and allowed for the introduction of structural complexity into the system in only one step.[384] Selective conversion of the enone using Pd(0) in combination with Bu_3SnH gave the respective ketone, which was further reduced with $LiAlH_4$ to the corresponding alcohol **163**. Radical deoxygenation afforded the dihydropyrrole **164**, which was transferred into pyrrolophane **165** in an aromatization/deprotecting sequence induced by treatment of **164** with potassium 3-aminopropylamide (KAPA).

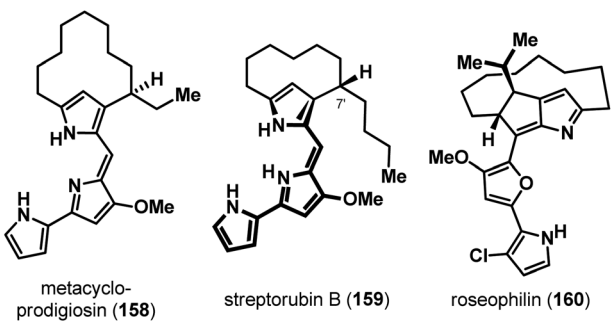
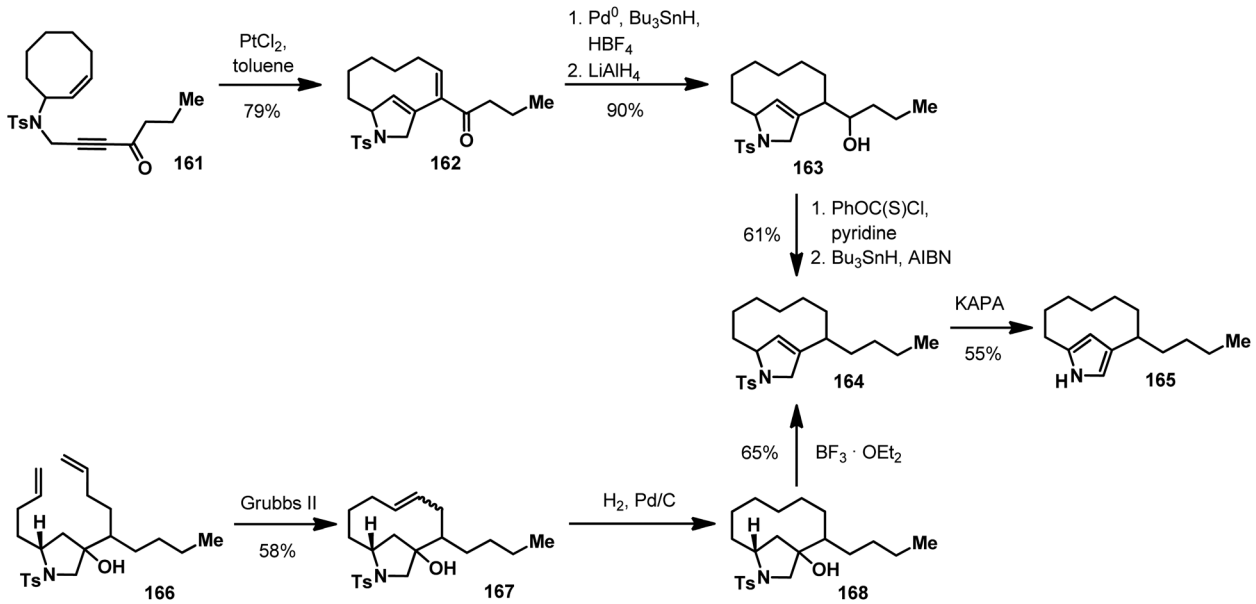


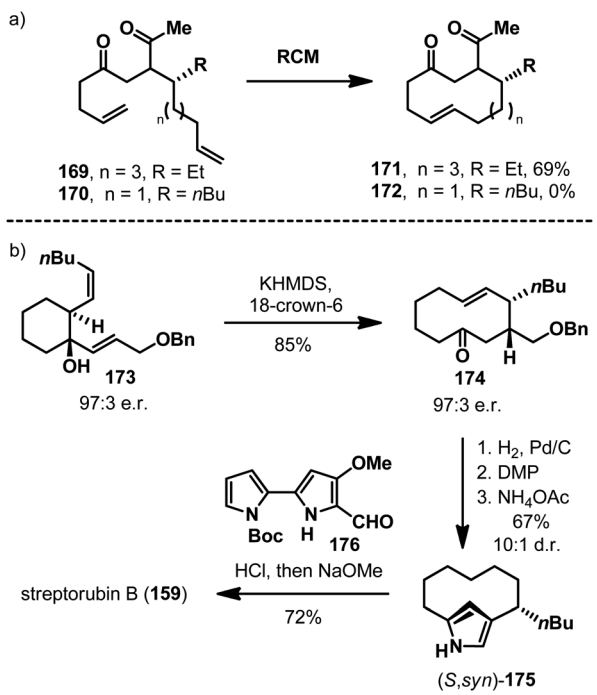
Fig. 10 Selected members of the prodiginine alkaloids: metacycloprodigiosin (**158**), streptorubin B (**159**), and roseophilin (**160**).



Scheme 25 Preparation of the pyrrolophane scaffold of streptorubin B (**159**) by Fürstner (top)[383] and Chang (bottom).[385]

Another approach to 'Fürstner's intermediate' **164** was reported by Chang *et al.* (Scheme 25, bottom).[385] Here, ring closure was achieved by metathesis of the prolinol derived compound **166**. Using the second generation Grubbs catalyst, the macrocycle was built in 58% yield. This reaction turned out to be very sensitive as already minimal variations of the reaction conditions (prolonged reaction time, elevated temperature, different solvents) resulted in the degradation or even inhibition of the generation of **167**. The dihydropyrrole **164** was finalized by hydrogenation of **167** and subsequent Lewis-acidic dehydration of **168**.

