Studies on Synthesis, Structures and Reactions of [2.*n*]Metacyclophan-1-enes

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Studies on Synthesis, Structures and Reactions of [2.*n*]Metacyclophan-1-enes

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By

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CERTIFICATE OF APPROVAL
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DEDICATION

For my Parents,

Abdus Sattar & Rowshan Ara

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ABSTRACT

The word "cyclophane" is a contraction of cyclo-, phenyl, and alkane. As the name implies, cyclophanes are cyclic molecules which contain both aromatic and aliphatic regions and are greatly in size and structure, ranging from small, simple molecules to large cage structures. The strained cyclophanes were synthesized as an intermediate by using trapping method. [*n*]MCP (MCP = metacyclophane)-dienes easily reacts with strong bases to achieve allenic and olefinic isomers which change the basic characteristics of cyclic diynes. Various [2.*n*]MCP derivatives have been prepared and characterized by a number of research groups and have been found to exhibit unique properties.

Firstly, a new synthetic route has been reported for *syn*- and *anti*-[2.10]MCP-enes with various derivatives. 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene from *p*-bromoanisole using a step by step reaction strategy was synthesized. ^{1}H NMR spectroscopy and X-ray analysis results confirmed the conformations present both in solution and in the solid state. This compound adopts an *anti*-conformation which forms an intramolecular hydrogen bond, which is an interesting finding for long carbon chain MCP compounds. The results from DFT computations were consistent with the observed experimental results.

Secondly, a simple and effective method for the synthesis of areno-bridged [2.10]MCPs by successive Diels–Alder reaction from 1,2-dimethylene[2.10]MCP, and its chiral conformation was described. To explore the rates of conformational behavior of the described [2.10]MCPs, a series of electrophilic substitution reactions including bromination, acylation and hydroxylation reactions of [2.10]MCPs were studied.

Finally, acid catalyzed rearrangements of [2.*n*]MCP-1-enes which afforded [*n*.1]MCPs was introduced. The ratios of the products are strongly regulated by the number of methylene bridges present. Characterization and the conformational studies of these products are described. Single crystal X-ray analysis revealed the adoption of *syn*- and *anti*-conformations.

In summary, the strategy to outline the synthesis, structural analysis of [2.*n*]MCP-1-enes and their chiral properties is expected to have significant contributions in supramolecular chemistry.

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Chapter 1

Developments of

Meta-bridged Cyclophanes and Their Recently

Developed analogues

In this chapter, general introduction of meta-bridged cyclophanes and their analogues with respect to their properties are presented, and a brief introductory outline of present thesis is also discussed.

1.1 General Introduction

Supramolecular chemistry refers to the area of chemistry beyond the molecules and focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components.[1] The forces responsible for the spatial organization may vary from weak (intermolecular forces, electrostatic or hydrogen bonding) to strong (covalent bonding), provided that the degree of electronic coupling between the molecular component remains small with respect to relevant energy parameters of the component.[2]

This chemistry focuses on the design and synthesis of molecular architectures by relying on the complementary recognition, and subsequent assembly, of well-defined subunits. The products of complementary synthesis, the so-called 'supermolecules,'[3] are sustained by noncovalent interactions such as hydrogen bonding,[4] halogen bonding,[5] coordination forces[6] and/or π···π stacking.[7] As natural products are strung together by covalent bonds between adjacent functionalities, supramolecular complexes are linked by complementary intermolecular interactions (Figure 1).[8]

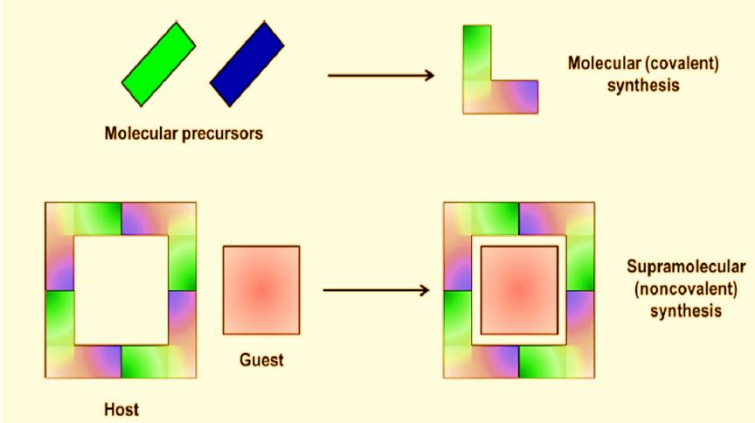


Figure 1. Construction of target molecules using covalent synthesis and noncovalent synthesis.

The area of supramolecular chemistry is of continued interest due to a wide variety of applications including materials technology, catalysis, medicine, analytical detection and sensing. Supramolecular chemistry involves the formation of complex molecular entities that have the capacity to participate in specific molecular recognition of guest molecules.[9,10] Host-guest chemistry is the result of weak non-covalent interactions between molecules such as hydrogen-bonding, metal coordination, hydrophobic forces, π···π interactions and van der

Waals forces. These types of interactions result in the complementarity of the host and guest molecules.[11]

Benzene and its aromatic derivatives are among the most important classes of compounds in the world of organic chemistry. Among these, cyclophanes are molecules formed from one aromatic part and a hydrocarbon chain connecting two carbon atoms of a ring **1** or from two or more aromatic rings connected by either saturated **2** or unsaturated chains **3**.[12-14] Atoms such as nitrogen and sulfur, in addition to the carbon and hydrogen atoms, may also be a part of a cyclophane system as is the case for heteraphanes **4a** with bridge heteroatom(s), heterophanes **4b** with ring heteroatom(s), and mixed hetero/heteraphanes **4c** (Figure 2). Some representative structures are shown below, whereas the detailed classifications and definitions can be found in the monograph by R. Gleiter and H. Hopf.[13]

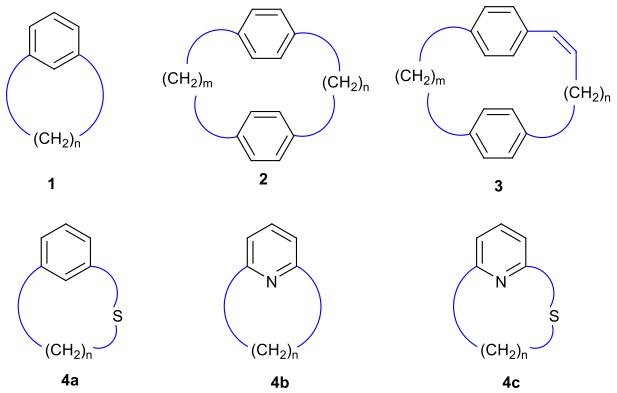


Figure 2. Different types of cyclophanes.

More complicated are the [*m.n*]cyclophanes, molecules which contain two tethers with methylene chains of lengths *m* and *n*, respectively. Once again, *meta*-, *para*-, and *ortho*-isomers are possible, in addition to adding the possibility of incorporating multiple tether and aromatic systems, as is the case with [*m*]para[*n*]metacyclophane **5**, [*m.n*]paracyclophane **6** and [*m.n*]metacyclophane **7** (Figure 3).

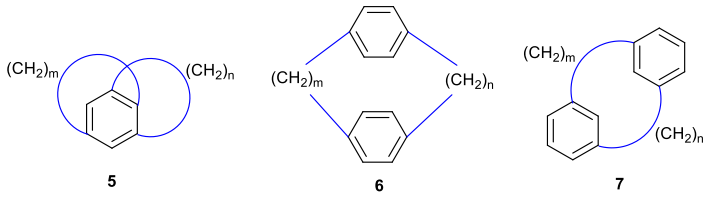


Figure 3. Some Examples of [*m.n*]cyclophanes.

1.2 The beginning of cyclophane chemistry

Cyclophane chemistry was born in 1949 when Brown and Farthing isolated [2.2]paracyclophane **8** from the thermolysis of *p*-xylene.[15] Cram reported the first designed synthesis of **8** in 1951[16] and his group cultivated the field of cyclophanes in the 1950's and 1960's.[17] His cyclophanes, such as **9** and **10** were mainly used to study the molecular strain on benzene rings, but their studies led others to create many different structurally interesting cyclophanes,[18-23] such as **11**-**13** (Figure 4).

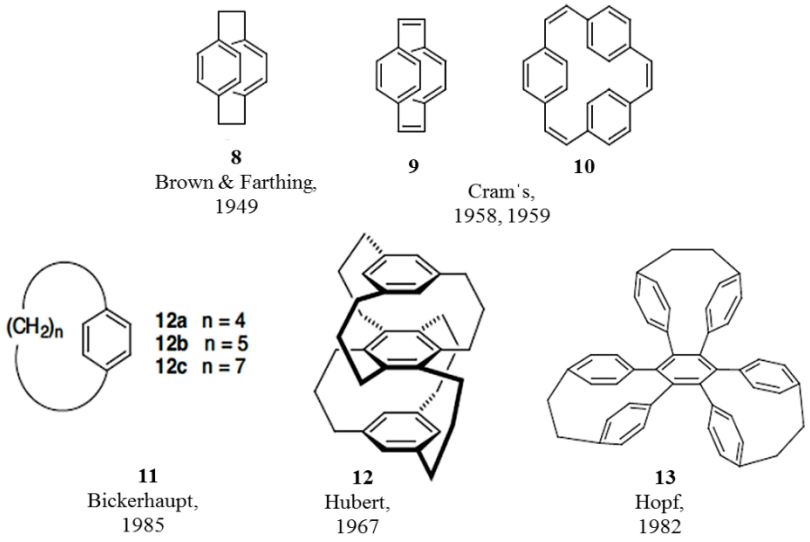
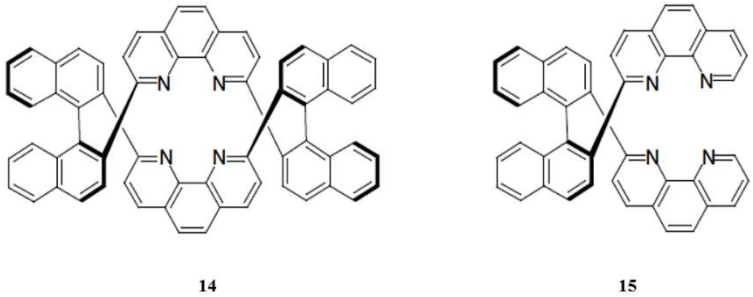


Figure 4. Structurally intriguing cyclophanes.

Cram eventually synthesized helically chiral cyclophane **14** and its acyclic analogue **15** from phenanthroline and binapthol[24] units (Figure 5). The macrocycle **14** is built with only aromatic atoms, and it possesses a chiral system, *D2* symmetry, whose six aromatic residues describe an enforced helical structure. Nitrogen atoms from the two phenanthroline units are in nearly tetrahedral arrangement, which makes it possible for them to bind small cationic metal ions, such as Li^+, Na^+, K^+, and Cu^+. The racemic mixture of **14** was isolated as a Cu^+ salt after the Ullman coupling reaction.[25] The *meso*-isomer of **14** was not found, probably because there were too many structural constraints for the two phenanthroline subunits to ligate the same metal ion at the same time. As expected, the entropic advantage of **15** over **16** causes increase in binding energy, having the difference of ***cal.*** 8.5 $kcalmol^{-1}$.



14 15

Figure 5. Cram's strongly binding, helically chiral ligand system.

Even with benzene as the only available aromatic system, a very large number of cyclophanes can be envisaged. In fact, benzene-based cyclophanes are by far the most numerous of known cyclophanes. In moving to the next largest benzenoid aromatic system, naphthalene, the situation becomes more complex and the possibilities for cyclophane formation increase considerably. Of the ten peripheral carbon atoms in naphthalene, the two quaternary atoms can be excluded from consideration as connection points for the bridges because the aromatic system would be destroyed if they were to function as bridgeheads. In addition to the basic bridging motifs present in benzene (intra-ring bridging), new motifs that connect positions in different rings (inter-ring bridging), e.g. (2,6), become available. By the same token, new ring-fusion-equivalent motifs, e.g. (1,8), also emerge (Figure 6). The exclusion of all ortho motifs as well as all peri motifs leaves seven basic bridging motifs for naphthalene: (1,3), (1,4), (1,5), (1,6), (1,7), (2,6) and (2,7), all of which have been realized.[26] Numerous bridging motifs for multi-bridged naphthalenophanes are also available.

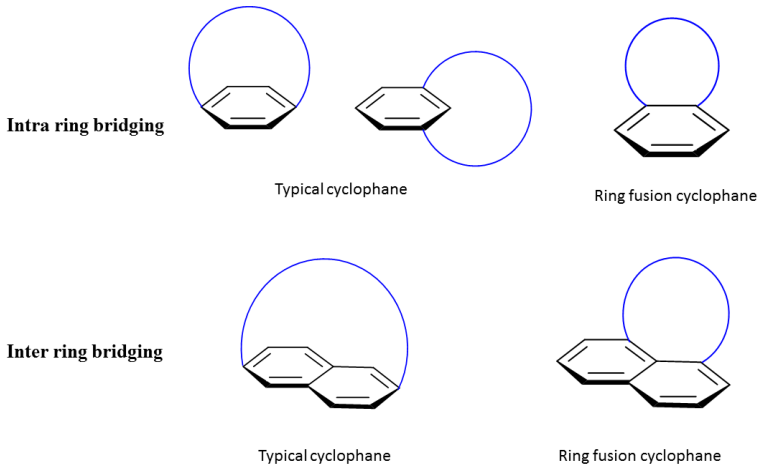


Figure 6. Basic bridging motifs for aromatic compounds.

As the aromatic system becomes progressively larger through the fusion of additional benzene rings, the number of bridging motifs and ring-fusion-equivalent motifs (where bridgeheads are connected by a peripheral pathway consisting solely of quaternary carbon atoms) increases dramatically. In stark contrast to this trend, the increase in size is accompanied by an even more dramatic drop in the number of known examples. Indeed, relatively few cyclophanes that contain aromatic systems with four or more rings are known. Considering that aromatic systems become increasingly interesting as they become larger, the relatively small set of cyclophanes containing large polycyclic aromatic hydrocarbons merits a closer look. Thus, the objective of this review is to provide information about how such systems are synthesized, how they behave and what has been learned from them. With the prime focus being on benzenoid PAHs, polynuclear heteroaromatic systems and partially hydrogenated PAHs have been excluded.[27]

1.2.2 Properties of Cyclophanes

D. J. Cram[17] began his studies of [*m.n*]paracyclophanes, with *m, n* = 2, 3 because of the close distance between the *p*-electron clouds in molecules with small bridges. In these molecules, the aromatic rings are nonplanar and aromatic hydrogen atoms lie significantly out of the plane of the C1, C2, C3 and C4 carbon atoms of one benzene ring, bent toward the other benzene ring. These deformations from the ideal benzene geometry reflect the strong *p-p* electron repulsions between the two benzene rings resulting in an increased *p*-electron density on the outside faces of the rings. Such unusual structures departing from that in benzene are worth studying. Substitution of hydrogen atoms of benzene by other substituents such as alkyl (for example dialkylbenzene **16**) leads to negligible changes to its ring planarity. Similarly, connecting two carbon atoms of a ring by a long alkyl chain (for example in [10]paracyclophane **17a**) has also negligible effect on the ring planarity. However, shortening of the chain connecting two carbon atoms of a ring (for example in [8]paracyclophane **17b**)[28] results in a nonplanar deformation of the ring. Similarly, in [6.6]paracyclophane **18** (Figure 7) the rings are nearly planar.[29]

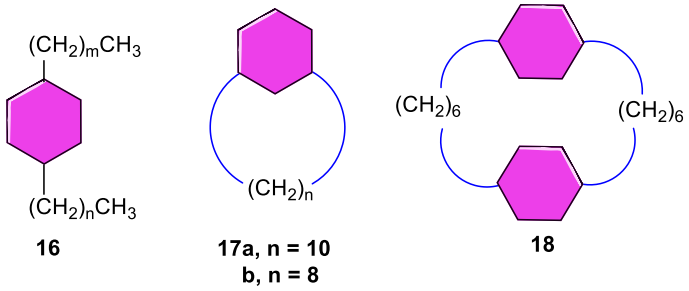


Figure 7. Cyclophanes with different bridging.

Whereas in [2.2]paracyclophane they are considerably deformed from planarity. For example, C1 and C4 of **19** are bent out of the plane of C2, C3, C5 and C6 toward the second ring by about 0.168 Å (14°) at 291 K.[30,31] In general, for paracyclophanes with shorter aliphatic chains, the aromatic rings are considerably deformed from planarity compared to the standard aromatic molecules making them interesting with respect to their structures and the influence of their nonplanar distortions on the properties of the cyclophanes.[32-35]

In a review paper by D. J. Cram and J. M. Cram[17] it was noted that the most important structural features of **19** (Figure 7), which also correlate with its unusual physical and chemical properties, are the stretched $C_{sp3}C_{sp3}$ bonds, the bent benzene rings, the abnormal bond angles, and in particular the small distance between the two benzene rings. The shortest distance between the two benzene rings (C1···C7 and C4···C10) of **7** is 2.780 Å, which is not only considerably less than the separation distance between the stacked aromatic molecules but also less than the sum of two carbon atoms van der Waals radii, *ca*. 3.4 Å. Moreover, the distance between the corresponding carbon atoms of the two aromatic rings in **10** (2.620 Å)[36] is considerably shorter than that in **19**.