Thomson *et al.* initially attempted to access streptorubin B (**159**) with the same strategy, which had been proven before to be successful in the preparation of the conformationally flexible metacycloprodigiosin (**158**).[386] In the synthesis of **158**, the medium sized ring of **171** was forged in 69% yield (Scheme 26a) by RCM of **169** prior to the construction of the pyrrole unit using a Paal–Knorr reaction. Unfortunately, all efforts to get the corresponding streptorubin-type C_{10} ring **172** from diene **170** resulted only in a mixture of dimeric species. The reason for the failure of **170** to undergo ring closure under metathesis conditions is most likely due to the severely increased transannular ring strain in the ten-membered macrocycle **172** when compared to its twelve-membered analog **171**. Therefore, an alternative macrocyclization method had to be envisaged for streptorubin B (**159**).[365] The new key step comprised an anion oxy-Cope rearrangement to build the ten-membered macrocycle from the cyclohexanol **173**, which was easily accessible in four steps and in a good enantiomeric ratio (97 : 3).[365] Formation of ketone **174** was achieved by exposure of **173** to KHMDS and 18-crown-6 ether in 85% yield without loss of enantiomeric purity (Scheme 26b). After hydrogenolytic removal of the alkene accompanied by *O*-debenzylation, the formed primary alcohol was oxidized to the corresponding aldehyde using Dess–Martin periodinane (DMP) followed by a Paal–Knorr pyrrole condensation. This three-step sequence yielded the pyrrolophane skeleton in 67% yield in favor of the kinetic product (10 : 1 d.r.), the *syn* isomer of **175**. The synthesis of **159** was completed by attaching the dipyrrole moiety to (*S*,*syn*)-**175** in a biomimetic condensation reaction with the aldehyde **176** and subsequent deprotection of the pyrrole nitrogen. The product was obtained as a 10 : 1-mixture of isomers, of which the spectroscopic data of the major one corresponded to the unnatural *syn* diastereomer of **159**, which spontaneously isomerized upon standing to the more stable *anti* compound, streptorubin B (**159**).



Scheme 26 a) Attempts to form the ten-membered macrocycle in the synthesis towards **159** by RCM and b) enantioselective total synthesis of streptorubin B (**159**).[365]

3.4 Cyclic bisbibenzyls

Bisbibenzyl compounds (perrottetins, marchantins, riccardins, plagiochins)[93,387,388] are – at first sight – structurally simple phenolic natural products, which are found exclusively in bryophytes and often exhibit remarkable biological activities.[93,387,388] These molecules feature fascinating stereochemical properties, being on the verge of strain induced, geometrical chirality (*cf.* chapter 2), and thus constitute an optimal playground for studies of the boundaries of conformational stability.[95,98,389,390] Although different disconnection strategies, such as the construction of the biaryl or aryl–aryl ether bond or the *de novo* synthesis of one aryl fragment, have been envisaged in the synthesis of the conformational flexible representatives, like *e.g.*, riccardin C (**20**), the macrocyclization of rotationally stable compounds was limited to the formation of the ethyl bridge by Wittig olefination. As exemplified for the preparation of isoplagiochin C (**19**) by Speicher *et al.* (Scheme 27),[391] both ends of tetraaryl **177** were tied together upon exposure to NaOMe, which gave *O*-methylisoplagiochin C (**178**) in 74% yield. Subsequent *O*-demethylation was conducted with BBr_3 to obtain the desired natural product **19**. Other macrocyclic bisbibenzyls, like the presumably configurationally stable isoriccardin C (**179**) and riccardin D (**21**, see chapter 2, Fig. 5), were accessible following the same pathway.[392]

3.5 Longithorones

From the tunicates of the genera *Aplidium*, Schmitz and coworkers isolated in 1994 the structurally unique terpene longithorone A (**10**) in enantiopure form (Fig. 11).[47,49] This fascinating natural product is composed of seven fused rings bearing six, ten, and 16 atoms. It is assumed that **10** biosynthetically originates from two farnesyl-derived paracyclophane units, which are stitched together by both inter- and intramolecular Diels–Alder reactions.[47,393] This biosynthetic hypothesis was supported by the isolation of other prenylated benzoquinones from the same species,[48] which constitute possible biosynthetic precursors of **10**. These secondary metabolites include longithorone B (**180**) and C (**181**), which might comprise the monomeric [12]paracyclophane species involved in the intermolecular cycloaddition, and longithorone I (**182**), the shunt product of the first cycloaddition step.

Due to the huge ring strain caused by the cyclic arrangement in this natural products, all nine longithorone derivatives known today are rotationally restricted in their macrocyclic rings. The resulting atropisomerism in combination with numerous stereogenic centers in the dimeric structures enhances dramatically the challenges associated with the preparation of this class of compounds, especially when conducted in an enantioselective manner.