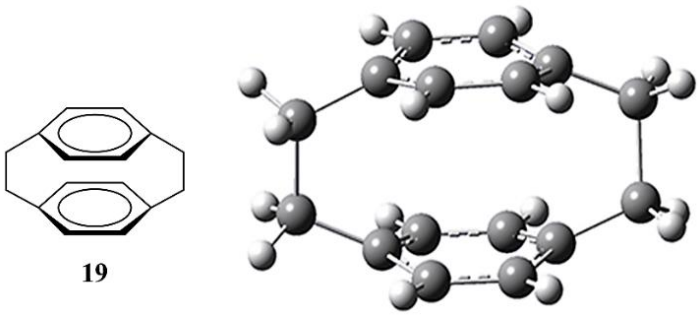


Figure 8. X-ray structure of [2.2]paracyclophane.

Its $C_{sp2}C_{sp3}$ bonds are out of the planes of the aromatic rings by *ca*. 20°. The data on the symmetry of **19** are equivocal; it is not clear whether the molecule has an eclipsed D_{2h} or twisted D_2 equilibrium geometry. In the latter case the mutual twist of the benzene rings is combined with a twist around the C13C14 and C15C16 bridges. The X-ray structure of **19** reported by Brown[37] in 1953 and by Lonsdale *et al.*[30] in 1960 resulted in the latter structure with disorder. However, the latest reported X-ray data (2003) by Lyssenko *et al*.[35] measured at 100 K unequivocally favor the former structure with no twist and no disorder.

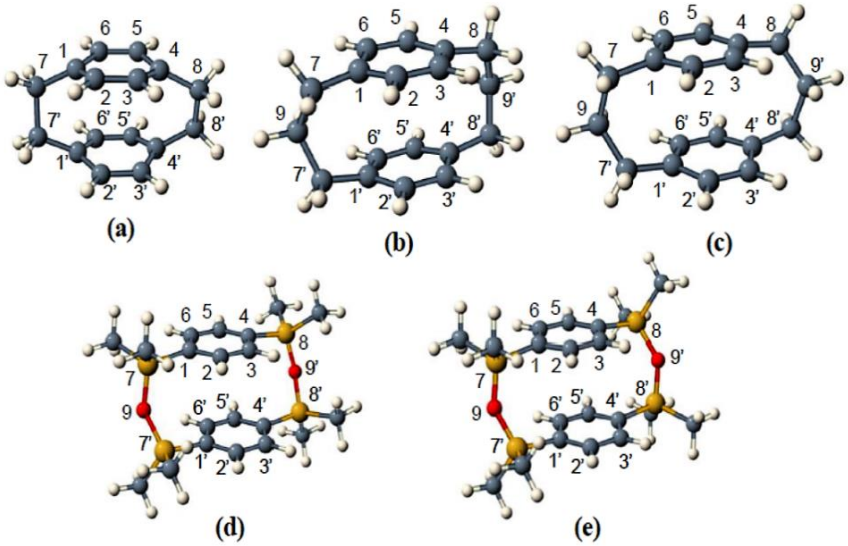


Figure 9. Identification numbers of atoms in the paracyclophanes: (a) [2.2]PCP, (b) boat [3.3]PCP, (c) chair [3.3]PCP, (d) boat SiPCP, and (e) chair SiPCP.

The origin for these very different X-ray results for [2.2]paracyclophanes are the very low energy difference between the two conformers (0.2 kcalmol^{-1} as calculated by Grimme[38]) and even smaller, quite unreliable, value in Ref. 30 and the significant temperature dependence of the structural parameters. For instance, the Csp^3Csp^3 bridge bond length was found to be longer than 1.558 Å at 93 K,[30] 1.579 Å at 100 K,[35] and 1.630 Å[30] and 1.569 Å at 297 K.[39] Computational studies on the structure of **7** have also been reported. The discussion of the results obtained in several computational studies[33,38,40-42] is blurred by the fact that in 2004[38] Grimme cited results that to date remain unpublished by Stalke measured at 19 K obtained for a different crystal structure (present below 50 K)[43] than that studied by Lyssenko *et al*.[35] The Grimme paper is then cited by theoreticians as the experimental one.[33,42] Walden and Glatzhofer[44] reported a twist angle of 3.9° using the hybrid Hartree-Fock/gradient-

corrected DFT B3LYP/4-21G(d) method, whereas Henseler and Hohlneicher[41] obtained 21.8°

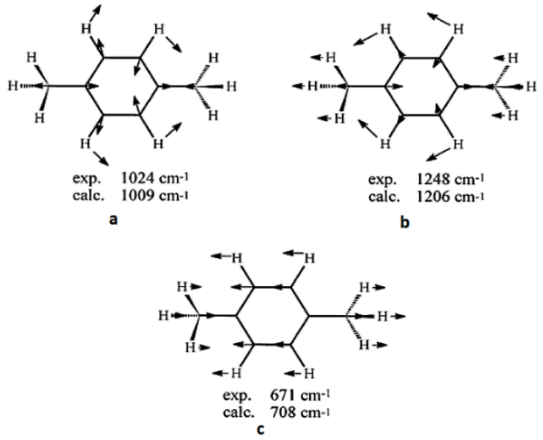


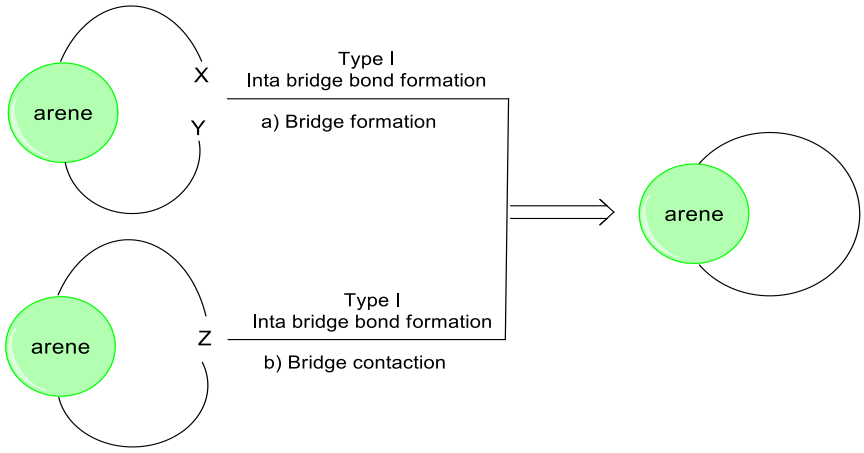
Figure 10. Diagrams of calculated (B3LYP/4-3) normal coordinates for three modes of *p-xylene*, distinctive normal harmonic vibrations of [2.2]paracyclophane" .

using MP2/6-31G(d). Bachrach[33] also reported varying twist angles based on the functional applied; 18.5° using M06-2X, 9.9° using B97-D, and 15.4° using B97X-D. The results reported by Grimme[38] also showed that the calculated twist angle of **19** is dependent on the type of functional used; where only the B3LYP functional results for the C1C13C14C7 twist angle of the D_{2h} structure agree with the latest experimental result reported by Lyssenko *et al.*[35]

1.2.3 General Synthetic Considerations

The diversity in cyclophane structure is far greater than that of the synthetic methodology that has been employed in their synthesis. From a strategic perspective, most cyclophane syntheses can be categorized neatly per the event that results in cyclophane formation (with the complete aromatic system under consideration) (Scheme 1). Type I strategies involve the formation of a bond between two atoms in a bridge, either during bridge (and cyclophane) formation (Type I-a) or during contraction of an existing bridge (Type I-b). This is easily the most common strategy for cyclophane synthesis. Since the cyclization step (cyclophane forming step) in a Type I-a reaction is intramolecular, moderate to high dilution conditions are normally beneficial, if not a necessity. This strategy is not generally very successful in the synthesis of even moderately strained cyclophanes, although some reactions (e.g. Wurtz

coupling) fare better than others (e.g. ring-closing metathesis).

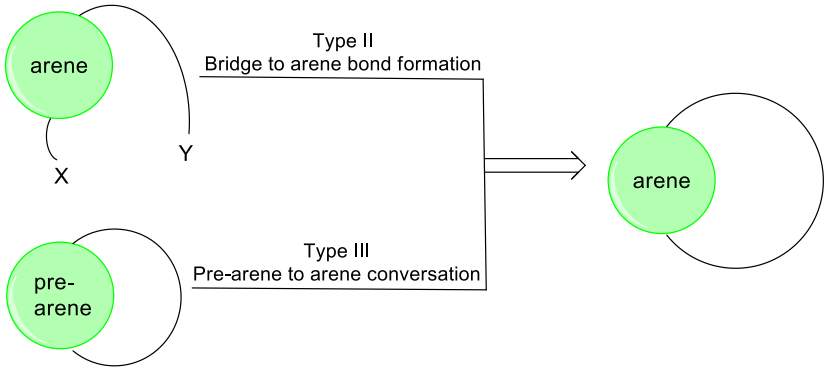


Scheme 1. Strategies for the synthesis of cyclophanes (Type I).

Type I-a reactions require one or more appropriately substituted aromatic compounds (most often disubstituted) as starting materials. Benzylic bromides and thiols feature prominently in this regard (S_N2 reactions). The synthesis of cyclophane precursors is not normally an issue when small aromatic systems are involved, but can be quite problematic for larger PAHs (poly aromatic hydrocarbon). Direct difunctionalization of large PAHs, if at all successful, provides access to only a very limited number of substitution patterns and can proceed with low regioselectivity for the ones that it does deliver. For example, the bromination of pyrene affords roughly equal amounts of 1,6- and 1,8-dibromopyrene. The separation of these two purchasable (but expensive) isomers from one another and small amounts of the 1,3 isomer is achievable, but laborious. Obviously, substitution patterns that are inaccessible through functionalization of a PAH must be accessed using multistep synthesis. In this regard, some substitution patterns can pose far stiffer synthetic challenges than others.[27] With low solubility (and even lability on occasion – e.g. benzylic bromides of certain PAHs) added to the equation, it becomes clear why there are so few cyclophanes with large PAHs.

Type I-b reactions involve the conversion of an existing cyclophane into another. In most cases, a larger cyclophane (such as a thiacyclophane obtained from thiol–bromide coupling) is subjected to a ring contraction reaction to form a smaller and usually more strained cyclophane.[45] In the process, a new bond is formed between two previously un bonded atoms

in the bridge. For many of the most frequently used ring contraction reactions (Stevens rearrangement, Wittig rearrangement, sulphone pyrolysis, photolysis in the presence of a phosphite), a bridge-opened reactive intermediate (Type 1-a reactions) is passed through. As such, this approach works best when the target cyclophane has two or more bridges. Bridge contraction is a tried and tested strategy for synthesizing moderately strained cyclophanes,[46] but it is usually ineffective when called upon to access highly strained systems.[47]



Scheme 2. Strategies for the synthesis of cyclophanes (Type II & III).

Type II strategies involve the formation of a bond between an aromatic unit and a bridge. Reactions in this category are also intramolecular and suffer from the same drawbacks as Type I-a strategies. They are much less common than Type I strategies and have typically been applied to the synthesis of relatively unstrained cyclophanes.[48] Transition metal-catalyzed cross-coupling reactions feature prominently in this category.

Type III strategies (Scheme 2) involve the generation of the aromatic system of a cyclophane from a bridged pre-arene in the cyclophane forming reaction. In many cases, the conversion of the pre-arene to the corresponding arene is accompanied by a substantial amount of aromatic stabilization energy (ASE), which can serve as a weighty counterbalance to developing strain. As such, this approach is the best-suited one for the synthesis of more highly strained cyclophanes.[49] In this regard, the pre-arene often has a shape that more easily accommodates the bridge than the aromatic system it is destined to become and is thus relatively unstrained. For the cyclophanes discussed in the following sections, only the key aspects of their syntheses will be presented at most. Full details of the synthetic pathways can be found in the cited publications.

1.3 Metacyclophanes and its Related Systems

The general structures for phenylacetylene macrocycles **20** and diethynylbenzene macrocycles **21** may represent prototypical metacyclophynes. In general, when the number (*n*) of the constituent units is small (*n* = 3), the macrocycles must be unstable because of bond angle distortion. When *n* is large (*n* =7), the macrocycles should adopt nonplanar conformations. On the other hand, medium-sized macrocycles (*n* = 4–6) should be stable and adopt approximate planar conformations. Metacyclophynes have been extensively studied during the last decade, because they have a persistent flat shape and can functionalize at both the interior and/or exterior of the macrocyclic framework. Aspects of their supramolecular chemistry that have been studied include guest-binding ability utilizing internal binding sites, construction of supramolecular structures using peripheral functionalities, self-association in solution, liquid crystalline phase, and solid state, and organization at various interfaces.[50,51]

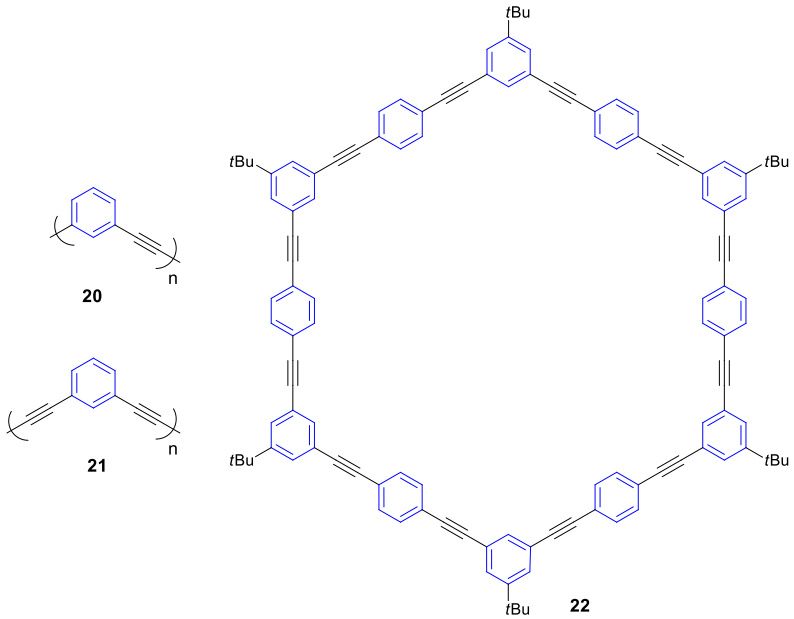
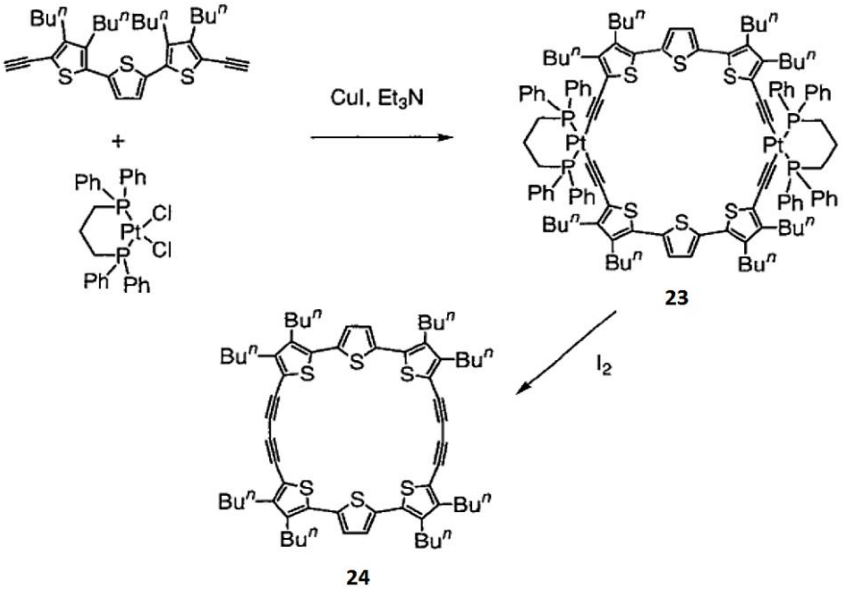


Figure 11. General structures for phenylacetylene macrocycles.

Most of the syntheses of this class of compounds have been achieved by the Sonogashira type C(sp^2)–C(sp) bond formation and by the Hay or Eglinton methods for C(sp)–C(sp) bond formation. By using a combination of selective protection/ masking of a terminal acetylene moiety by TMS group and aryl iodide by triazene group, respectively, Moore succeeded in the size-selective synthesis of a variety of nanoscale macrocycles such as **22** (Figure 11).[52]

An attempt at the solid phase synthesis of a derivative of the phenylacetylene macrocycle **20** (n = 6) was not successful presumably because of catenation of the macrocycle to the polymer support.[53] One-step synthesis based on alkyne metathesis was investigated by Bunz to furnish derivatives of **20** (n = 6), albeit in low yields.[54] A comprehensive survey regarding the synthetic strategy for construction of unsaturated macrocycles was reported recently by Schlüter.[51]

On the other hand, covalent template-directed method was employed by Höger *et al.* for the synthesis of ethynylene-butadiynylene macrocycles will be described later, giving the desired macrocycle more selectively than the macrocyclization without using a template.[55] A new method for oxidative coupling of a terminal acetylene was developed by Bäuerle based on efficient formation of a self-assembled platinum intermediate **23**, which then furnished butadiyne- bridged terthiophenophyne **24** (Scheme 3) by oxidative elimination of the metal.[56]



Scheme 3. A new method for oxidative coupling reaction.

Highly strained small metacyclophynes are not accessible by these coupling reactions. Thus, phenylacetylene trimer **25** and tetramer **26a**–**b** (Figure 12) were prepared by bromination–dehydrobromination sequences of the corresponding cyclophenes, which were obtained by using the McMurry reaction.[57] This method was applied to the synthesis of twisted biphenyl-based cyclophanediynes **27a**–**b**.[58]

X-ray structural analysis of **25**, **26a** and **27b** revealed that the triple bond of the former was deformed by 21.4°, while the largest distortion of the latter two was only 12.3° and 9.5°, respectively. Other methods for the synthesis of metacyclophynes include the McMurry coupling for dienetetrayne **28**[59] and the Williamson ether synthesis for oxygen- or sulfur-bridged compounds **29a** and **29b**.[60]

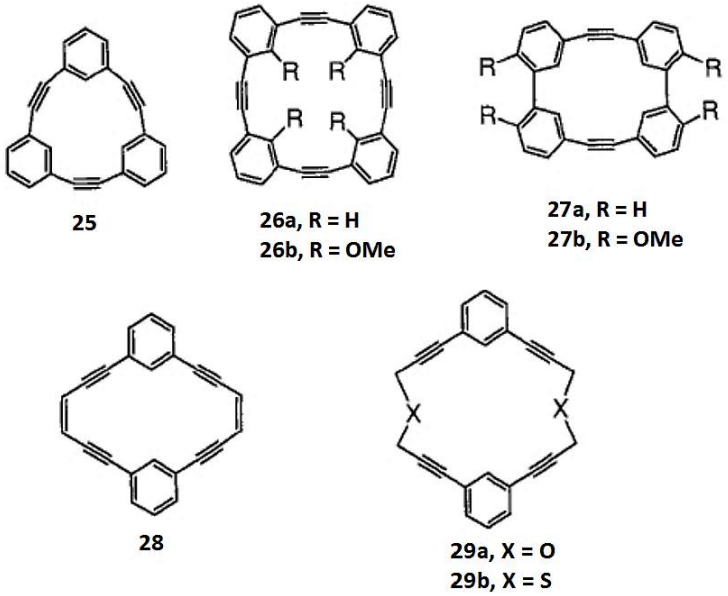
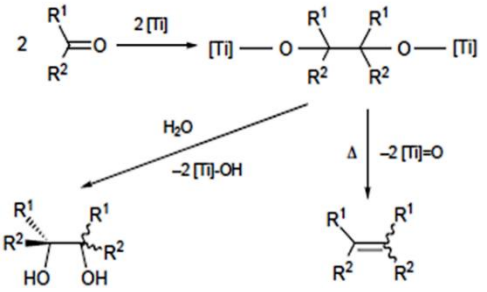


Figure 12. Highly strained small metacyclophynes.

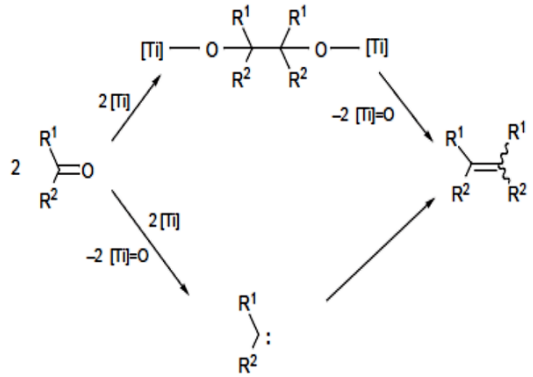
1.3.2 Metacyclophanes Via McMurry Coupling Reactions

Like the Wittig reaction, the McMurry reaction[61] holds the promise of a one-step pathway to alkene-containing cyclophanes, but the McMurry reaction has the advantage of being able to couple two identical functional groups, which can simplify the synthesis of the direct cyclophane precursors. Indeed, the McMurry reaction and other Ti based reductive couplings have been successfully applied to the synthesis of cyclophanes for over three decades. However, an inability to generate more highly strained cyclophanes also plagues the McMurry reaction. That having been said, many of moderately strained cyclophanes have been accessed through the McMurry reaction.



Scheme 4. Reductive coupling of ketones *via* a metallopinacol intermediate.

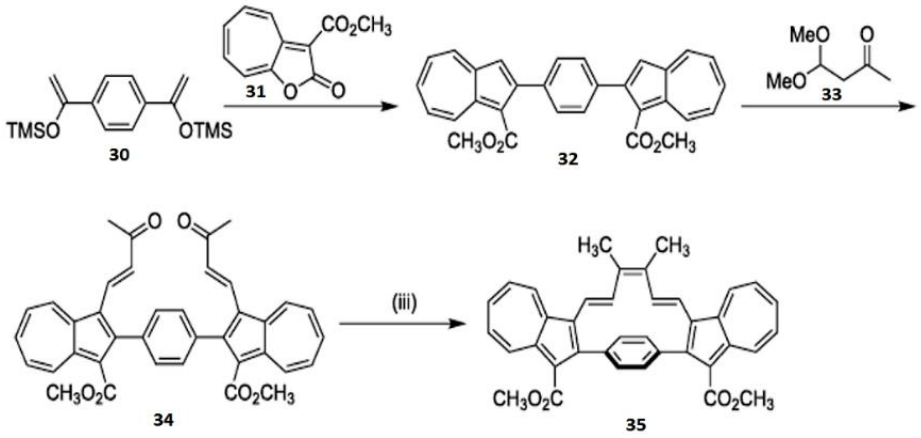
In 1972, Sharpless *et al.* reported that ketones and aldehydes could be reductively coupled into alkenes by reaction with WCl6 and RLi reagents.[5] One year after, two groups discovered that low-valent titanium complexes were also efficient in this coupling process. Tyrlik and Wolochowicz, who used the $TiCl_3$–Mg system, suggested that tetramethylethylene was obtained *via* the carbene species Me_2C:, resulting itself from deoxygenation of acetone. On the other hand, Mukaiyama *et al.*[63] proposed that metallopinacols were intermediates in the reductive coupling of aromatic ketones by means of the $TiCl_4$–Zn system; the mechanism shown in Scheme 4 explained how benzaldehyde and acetophenone were selectively transformed into the corresponding pinacols and alkenes when the reaction was performed in THF at low temperature or in refluxingdioxane.[64] The pinacolate intermediates would be formed either by dimerization of ketyl radicals resulting from one electron transfer from the low-valent metal species to the carbonyl and/ or, in the case of the more easily reducible and reactive aromatic ketones, by nucleophilic attack of a ketone dianion to the C=O bond. Therefore, at the very beginning in 1973, two mechanisms were envisaged for the reductive coupling of carbonyl molecules (Scheme 5).



Scheme 5. The two proposed mechanisms for the reductive coupling reactions.

In 1974, McMurry and Fleming described a 'new method for the reductive coupling of carbonyls to olefins' with $TiCl_3$ and $LiAlH_4$; they also proposed that pinacolate intermediates were involved in this reaction since pinacols could be isolated as byproducts in many cases.[65] The mechanism of Scheme 4 was then rapidly and generally accepted. Meanwhile, several studies on the reductive coupling of carbonyl compounds to olefins by low-valent molybdenum and tungsten compounds revealed that this reaction involved carbenoid intermediates; the relationship with the alkene metathesis reaction was noted.[65]

Kuroda and co-workers[66] have reported the synthesis of polyunsaturated [10]paracyclophane annulated by two azulene rings by using the McMurry reaction.[67] The bis(trimethylsilyl)enol ether **30** (Scheme 6) was reacted with 3-methoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one (**31**) in refluxing decaline to generate the 1,4-diazulenobenzene derivative **32**.

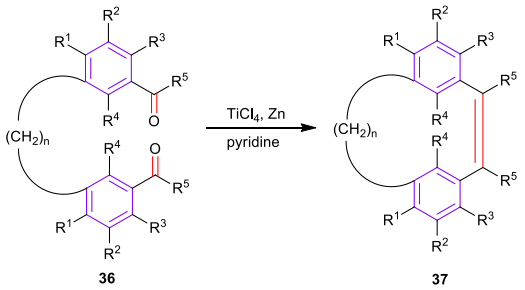


Scheme 6. Synthesis of the cyclophane **35** via McMurry coupling.

Double chain elongation of the bis-azulene derivative **32** with a four-carbon unit has been accomplished by electrophilic substitution with 4,4'-dimethoxybutan-2-one (**33**) under acidic conditions and subsequent elimination of methanol under basic conditions gave the advanced precursor **34** (28%).[68] The stereochemistry of the newly generated C–C double bonds in **34** was confirmed as *trans* with the aid of the NMR vicinal coupling constant. Finally, intramolecular McMurry coupling of **34** using titanium trichloride and lithium aluminum hydride (LAH) heated under reflux in THF provided the cyclophane derivative **35** (20%, Scheme 6).

1.3.3 [*n*.2]Metacyclophan-1-enes and reactions

There are quite a few examples of the McMurry reaction being used to synthesize simple [*n*.2]metacyclophanes **37** from tethered dialdehydes and diketones **36** (Scheme 7, Table 1). The first such report was the parent [3.2]metacyclophane-10-ene **37a**, which was isolated in 58% yield.[69] The introduction of methyl groups beside the carbonyl groups in **36b** and **36c** had an adverse effect on the yield, as **37b** and **37c** were obtained in 18% and 27% yield, respectively.[70] This was followed by a series of papers describing McMurry reactions of tethered dialdehydes and ketones **36d**–**q**, in which the tether length ranged from 2 to 10 and every available position on the aromatic rings was at some point substituted.[71–75] Some general comments can be made about the performance of the McMurry reactions.



Scheme 7. McMurry reactions leading to [*n*.2]metacyclophanes **37**.

First, the reaction failed for the syntheses of the smallest, most strained systems (n = 2, **37d**,[71] **37h**,[72] **37l**[73]) with one notable exception, [2.2]metacyclophan-1-ene **37q**,[74] which was obtained in 4.3% yield. This product stands out not only because it is a highly strained [2.2]metacyclophane, but also because it is a [2.2]metacyclophane with internal substituents, which add to the strain. This result is really quite remarkable in light of other attempts to use the McMurry reaction to synthesize [2.2]metacyclophane-1-ene derivatives, which only went as far as the pinacol.[76]

Table 1. Synthesis of [2.*n*]metacyclophan-1-enes.

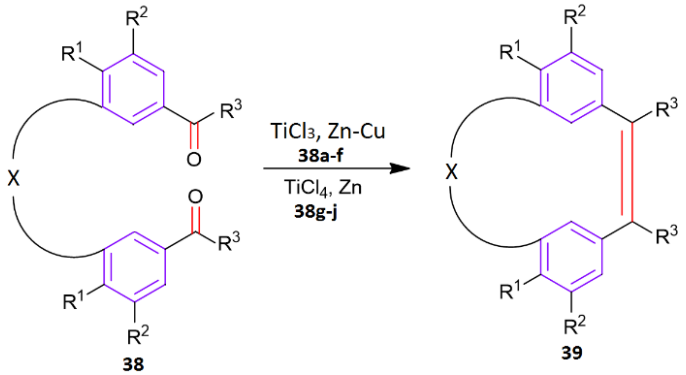
Compound	*n*	R^1	R^2	R^3	R^4	R^5
37a	3	H	H	H	H	H
37b	3	H	H	Me	H	H
37c	3	H	H	Me	H	Me
37d	2	H	*t*Bu	H	H	H
37e	3	H	*t*Bu	H	H	H
37f	4	H	*t*Bu	H	H	H

37g	5	H	*t*Bu	H	H	H
37h	2	H	H	OMe	H	Me
37i	3	H	H	OMe	H	Me
37j	4	H	H	OMe	H	Me
37k	3	H	H	OMe	H	H
37l	2	OMe	H	H	H	Me
37m	3	OMe	H	H	H	Me
37n	4	OMe	H	H	H	Me
37o	5	OMe	H	H	H	Me
37p	6	OMe	H	H	H	Me
37q	2	H	*t*Bu	H	H	H

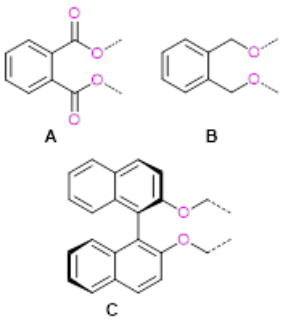
When $n>2$, the yields do not show any clear general correlation with the value of n, even within consistently substituted series, for example, **37d**–**g** and **37l**–**p**. However, the yields are usually better for diketones than dialdehydes. Indeed, in looking at all the reactions in this section, this seems to be more generally true. It should also be pointed out that pinacols were isolated in some instances (the same is true for many other McMurry reactions presented in this section) and even some products of pinacol rearrangement.[76]

Closely related to **37a**–**q** are the [2.*n*]metacyclophanes **39a**–**j**,[77-79] which have oxygen-containing long bridges ranging in length from $n = 5$ to $n = 14$ (Scheme 8). The yields for the intramolecular McMurry reactions of **38a**–**j** were very good (62–95%) apart from the ester containing system **38a**, which gave **39a** in just 10% yield.[78] This result is reminiscent of that of diester, which was also anomalously low-yielding.

Again, the bis(methyl ketone) **38d** outperformed the analogous dialdehyde **38c**.[78] Dialdehydes **38h** and **38i**, which have long, flexible tethers, reacted to give mainly the *E* isomers of **39h** and **39i**.[79]



38	R^1	R^2	R^3	R^4	X
a	OMe	H	H	OMe	A
b	OMe	H	H	OMe	B
c	H	H	H	H	B
d	H	H	Me	H	B
e	OMe	H	H	H	B
f	H	OMe	H	OMe	B
g	H	H	H	H	$O(CH_2)_3O$
h	H	H	H	H	$O(CH_2)_6O$
i	H	H	H	H	$O(CH_2)_{12}O$
j	H	H	H	H	C



Scheme 8. McMurry reactions leading to [*n*.2]metacyclophanes **39a–j**.

Three novel and aesthetically pleasing cyclophanes were constructed through McMurry reactions (Figure 13). [2.2.2]metacyclophane-1,9,17-triene (**41**),[80] [2.2.2]metametapara-cyclophane-1,9,17-triene (**43**)[81] and the enediyne-bridged [6.6]metacyclophane (**45**)[82] were all obtained in good yields from the respective precursors **40**, **42** and **44**. *Z*-selective Wittig reactions were used to synthesize **40** and **42**, while Sonogashira reactions were relied upon to reach **44**.

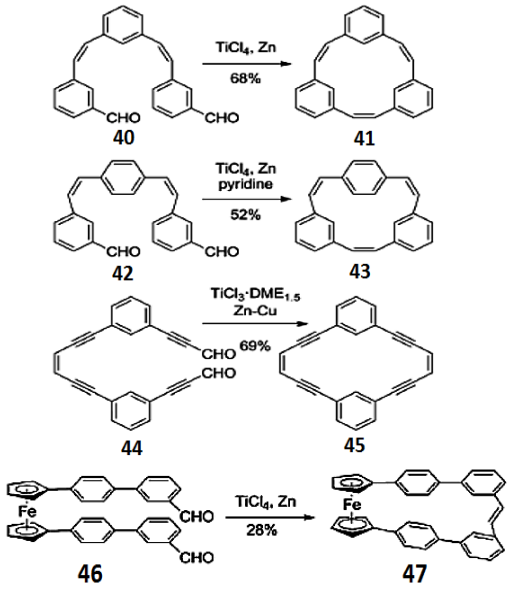


Figure 13. McMurry reactions leading to cyclophanes **41**, **43**, **45** and **47**.

Additionally, ferrocenophane **47** was obtained in 28% yield from dialdehyde **46**. In contrast to isomeric dialdehyde **46** afforded a product (**47**) with an exclusively *E*-configured double bond. The corresponding *ortho*-substituted dialdehyde (not shown) gave a mixture of *E* and *Z* ferrocenophanes.[83]

1.4 Chirality

The word "chiral" was derived from the Greek word for hand, because our hands display a good example of chirality since they are non-superimposable mirror images of each other. Chirality is one of the most important concepts in nature and science and particularly significant in biological processes. Chirality describes why seemingly similar molecules can behave very differently. Many of the molecules that are biologically important are chiral, these include proteins (and their constituent amino acids), and the nucleic acids DNA and RNA, which hold the information necessary for proteins to be synthesized.[84]

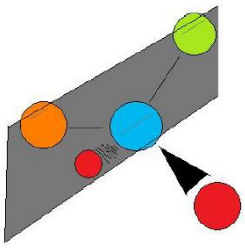


Figure 14. The images on either side of the plan.

Chirality implies the need for handedness when it comes to identifying the stereochemistry of chiral molecules. Molecules display chirality if they have non-superimposable mirror images. Common examples of chirality include hands and feet and the importance of this topic was evident in 1966 when Cahn, Ingold and Prelog famously stated “Chirality expresses the necessary and sufficient conditions for the existence of enantiomers”.[85]

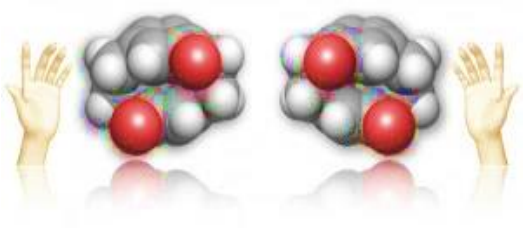


Figure 15. Chirality and handedness.