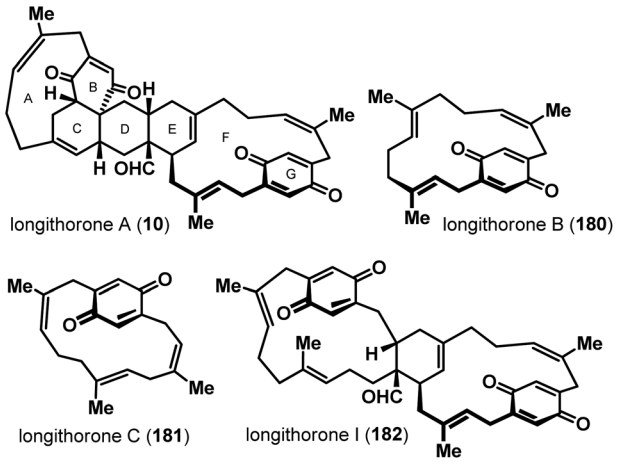
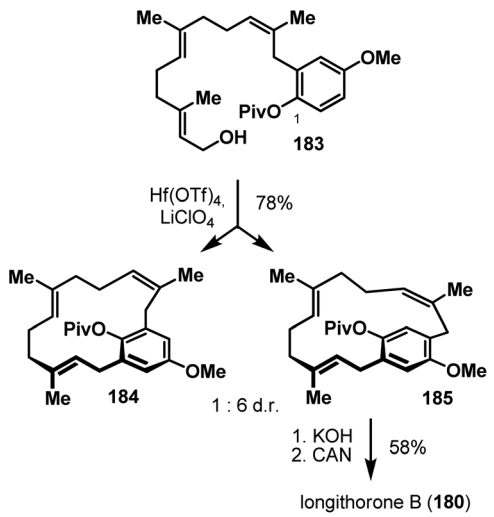
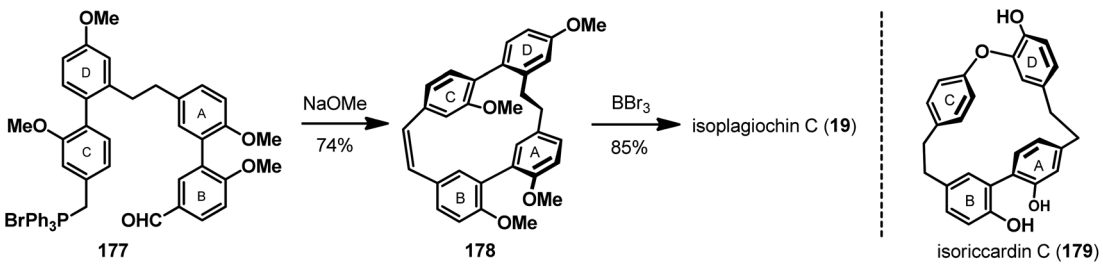


Fig. 11 The *p*-benzoquinone cyclophanes from *Aplidium longithorax*, longithorone A (**10**), B (**180**), C (**181**), and I (**182**).

The first synthetic route to longithorones was established by Kato with the synthesis of longithorone B (**180**, Scheme 28).[394] In the key step, $Hf(OTf)_4$ and $LiClO_4$ were added to the *O*-pivaloyl-protected aryl compound **183**. The intramolecular Friedel–Crafts alkylation reaction furnished the paracyclophane **185** in good 78% yield along with its metacyclophane regioisomer **184** in a 6 : 1 ratio. Interestingly, it turned out that the steric as well as the electronic properties of the protecting group at the *C*-1



Scheme 28 Preparation of longithorone B (**180**) by Kato.[394]



Scheme 27 Synthesis of cyclic bisbibenzyl natural products, like *e.g.*, isoplagiochin C (**19**) and isoriccardin C (**179**) by Wittig reaction.[391]

phenolic oxygen function have a decisive influence on the regioselectivity of the macrocyclization. If an electron-donating substituent, like *e.g.*, *t*-butyldimethylsily group, instead of the electron-withdrawing pivaloyl substituent was installed in cyclization precursor **183**, the formation of the corresponding TBS-ether cyclophane (not shown) led to 1 : 8 mixture in favor of the less constrained *meta* derivative. The regioisomers were separated by HPLC and transformed into the corresponding benzoquinones in a two-step hydrolysis/oxidation sequence, giving the natural product **180** in 58% yield.

With their synthesis of longithorone A (**10**), Shair *et al.* did not only succeed in the first, and yet only, enantioselective preparation of this structurally unprecedented compound, but, furthermore, provided support for Schmitz's provocative assumption on the biosynthetic origin of **10**.[395,396] The biosynthesis[47–49] inspired pathway chosen invoked an intermolecular as well as transannular Diels–Alder cycloaddition of two configurationally stable paracyclophanes **188** and **191** (Scheme 29), which resemble protected forms of the supposed biosynthetic starting materials for the intermolecular cycloaddition step, which may derive from longithorone B (**180**) and C (**181**) in nature. The formation of these two paracyclophane building blocks, **188** and **191**, was conducted *via* an ene–enyne ring closing metathesis in the key step in each case. To gain access to dienophile **188**, the cyclization precursor **186** was treated with the ruthenium catalyst under high dilution to give the twelve-membered macrocycle **187** in 47% yield and with a 3 : 1-mixture of *E* : *Z*-isomers (Scheme 29, top). Like the natural benzoquinone analogs **180** and **181**, the corresponding synthetic intermediate **188** also exhibited atropisomerism due to a restricted rotation of the aryl moiety. For the introduction of planar chirality into the cyclic system of **188**, a central-to-planar chirality transfer strategy was envisaged. Therefore, the benzylic silyl-protected alcohol function was strategically installed in enantiopure form, which transferred its stereochemical information during ring closure to give the desired atropdiastereomer in a moderate 5.2 : 1 ratio. Removal of the benzylic silyloxy group was achieved by ionic hydrogenation. Subsequent deprotection of the primary alcohol function and its oxidation to the corresponding aldehyde afforded **188** in 46% yield and as a single atropisomer.