The hands shown in Figure 15 are mirror images of each other. If they were stacked on top of each other, the thumbs would be pointing in different directions and are therefore deemed as chiral species. There are three types of chirality: central, axial, and planar. A molecule that exhibits central chirality usually includes a tetrahedral atom with four different substituents. A molecule that includes restricted rotation about an axis, such as DNA, can exhibit axial chirality, which is chirality about the axis. Planar chirality can be observed in a molecule when there is restricted rotation about a plane. Cyclophanes studied for this research all exhibit planar chirality.

Thalidomide is a **chiral** molecule. Something is chiral if it cannot be superimposed on its own mirror image – in other words, if it is **asymmetric** (lacking in symmetry). A pair of stereoisomers that are non-superimposable mirror images of one another are considered to have a specific type of stereoisomeric relationship – they are a pair of **enantiomers**. Thalidomide (Figure 16) exists as a pair of enantiomers. On the macro level, your left and right hands are also a pair of enantiomers.

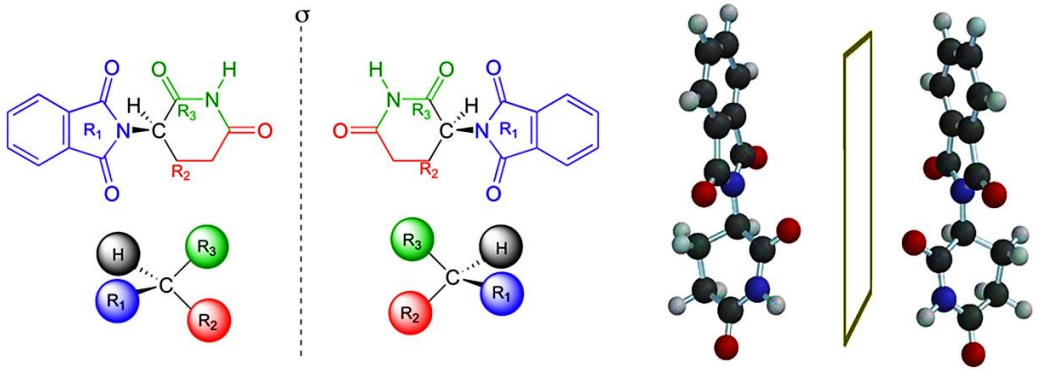


Figure 16. Chirality in Thalidomide.

Chirality in supramolecular chemistry implies the non-symmetric arrangement of molecular components in a non-covalent assembly. Chirality may arise in a supramolecular system if one of its component is chiral or if achiral components arrange in a non-symmetrical way to produce a supramolecule that is chiral. Important examples of the latter case have been reported by Jean-Marie Lehn.[86] The chemical properties of the chiral molecule differ from its mirror image, and in this lies the significance of chilarity in relation to modern organic chemistry.

1.4.2 Helical chirality

Helical chirality is a property of chiral systems[87] that do not contain stereogenic centers, that is, asymmetric units where four non-equivalent points represent the vertices of a tetrahedron. In a helical stereogenic unit, four points that can be identical are placed in a three-dimensional space such that the system is not superimposable on its mirror image. This type of chirality is also known as axial chirality because of the presence of a stereogenic axis instead of a center. The *chirality* of a helical, propeller or screw-shaped molecular entity. A right-handed helix is described as *P* (or plus), a left-handed one as *M* (or minus).

On the other hand, classical examples of molecular helices are helicenes (Figure 17), which are aromatic ortho condensed rings. When the number of rings is higher than four, the system cannot already be planar and adopts a helical structure to liberate the steric congestion. In the case of *[5]*-helicene the racemization barrier at 27 °C is 24.1 kJ/mol and it increases to 36.2 kJ/mol for *[6]*-helicene.

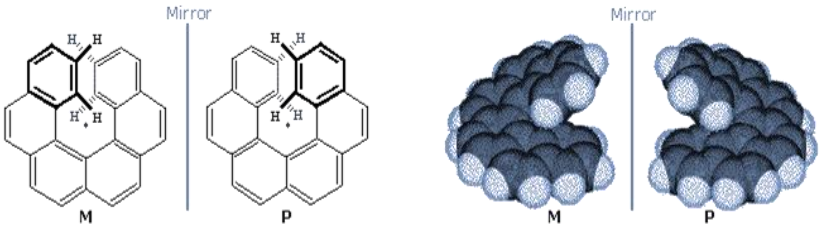


Figure 17. Enantiomeric configurations of Hexahelicene.

In molecules that are not inherently helically chiral, helicity can be induced. Flexible molecules, such as DNA (Figure 18), can be folded into a helical conformation by specific directional non-covalent interactions, for example, hydrogen bonding. In rigid molecules, helical conformations can arise if unfavorable steric interactions, or strain, are present in their non-helical conformations, which is the driving force towards formation of the energetically favored helical conformations.

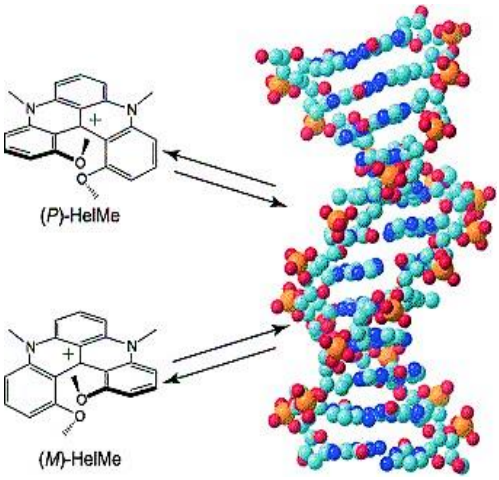


Figure 18. Helical conformations in nature.

1.4.3 Metacyclophanes with helical chirality.

'Phane' molecules template interactions between layered *p*-systems within constrained three dimensional architectures, and this unique feature has been extensively investigated and exploited.[50] The well-known [*n*]helicenes[88] are promising candidates for structure/chiroptics correlations, but there is hitherto no easy synthetic pathway[89] to substituted, well-soluble derivatives, which would allow a gradual variation of their pitch. The range of formulae **48** (Figure 19) show our own concept to reduce the size of helicene-type molecules.[90] Replacing benzene rings through aliphatic bridges one finally ends up with the *planar* chiral [2.2]metacyclophane **51** skeleton and with mononucleic [*n*]meta- or [*n*]paracyclophanes (**52**).

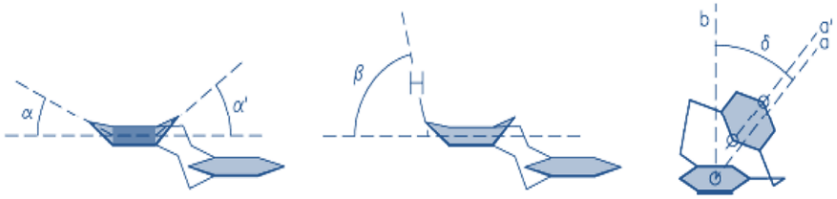


Figure 19. Molecular angles indicating distortion.

As one main topic of these studies we therefore used the rigid [2.2]metacyclophane **51** skeleton (Figure 20), which leads to small planar chiral compounds by suitable substitution and to small chiral molecules by insertion of heteroatoms into the cyclophane bridges. The advantages of this choice are the limited number of atoms, that made a reliable calculation of the CD spectra, and good solubility and the high crystallization tendency of

[2.2]metacyclophanes allowing X-ray crystallographic examination of torsion effects and absolute configurations.

It should be mentioned that the molecules considered here may be regarded as small in organic chemistry but are large for a quantum mechanical treatment of chiroptical properties. Synthetic planar chiral cyclophanes are, for example, [2.2]paracyclophane derivatives (pictured). They are of great interest as asymmetric catalysts, and in medicinal and polymer chemistry. Producing non-racemic planar-chiral [2.2]paracyclophanes in a catalytic manner is still a challenge.

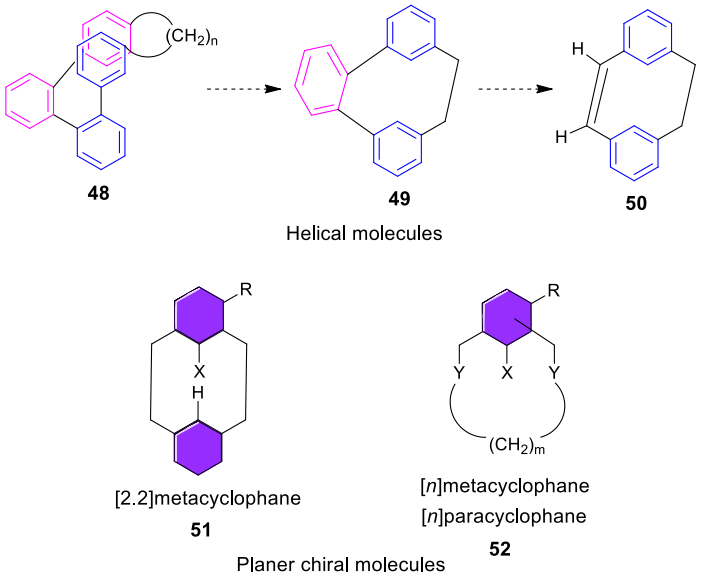


Figure 20. Evolution of more simple helical and planar-chiral molecules starting from **48** (or from heptahelicene) by continuous formal distraction of benzene rings; these molecules are chiral without having stereogenic centers.

1.4.4 Helical [2.2]metacyclophanes

Introduction of heteroatoms into the [2.2]metacyclophane's bridges (Figure 21), thus leading to symmetry breaking and to heteraphanes, allows a controlled increase of the twisting of the connected benzene rings against each other. The C4 mono- and C4/14 di-substituted carboxylic acid methyl ester racemates were readily separated by analytical and preparative chiral HPLC and their inversion barriers measured in heptanes at 373 K at 125.3 kJ/mol and 130.9 kJ/mol, respectively.[91]

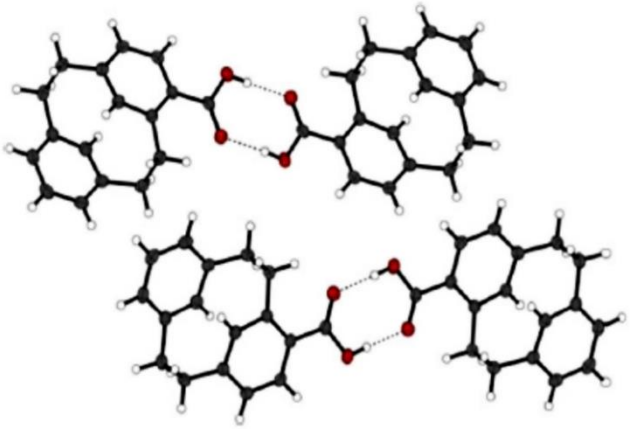


Figure 21. H-bonding in X-ray structure [2.2]metacyclophane-4-carboxylic acid.

In addition the internal deformation of the two-bladed propellers should be the more pronounced the closer the two benzene rings are pressed together by short cyclophane bridges -CH_2-X- and -CH_2-Y- in **53** (Figure 22). Therefore we synthesized a number of monohetera- and dihetera [2.2]metacyclophanes[90] in which the carbon–heteroatom distance determines the molecular strain. Figure 22 shows [2.2]metacyclophanes **54**–**56** in the order of increasing strain. The C-X bond length decreases from X=S to X=O, so that the 1-oxa [2.2]metacyclophane **56**[92] is the sterically most strained monohetera [2.2]metacyclophane with the highest boat-shaped deformation in the benzene rings.

The thiazacyclophanes of type **57** are comparatively easy to synthesize in one (cyclization) step[90], so that we could prepare a range of differently substituted representatives that allowed us to study the influence of intra-annular substituents R on the CD and other properties[93].

The chirality-inducing step is the formal substitution of one or more carbon atoms in the bridge of the [2.2]metacyclophane hydrocarbon **53b** to yield the heterocycles **53a** (X=/ Y). The length of the bridges and consequently helicity and strain can be influenced within wide limits. The first member of the [2.2]metacyclophane family to be synthesized was the achiral hydrocarbon **53b**[56] itself; the first molecule with heteroatoms in the bridge was 1,10-dithia [2.2]metacyclophane **53c**.[57] 1-Thia- **54** and 1-oxa[2.2]metacyclophane **56** were prepared many years later[91] by intramolecular ring closure methods.

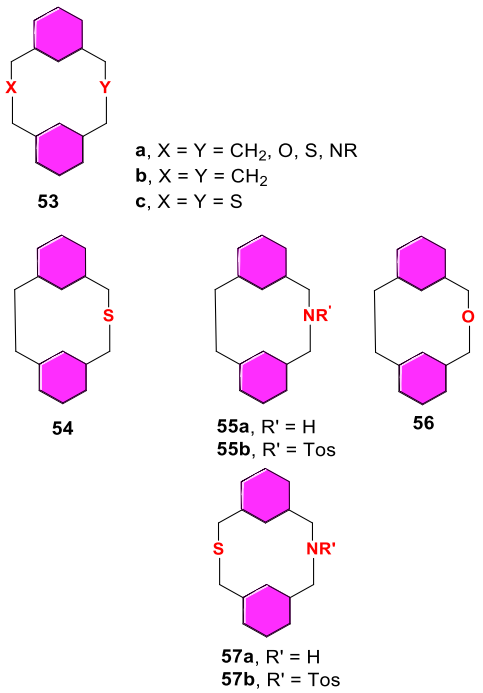


Figure 22. Two-wing propeller molecules.

Considering that these cyclophanes are ring-strained, the syntheses of **53c** and **57** and most cyclophanes mentioned in the following were carried out under high-dilution conditions,[58] using selected bases and by taking advantage of the cesium effect.[59]

1.5 Theoretical considerations through CD spectroscopy

Circular dichroism (CD) spectroscopy is a spectroscopic technique where the CD of molecules is measured over a range of wavelengths. CD spectroscopy is used extensively to study chiral molecules of all types and sizes, but it is in the study of large biological molecules where it finds its most important applications. A primary use is in analyzing the secondary structure or conformation of macromolecules, particularly proteins as secondary structure is sensitive to its environment, temperature or pH, circular dichroism can be used to observe how secondary structure changes with environmental conditions or on interaction with other molecules. Structural, kinetic and thermodynamic information about macromolecules can be derived from circular dichroism spectroscopy.

Circular dichroism = $\Delta A(\lambda) = A(\lambda)LCPL - A(\lambda)RCPL$, *where λ is the wavelength*

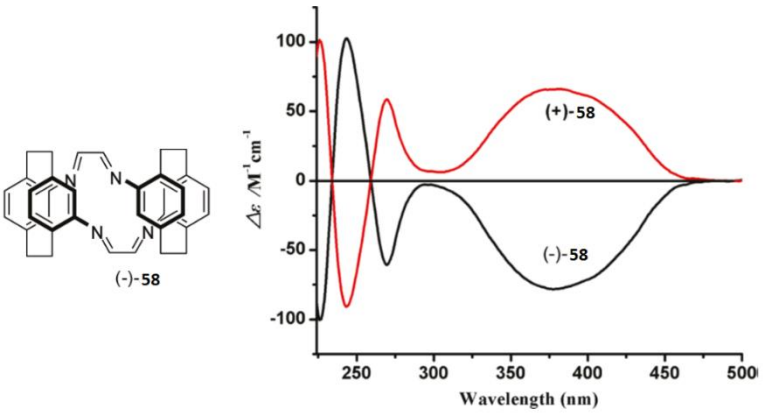


Figure 23. CD spectra of (-)-**58** and (+)-**58** in CH_2Cl_2.

The chirality of (-)-**58**, macrocyclic imine, was also reflected by its optical properties (Figure 23). The magnitudes of the specific rotation ($[\alpha]^{20}_D$ -4350) and the CD spectrum are both large. It is well known that the negative sign of specific rotation is usually found for *M* [*n*]helicenes and a positive sign for (*P*)-[*n*]helicenes.[94] For (-)-**58**, we found an agreement with the phenomenon. The CD spectrum of (*M*)-helical (-)-**58** is dominated by strongly negative dichroisms, and the CD spectrum of (+)-**58** is opposite in sign, but equal in magnitude, which reveals that the (-)-**58** and (+)-**58** are enantiomers, and (+)-**58**[95] is (*P*)-helical.

The triple layered tetraazacyclophane **59** was prepared in high yield by a fourfold bond connection in a one-pot reaction sequence. The helical chirality of **59** results from the unique crossed *meta*/*meta*-cyclophane linkage. A racemization process can only take place by breaking a covalent bond. The X-ray structure analysis of **59** proved the constitution of the isomer, difficult to determine by spectroscopy, and revealed a *face to face* arrangement of the skeleton arene rings. The unique chiral framework of the triple layered cyclophane **59** with a 1,2,3,4-substitution pattern of the central building block was proven by X-ray structure analysis and subsequent HPLC-separation (CD spectrum).[96] The CD spectrum of **59** is rather complex due to the number of different chromophores, especially the four mobile tosyl groups and the ester functions (Figure 24). We observed seven Cotton effects in the range between 190 and 282 nm. For this reason, a reasonable theoretical discussion and calculation of the CD spectrum for an assignment of the absolute configuration was not possible.[97]

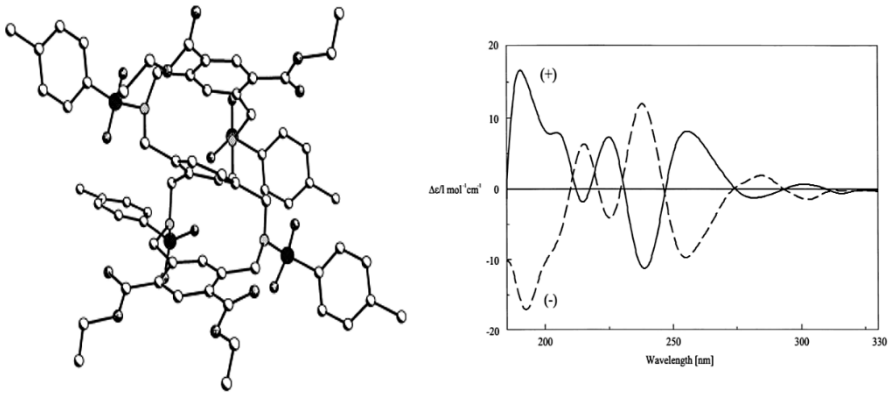


Figure 24. CD spectra of tetraazacyclophane **59** in CH_2Cl_2.

Following our optimized iterative procedure for elongation of azacyclophanes 5 and 6 it should be possible to get to a whole family of optically active multilayered cyclophanes especially five-layered derivatives in a three steps procedure starting with compound **3a**.

Because the CD spectra of various metacyclophanes have already been extensively discussed in the literature, only two examples are presented here. The 1-thia [2.2]metacyclophane **54** molecule was the first cyclophane CD spectrum ever studied by modern quantum chemical methods.[98] Compared with [2.2]paracyclophanes, the benzene rings are here aligned almost parallel and the chirality is induced a) by a tilting of the rings against each other due to one longer bridging bond and b) by the sulfur atom in the bridge. The experimental spectrum displayed in Figure 25 shows five CD bands A–E with very large calculated CD intensities up to $\Delta\varepsilon$ =120 l mol^{-1} cm^{-1}.

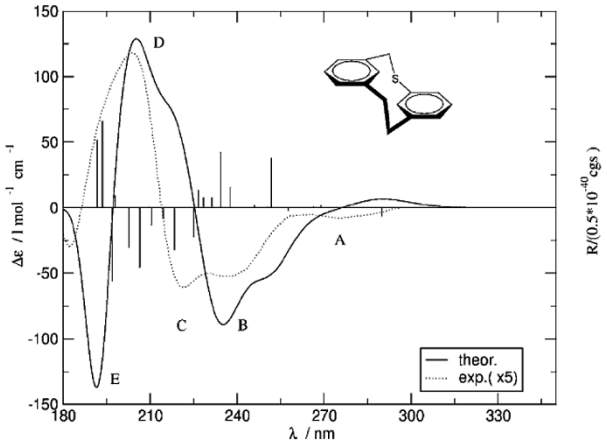


Figure 25. Comparison of experimental and theoretical (TDDFT-B3LYP/TZVP, DFTBP86/TZVP geometry) CD spectra for (*M*)-1-thia[2.2]metacyclophane **54**.

This compound (1-Thia-10-aza[2.2]metacyclophane **57a**) shows an interesting stereochemical detail. Replacing a CH_2 group in the thiaphane discussed above, by a NH group results in two conformers A and B (Figure 26) which differ by an inversion of the hydrogen atom connected to the nitrogen center.

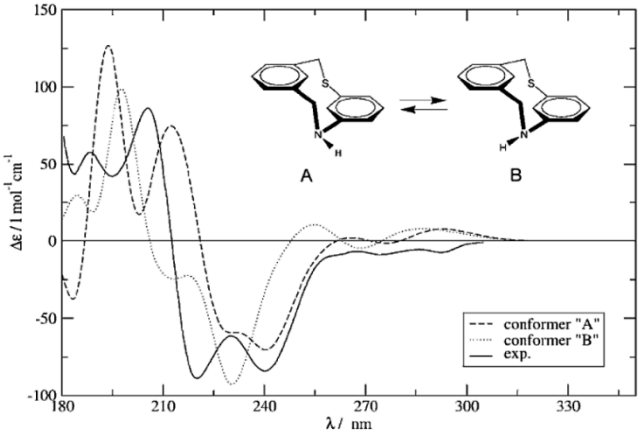


Figure 26. Comparison of experimental and theoretical (TDDFT-B3LYP/TZVP, DFTBP86/TZVP geometry) CD spectra for (*M*)-thia-10-aza[2.2]metacyclophane **57a**.

Because the barrier has been estimated to be very small (about 5 kcal mol^{-1}),[99] a rapid interconversion is to be expected which is not accessible by dynamic NMR spectroscopy. Nor are the results from X-ray studies decisive, because the conformer B observed experimentally forms intermolecular hydrogen bonds in the solid which may be absent in the fluid phase.

1.6 Conclusion

Cyclophane chemistry is an old and well-established field. For more than sixty years, cyclophanes have been the subject of intense experimental and theoretical research.[100] The interest in their study is directly related to the close distance between the benzene rings which makes their -electrons interact and causes the nonplanarity of the benzene ring(s) as discussed in the review paper by Cram and co-workers.[17] In addition; the structural, chemical and spectroscopic properties of the molecules as a consequence of the unusually deformed benzene ring(s) are also reasons for the broad interest in these compounds by researchers.[32] As already mentioned before, cyclophanes with nonplanar arrangement of benzene rings

offer another possibility to study the interaction of their p-electron clouds, which has not been explored previously.

As highlighted, cyclophanes with short bridges are structurally interesting due to their geometrical abnormalities. Comprehensive and detailed structural analysis of [*m.n*]paracyclophanes (*m*, *n* = 2–4) using density functional theory, DFT, combined with available experimental structures is rare and/or difficult to find in the literature.

Variable temperature NMR studies of cyclophanes, of which only one earlier study for metacyclophane has previously been reported,[101] facilitate the understanding of the dynamic phenomena taking place in the bridges of metacyclophane. Hence, static and variable temperature NMR studies of [*m.n*]metacyclophanes with short bridges combined with DFT calculations was undertaken as the second major objective of the PhD study.

Density functional theory (DFT) is a reliable standard tool for the theoretical treatment of the structures as well as NMR and UV/Vis absorption spectra of typical organic molecules. It simplifies the interpretation of the spectra and contributes to the understanding of the phenomena taking place during molecular motions. Here, cyclophanes with small bridges are used for testing the performance of different functional when applied for the study of strained molecules with electronic interactions.

The comparison of experimental and theoretical circular dichroism allows the assignment of the absolute configuration of the molecules, without use of X-ray (Bijvoet) or exciton-chirality methods. The comparison of theoretical circular dichroisms with the experimental data enables the analysis of conformational processes. Predominant conformers of different substituted [2.*n*]metacyclophanes could be assigned.

1.7 References

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Chapter 2

Synthesis, structures and conformational studies of 1,2-dimethyl[2.10]metacyclophane-1-enes

This chapter focused on the synthesis of 1,2-dimethyl[2.10]metacyclophan-1-enes (MCP-1-enes) containing different substituent groups. 4,22-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene 3 was synthesized by a Grignard coupling reaction, Friedel-Crafts acylation reactions and McMurry coupling reaction from 1,10-dibromodecane. The formation of 4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene 4 was carried out by demethylation of compound 3 with boron tribromide. From this reaction an interesting compound [10]tetrahydrobenzo-furanophane 5 was afforded on prolonging the reaction time. 5,21-diformyl-4,22- dihydroxy-1,2-dimethyl[2.10]MCP-1-ene 6 has been prepared from compound 4 by using the Duff method.

2.1 Introduction

In the world of organic chemistry, benzene and its derivatives are a pivotal class of compounds. A small sub-division is the so called cyclophanes, which are molecules that comprise of an aromatic part and a hydrocarbon chain which connects two carbon atoms of a ring. Additionally, cyclophanes can be formed from two or more aromatic rings connected by either saturated or unsaturated carbon chains.[1-3] [2.*n*]metacyclophane has a fascinating molecular structure, and consists of two benzene rings cross-linked together by two ethylene chains at the meta positions.[3-5] Various [2.*n*]MCP (MCP = metacyclophane) derivatives have been prepared and characterized by a number of research groups, and have been found to exhibit unique properties.[6-8] In 1953, Brown and Farthing reported the X-ray crystallographic analysis of an MCP and the conformational evaluation thereof.[9] Hata et al.[10] measured the ring inversion of different MCPs, where the length of the crosslinking chain was systematically varied. The conformation of a monomer unit plays a vital role for determining the behavior of such systems. Boekelheide[11] and Staab[12] accomplished the synthesis of *syn*-[2.2]MCPs, which are intra-annularly substituted.

However, early papers on the synthesis and reactions of *syn*-[2.*n*]MCPs did not appear. Bodwell et al. described the synthesis of [2.2.*n*](1,3,5)cyclophane-1,9-dienes leading to 1,*n*-dioxa[*n*](2,7)-pyrenophanes.[13] The rigid *syn*-conformation of cyclophanes was isolated by the overlaying of the aromatic rings. Mitchell and Weerawana group[14] synthesized cyclophanes bearing glycol units as bridges by the McMurry coupling reaction.[15] Latterly, Hopf and Mlynek,[16] Gru¨ tzmacher et al.[17] reported the cyclization of dialdehydes to yield unsaturated cyclophanes. The syntheses of the novel *anti*-transoid and *anti*-cisoid-[2.2](1,3)naphthalenophanes are have been reported by a sulfur extrusion process.[18]

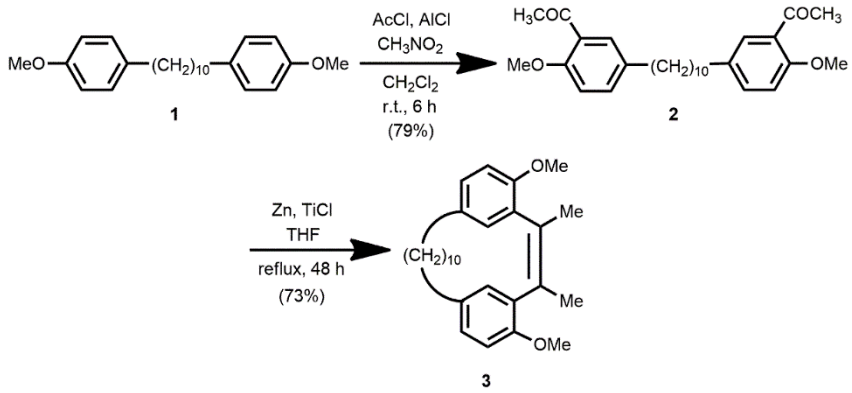
In more recent times, we have reported the preparation of 1,2-dimethyl[2.3]MCP-1-enes[19-21] by using the reductive coupling reactions of carbonyl compounds in the presence of low-valent titanium. Here, the McMurry reaction was applied as a key step.[22-25] For the [2.3]MCP-1-enes, the aromatic rings are predicted to adopt 'mobile' *anti*- or *syn*-conformations. Additionally, the synthesis and conformational studies on the [2.4]MCP-1-ene system, together with its conversion to *syn*-10-thia[2.3.4](1,3,5)-cyclophan-1-ene, has been reported.[26] Usually dimethoxy[2.*n*]MCPs with a *syn* conformation were used as a

elementary unit for the development of a more rigid calix[*n*]arene skeleton, because many macrocyclic type compounds constituted of a MCP skeleton are reported as an artificial receptors.[27]

In our laboratory, we are now focusing on the synthesis of small and medium sized metacyclophanes containing dihydrobenzofuran or benzofuran rings via intramolecular cyclization reaction. This interest stems from interest in their conformations and also exploring their possible applications.[27] We described the preparation of a series of [2.10]MCP-1-enes with different substituents as a monomer unit and their conformational studies in solution. In this chapter, we report on the synthesis, crystal structures and conformational properties of 1,2-dimethyl[2.10]metacyclophan-1-enes.

2.2 Results and Discussion

The starting compound 1,10-bis(4-methoxyphenyl)decane **1** was readily prepared from 1,10-dibromodecane according to our previous route.[28-34] In the presence of cuprous bromide (CuBr) as a catalyst in a mixture of hexamethylphosphoric triamide (HMPA) and tetrahydrofuran (THF), the cross-coupling reaction of 4-methoxyphenylmagnesium bromide with 1,10-dibromodecane was carried out at reflux temperature to afford the required 1,10-bis(4-methoxyphenyl)decane **1** in 82% yield.



Scheme 1. Synthesis of 4,22-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene **3**.

This was followed by a regioselective Friedel-Crafts acylation reaction at the meta positions of the respective 1,10-diphenylalkanes. Compound **1** was then reacted in an $AlCl_3$–$MeNO_2$ catalyzed acetylation using acetyl chloride at 20 °C to afford 1,10-bis(3-acetyl-4-

methoxy-phenyl)decane **2** in 79% yield (Scheme 1).[29-35] Under high dilution conditions, a McMurry coupling reaction afforded the desired 4,22-dimethoxy-1,2-dimethyl [2.10]MCP-1-ene **3** in 73% yield.

The conformation of **3** was elucidated from its ^{1}H NMR spectrum. [2.*n*]MCP-enes possessing overlaying aromatic rings adopt either a "staircase" *anti*-conformation or a *syn*-conformation.[36] The interconversion between the *syn*- and *anti*-conformers occurs by a ring flipping, the extent of which depends on the length of the bridge[37] and the presence or not of intra-annular substituents.[38-39] The ring current of the opposite benzene ring cause an upfield shift for the internal aromatic protons (δ 6.59–6.81 ppm).[4-7] The ^{1}H NMR spectrum of **3** exhibited a doublet of doublets for the intra-annular proton H_i at δ 6.81 (J = 8.3, 2.2 Hz) ppm. The other aromatic protons appear at δ 6.59 and 6.67 ppm. The methyl protons of the bridging double bond were observed as a singlet at δ 2.12 ppm, whilst the methoxy protons appear as a singlet at δ 3.60 ppm. For a rigid *anti*-[2.10]MCP-1-ene structure, the protons of the decamethylene bridge introduce a complicated signal pattern. The benzylic CH_2 protons were observed as two multiplets centered at δ 1.56 and 2.34 ppm, which are again split by coupling with the protons of the central CH_2 groups. These central CH_2 groups were also observed as a multiplets centered at δ 1.21 ppm. These results suggested that the *anti*-conformation of [2.10]MCP-enes **3** might be controlled by the presence of the double bond possessing substituents such as methyl or methoxy groups.

The single crystal X-ray crystallography clearly shows that the conformation adopted by compound **3** is the *anti*-conformation, in which two aromatic rings are part of a non-planar chain (Figure 1). Here the selected bond lengths of C19–C20 and C19–C4 in the decamethylene chains and C8–C2 and C12–C10 in the ethylenic chains have typical values at 1.54(3), 1.51(3), 1.49 (2) and 1.51(5) Å, respectively. The length of the double bond in C2–C10 is 1.34 Å, which is like that of ethylene. The bond angles defined by C8–C2–C10 and C2–C10–C12 are 120.3(2) and 121.0(2) Å, showing that **3** displays a slightly distorted conformation. The two benzene rings of 3 slightly deviate from planarity. The intramolecular distances of C8–C12, C1–C13, C5–C15, C4–C16, C6–C14, C3–C17 are 2.86, 4.82, 5.81, 5.21, 5.73 and 3.75 Å and the dihedral angle between the C3–C5–C6–C8 and C14–C15–C17–C12 planes is 61.36 Å. Both methoxy groups on the benzene rings of **3** point outwards,

away from the decamethylene bridge chain. This contributes to the lack of steric crowding with the hydrogens and carbons of the bridge chains.

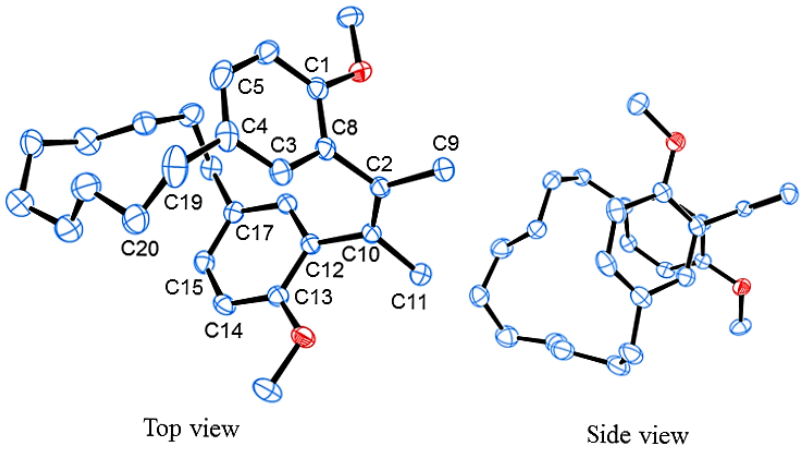


Figure 1. ORTEP drawing of 4,22-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene **3**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

To elucidate the effect of different substituents on the conformational properties of such systems, an attempt was made to functionalize **3** at its 5,21-positions by using the Rieche methodology[40] with dichloromethyl ether and titanium tetrachloride in dichloromethane. However, the resulting product was a complex mixture and subsequently attempts were undertaken to convert the methoxy groups into the hydroxyl groups to introduce a formyl group using Duff's method instead. Firstly, demethylation was carried out using boron tribromide, to afford the dialcohol, 4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **4**, within 0.5 h in 74% yield.