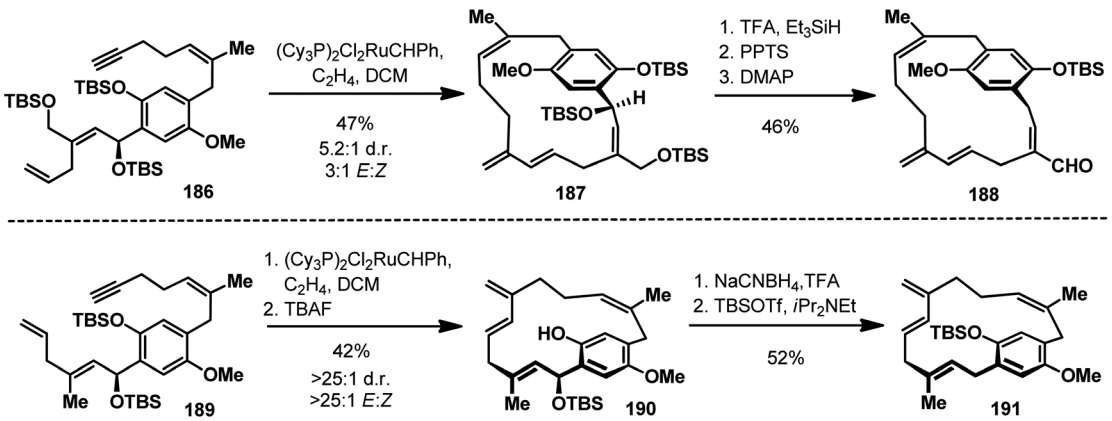
The second cycloaddition precursor, the diene **191**, was prepared using the same strategy as for **188** involving an atropdiastereoselective ene-yne metathesis,[397] here starting from compound **189** (Scheme 29, bottom). This time, the ring closure occurred with excellent selectivity (>25 : 1 d.r.; >25 : 1 *E* : *Z*) and under complete regiocontrol as no 1,2-disubstituted diene was detected,[398] which would produce a regioisomeric benzene compound tethered by eleven carbon atoms (not shown). It is anticipated that the exclusive formation of the twelve-membered scaffold is attributed to the reduced ring strain in the [12]paracyclophane **190** compared to its [11]cyclophane congener like **187**. Unfortunately, the metathesis was accompanied by the formation of unusual cyclophanes in which one methylene unit had been lost. The separation of these by-products was possible only after treatment of the reaction mixture with TBAF, thus losing the aromatic silyl ether moiety. Phenol **190** was isolated in 42%, still with an intact benzylic silyl ether substituent, which was reductively removed in the subsequent step. Re-installation of the aromatic TBS-ether afforded macrocycle **191** in 52% yield.

The two paracyclophanes **188** and **191** were connected by a Lewis-acid mediated Diels–Alder cycloaddition installing the cyclohexene ring (Scheme 30). This reaction suffered from low facial selectivity resulting in a 1 : 1.4 ratio of diastereomers of **192**. Variations of the Lewis acid did not improve the substrate-based diastereoselectivity of the cycloaddition, which implicates that a Diels–Alderase[399] might be involved in the synthesis of longithorone A (**10**) in nature. Silyl ether cleavage was carried out with TBAF followed by immediate oxidation of the phenol with hypervalent iodine. The so formed benzoquinone intermediate **193** underwent spontaneous intramolecular [4 + 2]-cycloaddition generating rings A, C, and D, thus finalizing natural product **10** with 90% yield.[395,396]

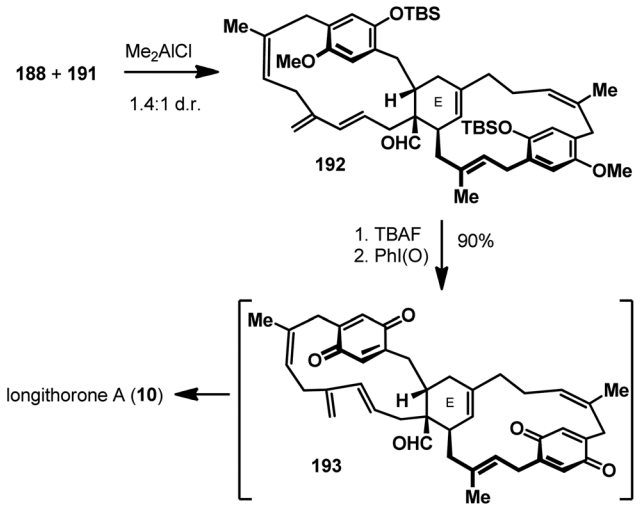
4 Synthesis of natural cyclophanes with bent benzene rings

4.1 Decahydrofluorene-containing natural products

Recently, the isolation of structurally novel highly bioactive cyclophanes from different fungi was reported. These natural products, such as hirsutellone B (**194**),[83] GKK1032A$_2$ (**195**),[400] pyrrocidine A (**196**),[401] and pyrrospirone A (**197**),[402] feature a common decahydrofluorene nucleus incorporated in an unusual twelve- or 13-membered macrocycle through an alkyl–aryl ether



Scheme 29 Synthesis of the paracyclophanes **188** and **191**, the two cycloaddition precursors.[395,396]



Scheme 30 Biomimetic formation of the heptacyclic longithorone A (**10**).[395,396]

linkage (Fig. 12). Furthermore, the paracyclophane motif contains an additional ring, a γ-hydroxylactam or succinimide, and the whole molecule shows altogether ten stereogenic centers. The huge ring strain caused by this cyclic architecture forces the atoms in the aryl portion in the cyclophane to be twisted out of plane, thus resulting in a bent benzene moiety.