The structure of **4** was elucidated from elemental analysis and its spectral data. Notably, the cyclic structure was supported by the mass spectral data for **4** (M^+ = 378). The conformation of **4** was proposed from its ^{1}H NMR spectrum. If the conformation is of the *syn*-type, then the internally positioned aromatic protons (H_a) would receive a deshielding effect via the *p* electrons of the opposite side benzene ring. The other two aromatic protons (H_b, H_c) chemical shifts compared to (H_a) should be located at lower field positions. The ^{1}H NMR spectrum exhibited a doublet for the intra-annular proton H_i at δ 6.75 (J = 1.9 Hz) ppm, indicating that isomerization occurring between the *anti*- and *syn*-conformations (Figure 2).

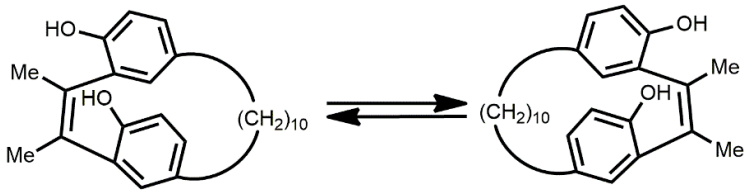


Figure 2. Conformational ring flipping of 4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **4**.

The aromatic protons of **4** are shifted to higher field at δ 6.56, 6.72 and 6.75 ppm than those of *anti*-compound **3** appearing at δ 6.59, 6.67 and 6.81 ppm. The ^{1}H NMR spectrum of **4** shows that its structure resembles entirely the *syn*-conformer. Furthermore, the protons of the decane bridge shows up as two multiplets centered at δ 1.43 and 2.38 ppm, respectively, via ring flipping fast *syn–syn* interconversion of the two *syn*-conformations of **4**; through this conversion **4** would exchange H_a and H_b of each CH_2 group. The peaks of the benzyl protons begin to merge and gradually a single peak is observed above 20 °C.

Thus, a single benzyl peak at δ 2.38 ppm is evident at 20 °C but when the temperature of the solution in $CDCl_3$ is decreased, it splits into two multiplets at δ 2.35 and 2. 43 ppm below –40 °C (Figure 3). This indicates that the rate of the conformational ring flipping of compound **4** is rapid on the NMR time-scale at this temperature. The energy barrier to the conformational ring flipping predicted from the coalescence temperature (T_c), which is 64 kJ mol^{-1}. This suggests that the introduction of a double bond in the ethylene bridge as well as substituents such as methyl and methoxy groups can control the *syn*- and *anti*-conformations of [2.10]MCP-1-ene **4**.

In addition, using NMR spectroscopy, intramolecular hydrogen bonding in compound **4** has been investigated in solution. In $CDCl_3$, the OH peak shifted to lower frequency at δ 5.47 ppm. Notably, the stretching vibration of the OH groups are at a lower frequency, which together with the resonance of the protons of the OH groups at lower field is characteristic of intramolecular hydrogen bonding.[31-33] Selected regions of the ^{1}H NMR spectrum of **4** which are exchanged by D_2O were analyzed in three different solvents, $CDCl_3$, acetone-d_6 and DMSO-d_6 to determine their solvation abilities. In acetone-d_6, the peak shifted to lower frequency at δ 7.47 ppm. In DMSO-d_6, a very sharp peak for the hydroxyl group was observed at δ 8.42 ppm. These results clearly indicate that the intramolecular hydrogen bonding is disrupted in polar solvents.

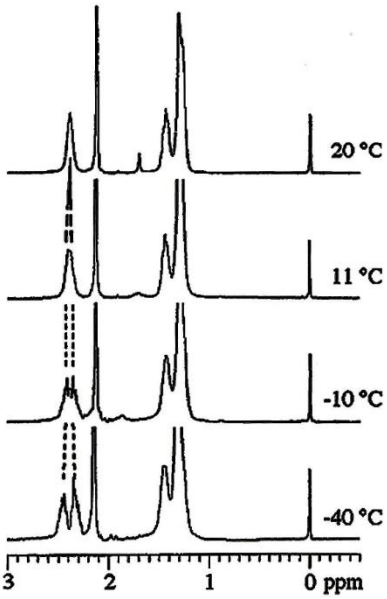


Figure 3. Dynamic ^{1}H NMR spectrum of **4** at 300 MHz ($CDCl_3$).

The single crystal structure of **4** (Figure 4) was determined by X-ray crystallography. The X-ray structure is that of the *syn* type, and the simultaneous formation of the partial hydrogen bonds between the two molecules thereby forming an intramolecular hydrogen bond between the two hydroxyl groups of compound **4** was confirmed and as predicted from the ^{1}H NMR spectroscopic data. The distance between H1 (OH) and O2 (OH) is 2.46 Å, which is a reasonable distance for intramolecular hydrogen bonding and which is less than the distance between H2 (OH) and O1 (OH) 3.59 Å. From the above results, it can be assumed that the hydrogen bonds of **4** contribute to the immobilization of the conformation.

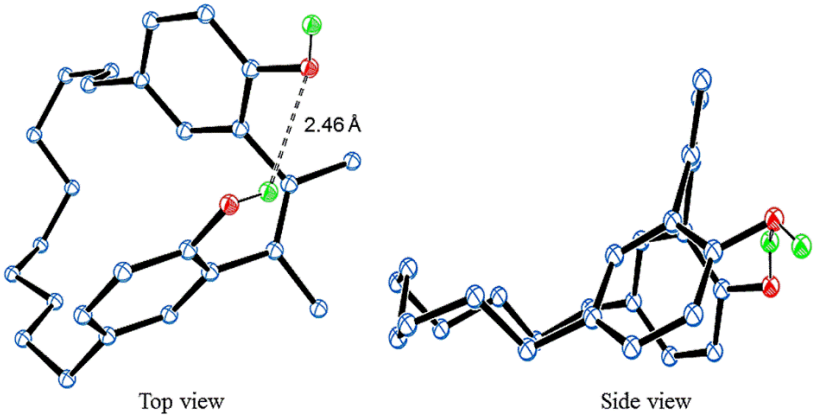
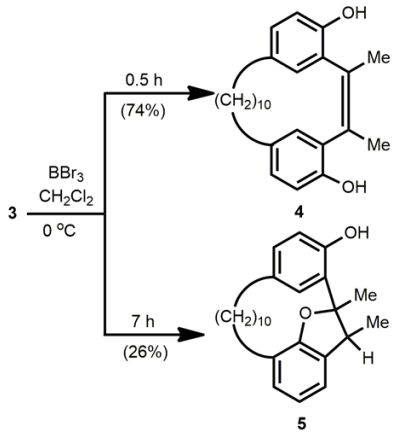


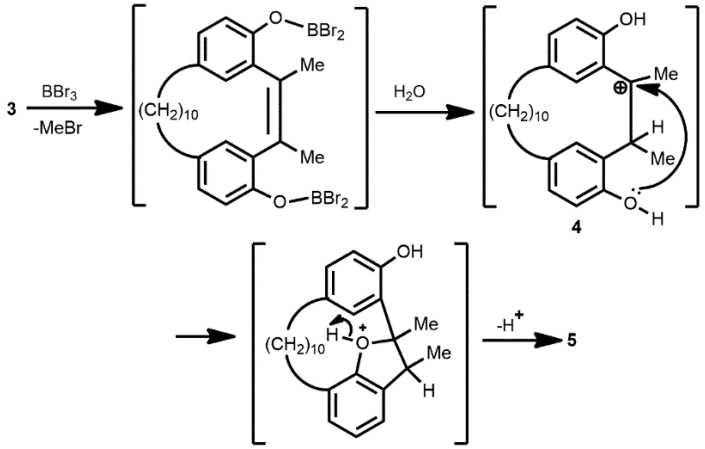
Figure 4. ORTEP drawing of 4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **4**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms except two are omitted for clarity.

Compound **3** was subjected to a further attempted demethylation reaction with boron tribromide in methylene chloride at 0 °C and prolonging the reaction time for 7 h. A new compound tetrahydro-benzofuranophane **5** was obtained in 26% yield (Scheme 2). 4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **4** is therefore considered as an intermediate to **5**.



Scheme 2. Synthesis of 1-(2'-hydroxyphenyl)-7,8-dimethyl[10](7,3')tetrahydro-benzofuranophane **5**.

Compound **3** was then converted to the expected compound **5** by a nucleophilic intramolecular cyclization reaction. Elemental analysis and spectral data were used to resolve the structure. The mass spectral data (M^+ = 378) strongly supported the cyclic structure. The generation of compound **5** was confirmed by the ^{1}H NMR spectrum; all the protons are non-equivalent. Seven aromatic protons are detected as a multiplets at δ 6.66–7.03 ppm, which are correlated with the unsymmetrical structure of **5**. On the basis of the spectral data and the chemical conversion, compound **5** is assigned to the structure, 1-(2'-hydroxyphenyl)7,8-dimethyl[10](7,3')tetrahydro-benzofuranophane.



Scheme 3. Possible reaction pathway of formation of **5**.

Although the mechanism of formation of compound **5** is not clear at this stage, a proposed reaction pathway is shown in Scheme 3. It is proposed that cyclization of ketonic **3** with the phenolic hydroxyl group forms the furan moiety which then is immediately transformed to the tetrahydrofuran ring by loss of a proton. Again, the BBr_3 induced conversion of **4** to **5** was probably followed by nucleophilic substitution at the C2 carbon to afford the five membered tetrahydrofuran skeleton which led to the desire product 1-(2'-hydroxyphenyl)-7,8-dimethyl[10](7,3')tetrahydro-benzofuranophane **5**.

The presence of hydrogen bonding which can be confirmed by analysis of crystal structure determinations can play a vital role in chemical reactions. Furthermore, such bonding can be useful in controlling unwanted association of specific functional groups in complex molecules.[41] It is well known that intermolecular hydrogen bonds play a significant role in the development of organized organic networks.[42]

Compound **5** contains hydrogen bonding donor /acceptor sites in the molecule which form inter- or intramolecular hydrogen bond interactions. In the IR spectrum, a peak at 3469 cm^{-1} was observed for the OH groups. The ^1H NMR spectrum also shows a signal for a single hydroxyl group proton at low field at δ 7.22 ppm in $CDCl_3$, which is exchanged by D_2O. The ^1H NMR spectra in three different solvents were then recorded to evaluate their solvation abilities: $CDCl_3$, acetone-d_6 and DMSO-d_6. In acetone-d_6, the peak shifted to lower field at δ 8.37 ppm. In DMSO-d_6, a sharp peak for the hydroxyl group was observed at δ 9.24 ppm. These results indicate that the intermolecular hydrogen bonding is disrupted in polar solvents. As shown in Figure 5, a single crystal X-ray diffraction analysis exposes the absence of intramolecular hydrogen bonding in the solid state.

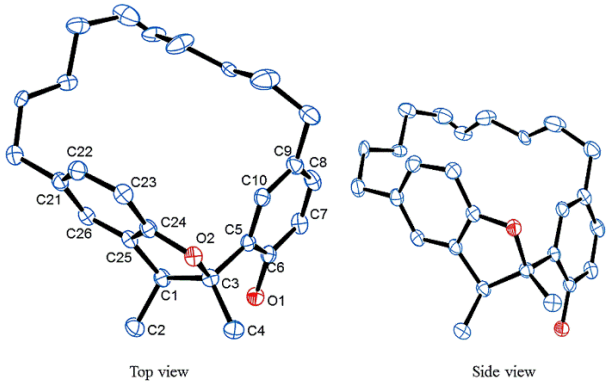
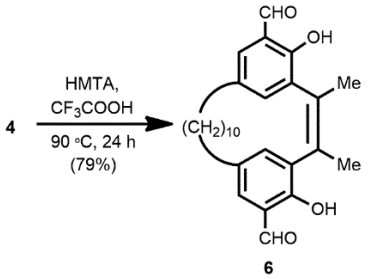


Figure 5. ORTEP drawing of 1-(2'-hydroxyphenyl)-7,8-dimethyl[10](7,3')tetrahydro-benzofuranophane **5**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

Examination of the crystal packing diagram of **5** reveals that the crystal lattice forms a hydrogen-bonded network, in which hydrogen bonding interactions between the oxygen atoms and the hydroxyl groups led to the construction of a chain extended along the crystal *c*-axis. The conformation of the molecule was influenced by these intermolecular OH···O hydrogen bonding. Parallel to the ab plane molecules are connected in a zig-zag chain fashion. There is a lack of intramolecular hydrogen bonding involving the aromatic cores, which adopt the gauche conformation to abstain a strong repulsion between rings. This conformation is evident by inspection of the torsion angle 178.67(2)°, between the two aromatic rings i.e. C6–C5–C3–O2, in Figure 5. The observed C6–O1 bond in **5** is 1.37 Å, considerably shorter than the C–O bond in phenol (1.38 Å).



Scheme 4. Synthesis of 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **6**.

Formylation at the 5,21-positions of **4**, using Duff's method with hexamethylenetetramine in trifluoroacetic acid at 90 °C for 24 h, afforded [2.10]MCP-1-ene **6** in 79% yield (Scheme 4). The mass spectrometry data for **6** (M^+ = 378) supported the cyclic structure. The ^{1}H NMR spectrum exhibited a doublet for the intra-annular proton H_i at δ 7.06 (J = 2.4 Hz) ppm, separated from the other aromatic protons of **6** at δ 6.98 ppm. The data is consistent with the structure resembling the *anti*-conformer. Furthermore, the compound forms an asymmetric conformation at –50 °C in solution as observed by the two sets of doublets for the methylene protons. The energy barrier to conformational ring flipping of compound **6** (Figure 6) was determined by a VT ^{1}H NMR experiment (from 20 °C to -50 °C) and the coalescence temperature (T_c = –50 °C) was found to be at 57 kJ mol^{-1}.

Furthermore, the compound appears to form an asymmetric conformation at –50 °C as observed by the two sets of doublets for the methylene protons (Figure 7). It is presumed that an intramolecular hydrogen bond formed between the hydroxyl groups and the formyl groups on the same benzene rings. There is a twist in the molecule and the two benzene rings are

oriented anti with respect to each other which can result due to the presence of the 10 cross-linking methylene groups.

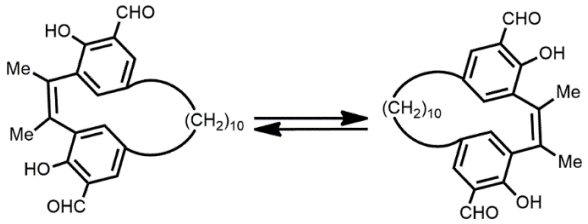


Figure 6. Conformational ring flipping of 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **6**.

As with compound **4**, the ^{1}H NMR spectra of **6** were recorded in each of the three different solvents: In $CDCl_3$, the low-field peak at δ 11.00 ppm shifted to δ 10.94 ppm; in acetone-d_6, the peak shifted to a higher frequency at δ 11.07 ppm. In DMSO-d_6, a sharp peak for the hydroxyl group was observed at δ 10.61 ppm, indicating that the intramolecular hydrogen bonding is disrupted in the polar solvent.

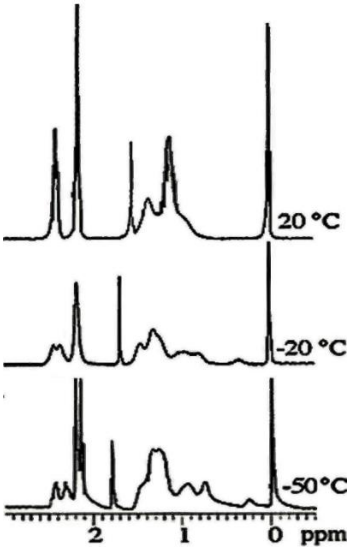


Figure 7. Dynamic ^{1}H NMR spectrum of 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **6** at 300 MHz ($CDCl_3$).

Crystals of **6** were grown from ethanol solution, and the structure was determined by single-crystal X-ray crystallography to confirm the conformation. [2.10]MCP-1-ene **6** crystallized in the monoclinic space group *P21/n* (Figure 8). The crystal structure reveals that the two carbonyl groups and two hydroxyl groups are orientated outwards. It is also clear that

the hydroxyl groups form intramolecular hydrogen bonds with the oxygen atoms of the formyl carbonyl groups, as predicted from the ^{1}H NMR spectroscopic data. The distance between H1 (OH) and O2 (CHO) is 1.78 Å, and that of H3 (OH) and O4 (CHO) is 1.71 Å, which are reasonable distances for intramolecular hydrogen bonding.

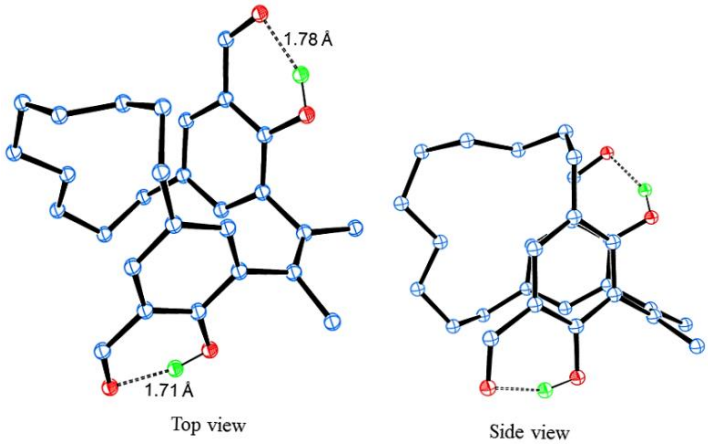


Figure 8. ORTEP drawing of 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **6**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms except two are omitted for clarity.

The distance between the two benzene rings in [2.10]MCP-1-ene **4** is somewhat greater than the equivalent distance in **6**. In the case of **4**, the intramolecular hydrogen bonding between the hydroxyl groups on the opposite aromatic rings is prevented in **6** due to the competing hydrogen bonding between the formyl group and hydroxyl group. The crystalline state of compound **6** is *anti*-type with the two benzene rings orientated at 180° to one another, as predicted from analysis of the ^{1}H NMR data.

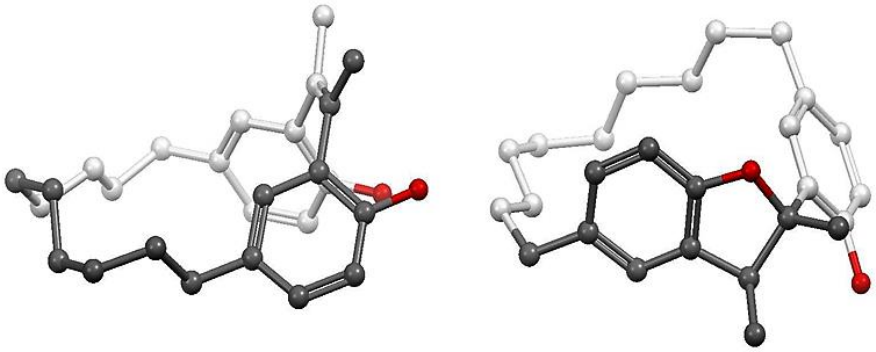


Figure 9. DFT geometry-optimized structures of **4** (top left) and **5** (top right). Color code: hydrogen = white, carbon = dark and light grey, and oxygen = red. Hydrogen atoms omitted for clarity.

Density functional theory (DFT) computational studies were carried out to determine the geometry-optimized energies of compounds **4** and **5** (Figure 9). The starting structures were generated with the initial geometries based upon their X-ray crystal structures. The DFT level of theory using the popular B3LYP (Becke, three-parameter, Lee-Yang-Parr)[43] exchange-correlation functional with the 6–31G(d) basis set. The individual geometry-optimized structures of these molecules were first conducted in the gas phase and then in solvent (chloroform) with the B3LYP/6-31G(d) basis set using Gaussian-09.[44] The DFT-geometry optimized B3LYP/6-31G(d) energies for the four conformers shown in Figure 9 for compounds **4** and **5** reveal that the order (in both the gas-phase or with the solvent correction term) of increasing stability is **5**>**4**.

Table 1. DFT geometry-optimized computed energies for the compounds **4** and **5** generated from the solid-state X-ray coordinates.

	Energy(kJmol^{-1})	
Compound	Gas-phase	Chloroform
4	-3050047.0	-3050063.6
5	-3050089.6	-3050103.3

The trend for the stabilities of **6**, **3** and **4** could presumably be rationalized both based on the *anti*-conformations of **6** and **3** vs the *syn* conformation of **4** (and the additional hydrogen bonding between the hydroxyl and adjacent formyl groups in **6**). However, the structure of **5** is sufficiently different making it inappropriate to compare with the other three compounds. The single crystal structure of **6** indicate that it adopts an *anti*-conformation and that the hydroxyl groups are pointed opposite to the benzene rings (Figure 8).

The estimation of the activation energy of the ring flipping:

By using Eqn (1) the rate constant (k_c) of the revealed conformational interconversion at the coalescence (T_c) can be calculated. The free energy of activation ($\Delta G_c^{\neq}$) at coalescence can be predicted by applying the Eyring equation [Eqn (2)].[45–46]

$$k_c = \pi\Delta\upsilon / 2^{1/2} \qquad (1)$$

$$\Delta G_c^{\neq} = 2.303RT_c\,(10.32 + \log T_c - \log k_c) \qquad (2)$$

2.3 Conclusions

In conclusion, a new synthetic route has been developed for *syn*- and *anti*-[2.10]MCP-enes with various derivatives. We report an expedient preparation procedure of 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]MCP-1-ene **6** from *p*-bromoanisole using a step by step reaction strategy. ^{1}H NMR spectroscopy and X-ray analysis of **3**–**6** confirmed the conformations present both in solution and in the solid state. The results from DFT computations were consistent with the observed experimental results. Further studies on the chemical behavior of compound **6** are now in progress.

2.4 Experimental Section

2.4.1 General

All melting points were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Nippon Denshi JEOL FT-300 spectrometer and Varian-400MR-vnmrs 400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. The IR spectra were obtained as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed with a Yanaco MT-5 analyser. Elemental analyses were performed by Yanaco MT-5. Gas–liquid chromatograph (GLC) analyses were performed by Shimadzu gas chromatograph, GC-14A; silicone OV-1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}.

2.4.2 Materials.

1,10-bis(4-methoxyphenyl)decane **1** was prepared following previous reports.[33]

2.4.2.1 Preparation of 1,10-bis(3-acetyl-4-methoxyphenyl)decane (2)

1,10-Bis(4-methoxyphenyl)decane **1** (5.32 g, 15.0 mmol) was dissolved into acetyl chloride (3.2 mL, 45.0 mmol) and methylene chloride (60 mL) at 0 °C. Aluminum chloride (8.91 g , 68.0 mmol) and nitromethane (15 mL) solution was slowly added to the solution

of compound **1** at 0 °C. After the reaction mixture was stirred at room temperature for 3 h, it was poured into ice-water (100 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined extracts were washed with water (50 mL × 2), dried over $MgSO_4$ and concentrated in *vacuo* to leave a residue. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-$CHCl_3$ (1:3) and $CHCl_3$ as eluent to give crude compound **2** as a colorless solid. Recrystallization from MeOH gave 1,10-bis(3-acetyl-4-methoxyphenyl)decane **2** (5.19 g, 79%) as colorless prisms; m.p. 72–76 °C. IR (KBr): ν_{max} = 3002, 2922, 2842, 2362, 1671, 1605, 1561, 1496, 1460, 1416, 1256, 1168, 1038, 804, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (16H, broad s), 1.55 (4H, broad s), 2.63 (6H, s), 3.73 (6H, s), 7.25 (2H, dd, *J* = 8.4, 2.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz) and 7.41 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.18, 29.41, 29.50, 31.47, 31.81, 34.78, 55.30, 55.52, 111.51, 114.13, 114.21, 126.96, 127.68, 127.87, 127.94, 129.95, 133.45, 133.50, 135.00, 157.11, 158.66 and 200.06 ppm. MS (EI): *m*/*z* 438 [M^+]. $C_{28}H_{38}O_4$ (438.60): calcd. C 76.68, H 8.73; found: C 76.54, H 8.71.

2.4.2.2. McMurry coupling reaction of 1,10-bis(3-acetyl-4-methoxyphenyl)decane (2)

The McMurry reagent was prepared from $TiCl_4$ (13.79 mL, 130 mmol) and Zn powder (18 g, 278 mmol) in dry THF (200 mL), under nitrogen. A solution of 1,10-bis(3-acetyl-4-methoxyphenyl)decane **2** (4.0 g, 0.091 mmol) in dry THF (150 mL) was added within 24 h to the black mixture of the McMurry reagent by using a high-dilution technique with continuous refluxing and stirring. The reaction mixture was refluxed for an additional 5 h, cooled to room temperature and hydrolyzed with aqueous 10% K_2CO_3 (500 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (200 mL × 3), and the combined extracts were washed with water, dried with Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (Wako C-300, 500 g) with hexane/$CHCl_3$ (1:2) as eluent to give crude compound **3** as a colorless solid. Recrystallization from EtOH gave 4,22-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene **3** (2.71 g, 73%) as colorless prisms; m.p. 123–124 °C. IR (KBr): ν_{max} = 2994, 2931, 2849, 2363, 2329, 1596, 1487, 1459, 1446, 1227, 1179, 1103, 1055, 1035, 891, 802, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (12H, broad s), 1.56 (4H, broad s), 2.12 (6H, s), 2.34 (4H, broad s), 3.60 (6H, s), 6.59 (2H, d, *J* = 8.3 Hz), 6.67 (2H, d, *J* = 2.2 Hz) and 6.81 (2H, dd, *J* = 8.3, 2.2 Hz) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 20.30, 26.13, 26.36, 26.88, 29.87, 34.33, 55.12, 109.99, 126.71, 130.00, 133.61 and 154.36 ppm. MS (EI): *m*/*z* 406 [M^+]. $C_{28}H_{38}O_2$ (406.60): calcd. C 82.71, H 9.42; found: C 82.43, H 9.30.

2.4.2.3. Demethylation of 4,22-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene 3 with BBr_3

To a solution of 4,22-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene **3** (1.01 g, 0.248 mmol) in CH_2Cl_2 (30 mL) at 0 °C was gradually added a solution of BBr_3 (4.8 mL, 49.62 mmol) in CH_2Cl_2 (50 mL) over 1 h. After stirring the reaction mixture at room temperature for 30 min, it was poured into ice-water (50 mL), extracted with CH_2Cl_2 (30 mL × 2). The combined extracts were washed with water (30 mL × 2), dried over $MgSO_4$ and concentrated in *vacuo* to leave a residue. Recrystallization from EtOH gave 4,22-dihydroxy-1,2-dimethyl[2.10]metacyclophan-1-ene **4** (789 mg, 74%) as colorless prisms; m.p. 126–127 °C. IR (KBr): ν_{max} = 2942, 2850, 2359, 1601, 1496, 1453, 1428, 1256, 1180, 1143, 1112, 1068, 1024, 894, 808, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (12H, broad s), 1.43 (4H, broad s), 2.12 (6H, s), 2.38 (4H, broad s), 5.47 (2H, s), 6.56 (2H, d, *J* = 8.4 Hz), 6.72 (2H, dd, *J* = 8.4, 1.9 Hz) and 6.75 (2H, d, *J* = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.73, 26.24, 26.88, 27.41, 30.27, 34.87, 114.94, 127.62, 129.69, 130.28, 131.51, 134.42 and 149.77 ppm. MS (EI): *m*/*z* 378 [M^+]. $C_{26}H_{34}O_2$ (378.55): calcd. C 82.49, H 9.05; found: C 82.83, H 9.06.

2.4.2.4. Preparation of 1-(2'-hydroxyphenyl)-7,8-dimethyl[10](7,3')tetrahydro-benzofuranophane 5

To a solution of 4,22-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene **3** (600 mg, 1.48 mmol) in CH_2Cl_2 (20 mL) at 0 °C was gradually added a solution of BBr_3 (2.99 mL, 31.7 mmol) in CH_2Cl_2 (40 mL). After the reaction mixture has been stirred at room temperature for 7 h, it was poured into ice-water (50 mL), extracted with CH_2Cl_2 (30 mL × 2). The combined extracts were washed with water (30 mL × 2), dried over $MgSO_4$ and concentrated in *vacuo* to leave a residue. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane/ethyl acetate (5:1) as eluent to give crude compound **5** as a colorless solid. Recrystallization from hexane gave 1-(2'-hydroxyphenyl)-7,8-

dimethyl[10](7,3')tetrahydro-benzofuranophane **5** (186 mg, 26%) as colorless prisms; m.p. 159–161 °C. IR (KBr): ν_{max} = 3454, 2929, 2849, 1612, 1511, 1489, 1460, 1424, 1380, 1336, 1263, 1220, 1199, 1125, 1088, 1052, 907, 884, 804, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84–1.17 (16H, m), 1.29 (3H, d, *J* = 5.3 Hz), 1.80 (3H, s), 2.46 (2H, t, *J* = 6.3 Hz), 2.55 (2H, t, *J* = 9.3 Hz), 3.73 (1H, q, *J* = 10.6, 5.3 Hz), 6.66–7.03 (6H, m) and 7.22 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.94, 21.98, 25.37, 27.32, 27.53, 27.55, 27.67, 28.49, 29.34, 31.17, 34.01. 34.88, 43.95, 93.63, 109.12, 116.84, 124.59, 125.72, 128.03, 128.96, 130.40, 133.63, 133.70, 135.01, 152.13 and 154.61 ppm. MS (EI): *m*/*z* 378 [M^+]. $C_{26}H_{34}O_2$ (378.26): calcd. C 79.15, H 8.69; found: C 79.01, H 8.79.

2.4.2.5. Formylation reaction of 4,22-dihydroxy-1,2-dimethyl[2.10]metacyclophan-1-ene 4

4,22-dihydroxy-1,2-dimethyl[2.10]metacyclophan-1-ene **4** (386 mg, 1.02 mmol) was added into trifluoroacetic acid (3 mL) with hexamethylenetetramine (358 mg, 2.55 mmol) and the mixture stirred for 24 h at 90–100 °C. After cooling the reaction mixture to room temperature, it was again stirred for additional 1 h with 10% HCl (10 mL) and extracted with styrene (10 mL × 3). The combined extracts were washed with 10% HCl and water (10 mL × 2), dried over $MgSO_4$ and concentrated in *vacuo* to leave a residue. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane/$CHCl_3$ (1:3) as eluent to give the crude compound **6** as a colorless solid. Recrystallization from EtOH gave 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl[2.10]metacyclophan-1-ene **6** (350 mg, 79%) as yellow prisms; m.p. 139–140 °C. IR (KBr): ν_{max} = 2922, 2849, 2356, 2318, 1641, 1445, 1372, 1256, 1227, 1088, 768, 718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 27 °C): δ 1.12 (12H, broad s), 1.36 (4H, broad s), 2.14 (6H, s), 2.40 (4H, broad s), 6.98 (2H, d, *J* = 2.4 Hz), 7.06 (2H, d, *J* = 2.4 Hz), 9.76 (2H, s) and 10.94 (2H, broad s) ppm. ^1H NMR (300 MHz, $CDCl_3$, –50 °C): δ = 1.31 (12H, broad s), 1.78 (2H, broad s), 2.16 (6H, m), 2.35 (4H, broad), 6.95 (2H, d, *J* = 2.4 Hz), 7.06 (2H, d, *J* = 2.4 Hz), 9.75 (2H, s), 10.93 (2H, broad s) and 11.23 (2H, broad s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.40, 26.22, 26.26, 26.48, 29.05, 30.86, 33.58, 119.90, 131.41, 133.14, 133.46, 137.88, 156.84, 196.35 and 206.8 ppm. MS (EI): *m*/*z* 434 [M^+]. $C_{28}H_{34}O_4$ (434.57): calcd. C, 77.39; H, 7.89; found: C, 77.32; H, 7.89.

2.4.3 Crystallography

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation for **1** and **9**. Data were corrected for Lorentz and polarisation effects and for absorption. The structures were solved by charge flipping or direct methods algorithms and refined by full-matrix least-squares methods, on F^2.

Table 2. Summary of crystal data for the compounds **3**–**6**.

Parameter	**3**	**4**	**5**	**6**
Empirical formula	$C_{28}H_{38}O_2$	$C_{26}H_{34}O_2$	$C_{26}H_{33}O_2$	$C_{28}H_{34}O_4$
Formula weight	406.61	378.53	377.55	434.55
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P 2₁/n*	*P 2₁/n*	*P 2₁/c*	*P 2₁/n*
a[Å]	12.8863(3)	13.2771(4)	12.1961(4)	8.9173(3)
b[Å]	12.7499(3)	8.3928(2)	17.6743(5)	17.6623(5)
c[Å]	14.5674(3)	19.8876(7)	10.2343(3)	15.1218(5)
α[°]	90.0000	90.0000	90.0000	90.0000
β[°]	98.6950(7)	98.6950(7)	98.6950(7)	98.6950(7)
γ[°]	90.0000	90.0000	90.0000	90.0000
Volume[Å^3]	2365.90(9)	2365.90(9)	2365.90(9)	2365.90(9)
Z	4	4	4	4
Dcalcd[Mg/m^3]	1.141	1.141	1.141	1.141
Temperature [K]	123	123	123	123
Unique reflns	4340	4340	4340	4340
Obsd reflns	3982	3982	3982	3982
Parameters	273	273	273	273
R(int)	0.0361	0.0361	0.0361	0.0361
$R[I > 2\sigma(I)]$[a]	0.0629	0.0629	0.0629	0.0629
*wR*2[all data][b]	0.1627	0.1627	0.1627	0.1627
GOF on F^2	1.074	1.074	1.074	1.074

[a]Conventional R on Fhkl: Σ||Fo| – |Fc||/σ|Fo|. [b] Weighted R on |Fhkl|2: Σ[w(Fo2 – Fc2)2]/Σ[w(Fo2)2]1/2

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1495165, CCDC 1495166, CCDC 1495167 & CCDC 1495168. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ,

UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Chapter 3

Synthesis and structure of 1,2-dimethylene[2.*n*]metacyclophane and its conversion to chiral [*n*]benzenometacyclophanes

Bromination of 5,n-di-tert-butyl-8,n-dimethoxy-1,2-dimethyl[2.n]metacyclophan-1-ene (MCP-1-ene) with benzyltrimethylammonium tribromide exclusively afforded 1,2-bis (bromomethyl)-5,n-di-tert-butyl-8,n-dimethoxy[2.n]MCP-1-ene. Debromination of this compound with Zn and AcOH in CH_2Cl_2 produced the identical dimethylene[2.n]MCP. Subsequently, dimethylene[2.n]MCP was reacted with dimethyl acetylenedicarboxylate (DMAD) to provide 1,2-(3',6'-dihydrobenzo)-5,n-di-tert-butyl-8,n-dimethoxy[2.n]MCP-4',5'-dimethylcarboxylate which was converted to a novel and inherently chiral areno-bridged dimethoxy[2.n]MCP-4',5'-dimethylcarboxylate by aromatization.