Despite their structural similarity, these compounds differ in their bioactivities, ranging from antibacterial, antifungal to antitumoral properties.[83,400,401] Because of their unprecedented structure and their pronounced bioactivities, especially against *Mycobacterium tuberculosis*, the deathly pathogen of tuberculosis,[83] these substrates have become an interesting target for synthetic chemists[403–409] with the assembly of the cyclophane ring, including the formation of the distorted benzene ring being the most challenging part within the synthetic pathway.

Until now, total syntheses have only been described for hirsutellone-type compounds.[405–407] In 2009 Nicolaou and co-workers achieved the enantioselective preparation of hirsutellone B (**194**), in which the macrocyclization and twisting of the aromatic ring was conducted in a two-step procedure (Scheme 31).[405] This concept envisioned the construction of a larger, more flexible cyclophane first, whose formation should be facilitated by its reduced ring strain compared to the more rigid 13-membered macrocycle in the natural product. Subsequent ring contraction affiliated with extrusion of one atom of the macrocycle gives then the desired ring size, which is also accompanied with the bending of the aromatic portion. The 14-membered macrocycle was forged by treatment of iodoacetate **198** with NaOMe, which was followed by the immediate attack of the now deprotected thiol functionality to close the macrocycle by substitution of iodide. Subsequent oxidation of the sulfur ether led to sulfone **199** in good 79% yield. The ring was downsized by one atom utilizing a Ramberg–Bäcklund rearrangement triggered by alumina-impregnated KOH giving the corresponding styrene double bond exclusively as its *Z* isomer. The driving force for this reaction originates from the liberation of volatile sulphur dioxide. Subsequent carboxymethylation and chemoselective dihydroxylation of the benzylic olefin afforded diol **200** in 55% yield and as a single diastereomer. Taking benefit of the enhanced reactivity of the benzylic secondary alcohol the hydroxy function at *C*-3′ was selectively removed under Barton's deoxygenation conditions to yield **201**. Oxidation of the remaining OH-substituent at *C*-2′ proceeded smoothly to the ketone. A cascade sequence was initialized upon addition of ammonia to the reaction mixture composed of amidation of the methyl ester function, epimerization of the stereocenter at *C*-17, and cyclization to the γ-hydroxylactam finally leading to hirsutellone B (**194**).

Starting from the advanced intermediate **200**, Nicolaou published a second-generation synthesis to hirsutellone B (**194**) as well as the first to hirsutellone A (**13**, Fig. 3, chapter 2) and C (**202**), in which the end-game was changed to a more bioinspired late-stage sequence.[406]

An approach involving the direct construction of the 13-membered macrocycle of **194** was tackled by Uchiro using an Ullmann-type cycloetherification.[407] Therefore, iodobenzene **203** was treated with copper(I) salt under basic conditions (Scheme 32). The Buchwald protocol for this transformation succeed in the formation of the aryl–alkyl ether linkage not until the reaction mixture was heated to 160 °C. Under these harsh conditions the 13-membered macrocycle **204** was obtained in 42% yield. Further functional group manipulations of the cyclophane bridge including silyl ether deprotection and subsequent oxidation of the alcohol delivered ketone **205** in 90%. The nitrile moiety in **205** was then hydrolyzed to the amide, which spontaneously formed the γ-hydroxylactam fragment after removal of the MOM enol ether, thus completing the preparation of **194**.

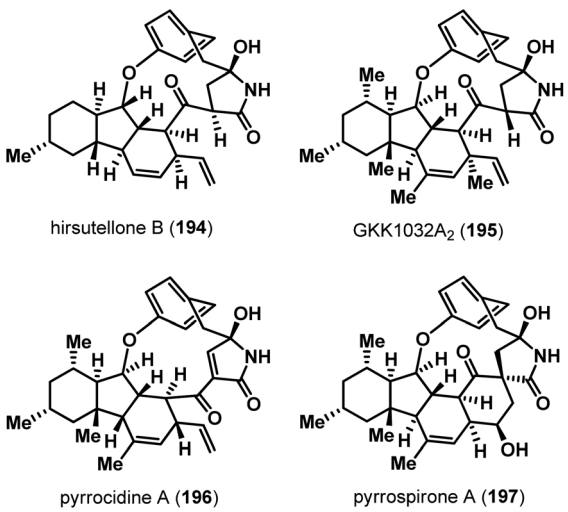
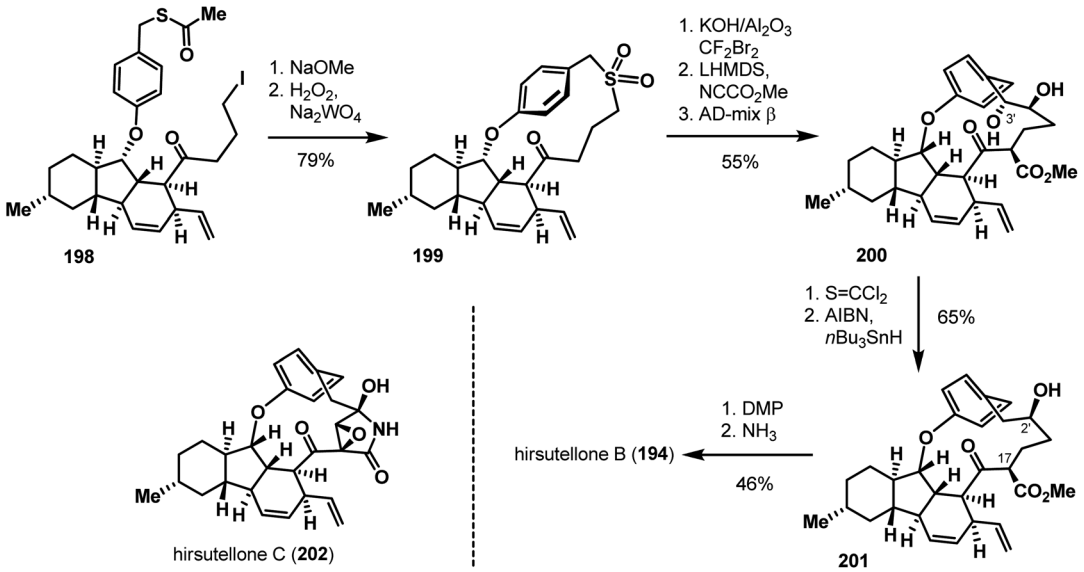


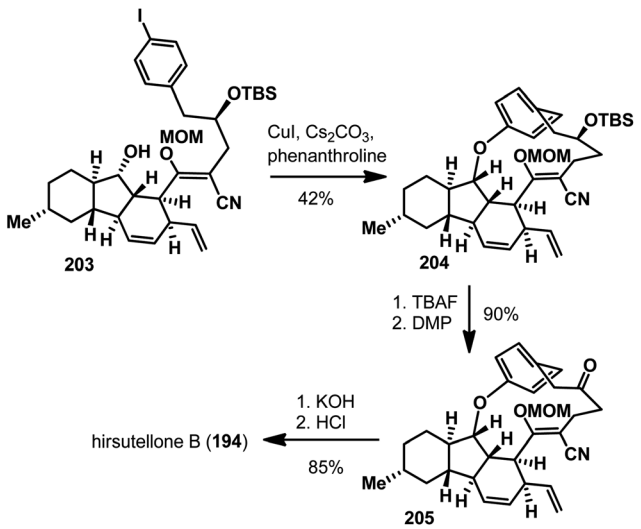
Fig. 12 Decahydrofluorene-class natural products: hirsutellone B (**194**), GKK1032A_2 (**195**), pyrrocidine A (**196**), and pyrrospirone A (**197**).

4.2 Haouamines

The ascidian *Aplidium haouarianum*, which can be found at the southern coast of Spain, produces structurally fascinating alkaloids, like haouamine A (**206**) and B (**12**, see chapter 2, Fig. 3).[81] The heptacyclic architecture of **206** and **12** assembles a congested indeno-pyrridine ring system, a highly strained [7]azaparacyclophane unit containing a bent benzene ring, and an unusual



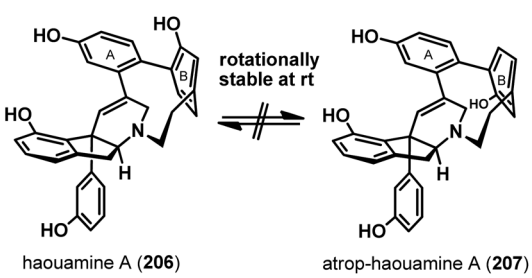
Scheme 31 Formation of the 13-membered cyclophane skeleton of **194**, including a bent benzene ring, by Nicolaou *et al.*[405]



Scheme 32 Synthesis of the paracyclophane scaffold by an Ullmann-type macrocyclization.[407]

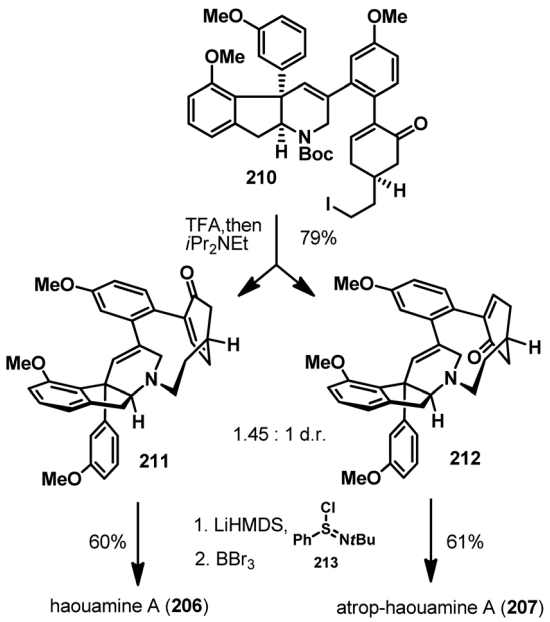
oxygenation pattern. All these features contribute to the structural uniqueness of these molecules. In solution haouamine A (**206**) and B (**12**) occur as two rapidly interconverting isomers. In general, this phenomenon can be traced back to either a slow pyramidal inversion of the tertiary nitrogen in the indeno-tetrahydropyridine moiety or to a semi stable biaryl axis between ring A and B thus resulting in a restricted rotation of the bent aryl ring B. Since intensive NMR investigations supported by chemical calculations, could not solve this mystery unambiguously,[410] Baran *et al.* approached this problem by conducting an atroposelective total synthesis of haouamine A (**206**) accompanied by X-ray analysis of both atropdiastereomers. These studies proved that **206** is configurationally stable at the *C*,*C* aryl–aryl bond,[411] that leaves the appearance of two isomers of **206** to a conformational instability of the nitrogen atom (Scheme 33). The intriguing structural features of the haouamines together with an, as yet, unknown biosynthesis[412,413] and the exquisite antitumoral activities[81,411] have stimulated numerous synthetic efforts towards **12** and **206**,[413–423] which culminated in two total synthesis of haouamine A (**206**).[411,424]

After several failed attempts to close the strained paracyclophane unit using standard approaches, such as transition-metal catalyzed biaryl couplings, Witkop photocyclization, and intramolecular alkylation,[424] Baran and co-workers adopted a completely new strategy constructing a saturated precursor *via* a pyrone-alkyne Diels–Alder cycloaddition. There, the bridged intermediate **209** served as a conformational mimic of the boat-like ring B on the one hand and was susceptible to subsequent oxidation/aromatization on the other leading to the *de novo* synthesis of the aromatic ring B (Scheme 34). This concept was put into action by heating precursor **208**, containing both reaction partners, diene (pyrone) and dienophile (alkyne), to 250 °C in the microwave.[424] These harsh reaction conditions were necessary to trigger the formation of the intermediate cyclohexadiene **209**, which already represents the desired boat conformation. Spontaneous elimination of the embedded leaving group in a retro-Diels–Alder reaction provided the carbo skeleton of haouamine A (**206**). Hydrolysis of all acetyl groups delivered the final product **206** in a 10 : 1 ratio in favor of the natural atropisomer, but in insufficient 21% yield over the last two steps.



Scheme 33 The rotationally stable haouamine A (**206**).

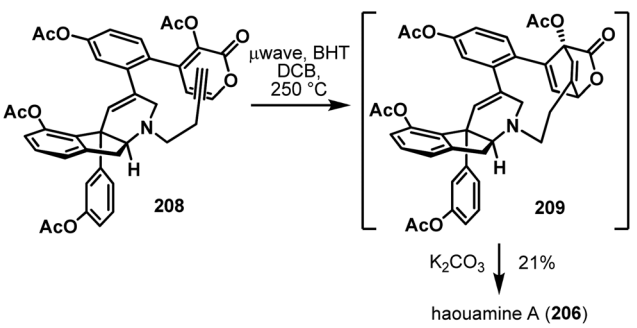
Since an extensive evaluation of the antitumoral potential of haouamine A (**206**) was hampered by both its poor availability from natural sources[81] and the inefficiency of the key step in the first-generation route, Baran and co-workers designed a second synthetic approach to **206**, this time focusing on scalability and atroposelectivity.[411] In this route a cyclohexanone moiety was chosen as a precursor for phenyl ring B (Scheme 35) as it was assumed that the change in hybridization of the carbon atoms in one of the rings of the cyclophane (ring B) from sp^2 to sp^3 should significantly alleviate strain within the macrocycle, thus allowing the ring-closure to proceed more smoothly. Furthermore, phenol surrogate **210** can act as a chiral template, giving the opportunity to conduct a stereocontrolled, atrop-programmed synthesis of **206** by selectively transferring the centro-chirality of **210** to the planar-chirality present in **206**.[411] With this concept in mind, the Boc-group in the indeno-tetrahydropyridine **210** was removed, followed by immediate cyclization *via* nucleophilic substitution upon addition of base. The macrocyclic products **211** and **212** were obtained as a 1.45 : 1-mixture of diastereomers, which were easily separated by column chromatography. Each isomer was subjected to the same consecutive reaction steps. The second key transformation, the aromatization of the cyclohexanone, was achieved chemoselectively by treatment of the *in situ* formed lithium enolate with *N-tert*-butylbenzenesulfinimidoyl chloride (**213**) giving after exhaustive *O*-demethylation haouamine A (**206**) and its atrop-diastereomer **207**. As a result of this work, the longstanding question of the origin of the two isomers observed in solution as well as the shortage in supply of haouamine A (**206**) for further extensive biological studies was no longer an issue.



Scheme 35 Second-generation synthesis of haouamine A (**206**) and its atropdiastereomer **207**.[411]

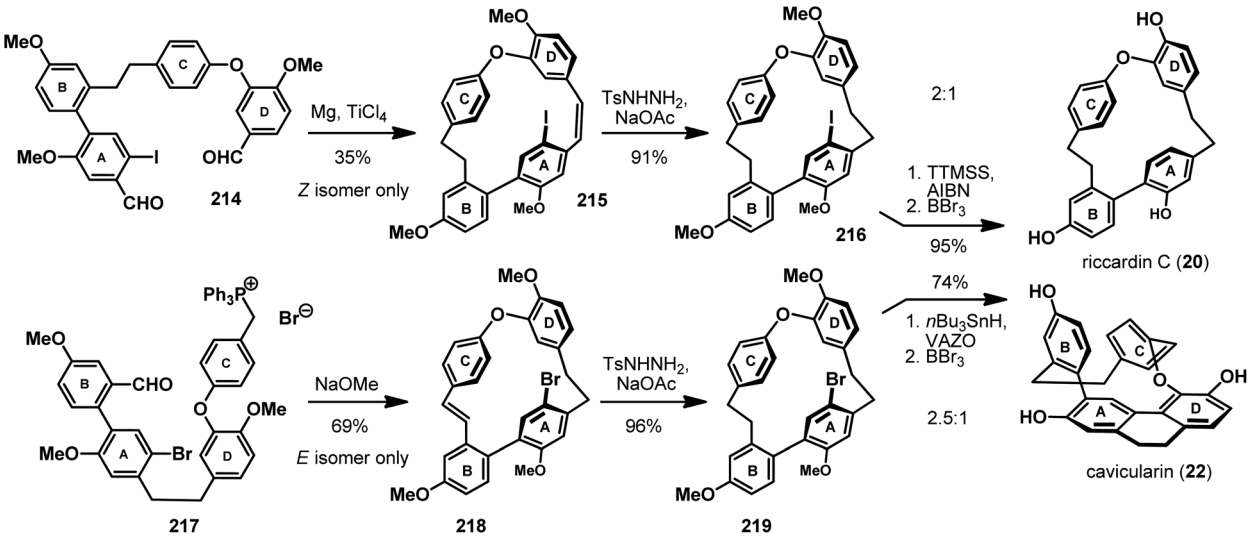
4.3 Cavicularin

From a structural point of view, cavicularin (**22**)[91] is the most fascinating member of the family of cyclic bisbibenzyl natural products (*cf.* chapter 2). With its bent aromatic ring and its inherent helical chirality, which arises only from restricted conformational freedom caused by the immense strain exhibited by the biased cyclic array, the preparation and, in particular, the enantioselective formation of cavicularin (**22**), poses an exceptional challenge to synthetic chemists. In 2005, Harrowven described the synthesis of racemic **22** utilizing a two-step ring-closing sequence, establishing more strain in the cyclic array with each transformation.[425] At first, the macrocycle was formed from dialdehyde **214** by joining ring A and D (Scheme 36, top). This was done by a McMurry reductive coupling reaction leading exclusively to the *Z* configured 18-membered intermediate **215** (35% yield) resembling the riccardin C framework. After reduction of the olefin the macrocycle was further tightened along with twisting benzene ring A by directly linking ring A and D in a radical-induced transannular ring contraction. In this process tris(trimethylsilyl)silane (TTMSS) together with the radical initiator azobisisobutyronitrile (AIBN) was added to cyclophane **216** and the mixture was heated to 90 °C. This procedure provided an inseparable 2 : 1-mixture of the trimethyl ethers of riccardin C (**20**) and cavicularin (**22**), which were finally transformed into the natural products **20** and **22** by complete *O*-demethylation.



Scheme 34 First total synthesis of haouamine A (**206**) by Baran *et al.*[424]

Since the macrocyclization step using a McMurry reaction proceeded in unsatisfying yields,[425] Harrowven reported in 2011 on a route to cavicularin (**22**), in which he improved certain steps within the pathway but kept the overall strategy basically the same (Scheme 36, bottom).[94] This time, the overall cyclophane scaffold was constructed by an intramolecular Wittig olefination of cyclization precursor **217** forming the ethylene bridge between ring B and C in 69% yield. The change in the macrocyclization method constituted a huge improvement by doubling the yield when compared to the first-generation synthesis. X-Ray analysis of *E*-stilbene **218** revealed that already in this intermediate the transannular ring strain causes a distortion of benzene ring A, which is comparable with that in the natural product. This result might explain why previous attempts to close the macrocycle by ring-closing metathesis were not successful and resulted in a complex product mixture with a dimeric species being the major product (32%). In this case, the observed ring strain in the desired product can lead to reversibility of the ruthenium-catalyzed ring-closing reaction and thus assists for an intermolecular cross-metathesis.



Scheme 36 Synthesis of cavicularin (**22**) by Harrowven *et al.*[94,425]

After reduction of the stilbene double bond, bromocyclophane **219** was obtained in 96% yield, which was then subjected to standard radical conditions applying nBu$_3$SnH and 1,1′-azobiscyanocyclohexane (VAZO) in order to execute the desired ring contraction. Unfortunately, this transformation gave the cavicularin skeleton only in poor yield, with bromo-hydrogen exchange being the major pathway. Subsequent complete *O*-demethylation delivered riccardin C (**20**) and cavicularin (**22**) in 74% over the last two steps in a 2.5 : 1 mixture.

5 Conclusion and outlook

The group of cyclophane natural products comprises a huge variety of most diverse compounds with unprecedented structures and outstanding biological activities. Regardless of their overall constitution, including the size of the macrocycle, ring closure is certainly the central issue faced in the preparation of these targets and determines the efficacy of the overall synthetic strategy. In general, the outcome of this key step highly depends on both, the choice of the strategic bond formation and the method selected for this reaction. Not surprisingly, this problem has attracted tremendous attention of synthetic chemists and provided impetus for the alteration of existing and the development of new synthetic methodologies in this field.

While the synthetic strategies described above constitute the frontier of organic synthesis, there is still room for improvement. The inherent challenge exhibited by cyclic compounds is further increased in the case of cyclophanes which show restricted rotation due to the lack of conformational and configurational freedom caused by transannular strain. Because of the hindrance in rotation of aryl–aryl and aryl–alkyl bonds one has not only to account for entropic factors in the construction of the cyclic core, but also has to control the atropisomerism in the macrocyclization step. Such atropselective syntheses are highly desirable, but still feasible only under substrate control. Therefore, the stereoselective preparation of cyclophanes, which are devoid of any traditional stereo element, such as the diarylheptanoids or cyclic bisbibenzyls, remains elusive even today and the synthetic challenge persists in spite of their ‘simple’ structure. Since the chiral axes and chiral planes in these molecules were created only upon cyclization, the development of an enantioselective macrocyclization becomes a precondition for realizing this goal. However, to the best of our knowledge, such a method has yet to be invented.

6 Abbreviations

ACE	angiotensin-converting enzyme
AIBN	azobisisobutyronitrile
DMP	Dess–Martin periodinane
1,2-DCB	1,2-dichlorobenzene
FDPP	pentafluorophenol
4-Hpg	4-hydroxyphenylglycine
RCM	ring-closing metathesis
S_NAr	nucleophilic aromatic substitution
SPase I	signal peptidase I
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TTMS	tris(trimethylsilyl)silane
TTN	thallium(III) nitrate
VAZO	1,1′-azobiscyanocyclohexane

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