3.1 Introduction

Cyclophanes are a class of compound that has undergone extensive studies in recent decades.[1] Metacyclophanes (= MCPs) have been known for nearly 45 years,[2] with the short chain (n = 4–6) members having attracted the appreciation of chemists as exemplary compounds to test the limits of bending aromatic rings.[3] Some of the reports focus on synthesis and conformational studies of the macrocyclic compounds, but few researchers have investigated the flexible conformations of the synthesized macrocyclic compounds and their conversion into rigid structures to provide as suitable platforms for diverse complexation experiments.[4] Our interest in this field stems from investigations of cyclic diynes in which two double bonds were part of the ring system.[5]

The syntheses of [*n*]MCP-diynes and conversion of the propargylic moieties into allenic moieties in the presence of strong bases was reported by Ramming and Gleiter.[6] Kawase and co-workers described the synthetic procedure for [2.*n*]MCP-ynes by bromination–dehydrobromination of the corresponding MCP-enes, which are considerably strained with bent triple bonds.[7] On the other hand, although the parent [2.2]MCP was first explored as early as in 1899 by Pellegrin,[8] the synthesis of *syn*-[2.2]MCP was achieved 85 years later. A successful preparative method for *syn*-[2.2]MCP has been introduced which uses (arene) chromium–carbonyl complexation at low temperature.[9] Further, Boekelheide[10] and Staab[11] have succeeded in synthesizing intra–annularly substituted [2.2]MCP, respectively. For alkene-containing MCPs, the McMurry reaction holds is a promising one-step pathway, but this reaction route prefers coupling two identical functional groups to facilitate the synthesis of the direct cyclophanes precursors.[12–16]

However, reports on the synthesis of [2.*n*]MCP-dienes containing long carbon chain as well as their chirality have not yet been published. Inherent chirality is a property of molecules whose lack of symmetry does not originate from a classic stereogenic element, but is rather the effect of the presence of curvature within a structure that would be lacking of symmetry axes in any two-dimensional representation.[17] A large number of inherently racemic chiral macromolecules have been reported, and some of them have been resolved into enantiomerically pure form.[17] Applications of inherently chiral molecules in molecular recognition[18] and asymmetric catalysis[19] have been reported.

Our group has published a series of papers describing McMurry coupling reactions of tethered dialdehydes and ketones, in which the restrain length ranged from 2 to 10 and every accessible position on the aromatic rings was at some point substituted.[20] In this paper, we describe the first preparation of inherently chiral areno–bridged [2.*n*]MCP (*n* = 10, 4) by using a bromination reaction and Diels–Alder reactions followed by aromatization with DDQ.

3.2 Results and Discussion

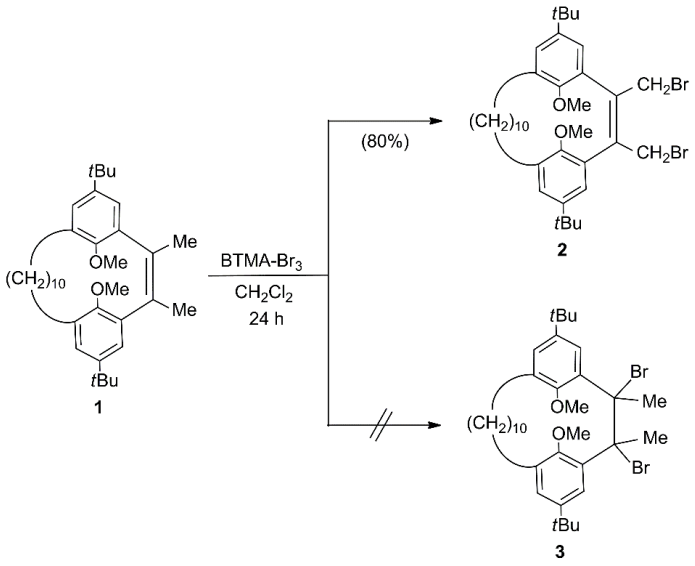
Very recently, we reported a synthesis and conformational study of [2.*n*]MCP-1-enes and the reaction with BBr_3 to afford tetrahydrobenzofuranophane.[21] We also reported inherent chirality in the MCP structure.[22] As part of our continued interest in the synthesis of inherently chiral MCPs, we undertook a systematic investigation of the starting compound 5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene **1** containing both decane (longer carbon chain) and ethylene bridges, which were synthesized from 1,10-bis(5-*tert*-butyl-2-methoxylphenyl)decane in four steps by using the *tert*-butyl group as a positional protective group on the aromatic ring.[23] Formylation of 1,10-bis(5-*tert*-butyl-2-methoxyl-phenyl)decane with dichloromethyl methyl ether (Cl_2CHOCH_3) in the presence of titanium tetrachloride in CH_2Cl_2 for 2 h afforded 1,10-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl) decane. The bisformylated compound was converted to the bis-alcohol derivative in 87% yield by reaction with the Grignard reagent MeMgI in ether and then oxidation with pyridinium chlorochromate (PCC) to afford the bisacetyl derivative in 71% yield, which was subjected to reductive coupling by the McMurry reaction following the improved Grützmacher's procedure[16] to afford the desired compound **1** in 90% yield.[24]

None of the corresponding *anti*-isomer was observed under the conditions used. The structure of **1** was confirmed by comparing the melting point and ^{1}H NMR spectroscopic data with the reported data. Previously we failed to get single crystal of compound **1**, although we tried several times using different conditions. However, we have now succeeded in growing single crystals by slow evaporation of a saturated dichloromethane solution. The conformation was assigned by using both single crystal X-ray crystallography and ^{1}H NMR ($CDCl_3$, 300 MHz) spectroscopic analysis. The ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **1**

exhibits a single peak at δ 3.65 ppm for the methoxy protons indicating that the two methoxy groups are outside of the two benzene rings (*syn*-conformation) and methoxy protons appear at the normal position as for anisole. The aromatic protons appear in the high field region at δ 6.77 and 6.85 ppm due to shielding by the adjacent ring current; this is a common consequence of face-to-face benzene rings due to the *syn*-conformation.[24] The crystal structure was found to belong to the monoclinic crystal system with space group $P\ 2_1/n$ and is fully consistent with the ^{1}H NMR spectroscopic data for compound **1**.

The X-ray structure (CCDC no: 908365) of **1** (Figure 1) clearly demonstrates that **1** exists as the *syn*-conformer in the solid state and that the two methoxy groups lie on the correlative side of the 18-membered inner ring, which contains the long bridging C19–C27 chain pointing toward the outer direction thereby minimizing steric repulsion with the bridge chain. The selected bond lengths of C27–C28 and C1–C27 in the decamethylene chains and C3–C12 and C16–C13 in the ethylenic chains have typical values at 1.53, 1.50, 1.50 and 1.49 Å, respectively. The length of the double bond in C12–C13 is 1.34 Å, which is like that of ethylene. The bond angles defined by C3–C12–C13 and C12–C13–C16 are 123.6(2)° and 122.7(2)°, reveal that compound **1** displays a non-distorted conformation. The two benzene rings of **1** slightly deviate from planarity. The intramolecular distances of C3–C16, C2–C17, C5–C20, C4–C21, C1–C18, C6–C19 are 2.98, 4.18, 5.07, 3.59, 5.67 and 6.04 Å.

Bromination of **1** with 4.4 equiv. of benzyltrimethyl-ammonium tribromide (BTMA-Br_3)[25] in dry CH_2Cl_2 solution at room temperature for 24 h afforded the corresponding 1,2-bis(bromomethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene **2** in 80% yield (Scheme 1). Here we use BTMA-Br_3 because it is easy to handle and a mild brominating reagent allowing us to control the reaction pathway. No bromination of compound **2** at the alkene bridge (double bond) was observed. This result is entirely different from the bromination of the corresponding [2.10]MCP-1-ene which afforded the *cis*–addition product (to the bridging double bond).[25] The presumed mechanism involves the initial formation of the bromonium ion followed by consecutive deprotonation and HBr elimination to afford diene **2**.[26,27]



Scheme 1. Synthesis of *syn*-1,2-bis(bromomethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP **2**.

On changing the amount of BTMA-Br_3 used in this reaction there is the possibility of recovering the starting material. For example, when the compound **1** was treated with 1.2 equiv. of BTMA-Br_3 at room temperature for 24 h, **2** was formed in 30% yield with 60% recovery of compound **1** (Table 1). When the ratio was increased to around 2.4 equiv. under the same reaction conditions, the yield of compound **2** increased to about 65% and became 80% when employing 4.4 equiv. of BTMA-Br_3. Here, isolated yields are decreased in terms of the purification process.

Table 1. Bromination of 5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene **1**.

Run	$BTMABr_3$ [equiv.]	Products yield [%][a]	
		2	Recovery of **1**
1	1.2	30	65
2	2.4	65	30
3	4.4	80	20

[a] Isolated yields are shown in parentheses.

The structure of product **2** was estimated on the basis of elemental analyses and spectral data. The mass spectral data for diene **2** (M^+ = 676, 678 and 680) strongly supported a dibominated structure. The ^1H NMR spectrum of **2** disclosed a singlet for the methoxy protons at δ 3.65 ppm as well as resonances at δ 6.67 and 6.91 ppm (J = 2.4 Hz) for the two

protons of the aromatic rings. Previously reported[17b] 1,2-bis(bromomethyl)[2.3]MCP-1-ene exhibited a lower-field shift for the methoxy protons at δ 3.22 ppm along with δ 6.99 and 7.19 ppm (J = 2.4 Hz) for the two aromatic protons because of the short carbon chain length. The methylene protons of the bromomethyl group were observed as a doublet at δ 4.52 and 4.84 (J = 10.0 Hz) ppm. Thus, the introduction of the bromo group at the methyl group might restrict the rotation throughout the single bond of C–CH_2Br, thereby causing the methylene protons to be in a diasterotopic environment.

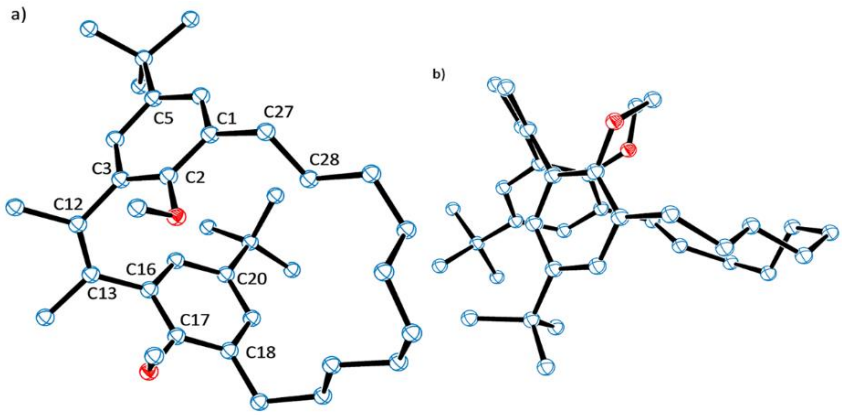
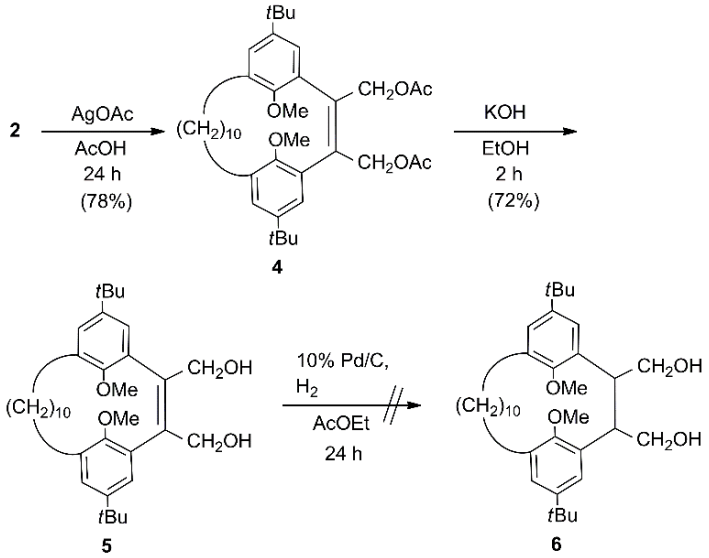


Figure 1. Single-crystal structure of **1** showing (a) the side view (b) the top view. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

Treatment of 1,2-bis(bromomethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene **2** with silver acetate in acetic acid at 100 °C for 24 h resulted in the analogous acetate compound **4** in 78% yield. Compound **4** was further converted to the 1,2-bis (hydroxymethyl) derivative **5** in quantitative yield by hydrolysis with KOH in presence of EtOH for 2 h in 72% yield (Scheme 2). After that, hydrogenation of compound **5** in presence of 10% Pd /C for 24 h failed to afford the expected compound **6**. Only the starting compound **5** was recovered. This result might be due to the cyclophane structure of compound **5**. However, the explanation of the present result is pending definition.

The cyclic dimeric structure was strongly supported by the mass spectral data for compound **4** (M^+ = 634). The 300 MHz ^{1}H NMR spectrum of **4** in $CDCl_3$ showed a single peak at δ 3.68 ppm for the methoxy protons together with δ 6.79 and 6.95 (J = 2.4 Hz) ppm for the two aromatic protons. The methylene protons of the acetate group were observed as a doublet at δ 5.14 and 5.20 (J = 12.6 Hz) ppm. On the basis of the spectral data and the

chemical conversion, compound **4** is assigned to the structure, 1,2-bis(acetoxymethyl)-5,21-di-*tert*-butyl-8,24-dimeth- oxy[2.10]MCP-1-ene **4**.



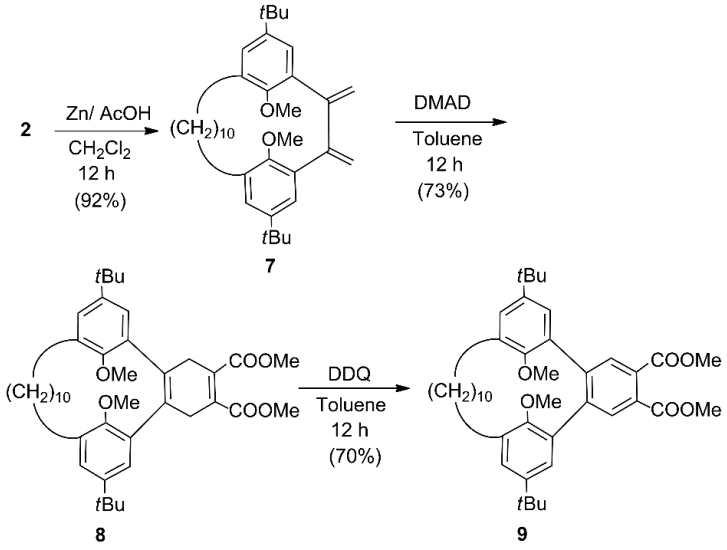
Scheme 2. Synthetic strategy for debromination of 1,2-bis(bromomethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene **2** via diol **6**.

Elemental analysis and spectral data were used to evaluate the structure of compound **5**. The structure of compound **5** was confirmed by the ^{1}H NMR spectrum. The methoxy protons were detected by a single peak at δ 3.74 ppm, and additional peaks at δ 6.77 and 6.95 (J = 2.4 Hz) ppm for the two aromatic protons. The methylene protons of the hydroxyl group were observed as a doublet at δ 4.50 and 4.80 (J = 12.6 Hz) ppm. Using the spectral data, compound **5** is assigned to the structure *syn*-1,2-bis(hydroxymethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene **5**.

To synthesize the diene body in the dehydration reaction for the Diels-Alder reaction, the reduction reaction of the double bonds does not proceed. Interestingly, treatment of **2** with Zn and dropwise addition of AcOH in dry CH_2Cl_2 solution at room temperature for 24 h afforded the identical 1,2-dimethylene[2.10]MCP **7** in 75% yield (Scheme 3). This type of reaction has been widely used to eliminate a bromine group to form a double bond.

The structure of the diene obtained in the present work was determined from the elemental analyses and spectral data. The 300 MHz ^{1}H NMR spectrum of **7** in $CDCl_3$ exhibited a doublet at δ 6.92 and 7.05 ppm for the two protons of the aromatic rings. The *exo*-methylene protons of the ethano-bridge were displayed as broad singlets at δ 5.53 and 5.69 ppm, and

the protons of the methoxy group were observed at δ 3.64 ppm. The decamethylene bridge protons gave rise to a abstruse signal pattern as predicted for a rigid [2.10]MCP.



Scheme 3. Synthesis of *syn*-1,2-dibenzo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-4′,5′-dimethylcarboxylate **9**.

The protons of the benzylic CH_2 group were observed as two multiplets at δ 2.11–2.38 and 2.73–2.90 ppm, which were additionally split by coupling with the protons of the central CH_2 groups. This central CH_2 groups was also observed as multiplets centered at δ 0.91–1.15 ppm. It was also observed that these methylene peaks did not merge up to 120 °C in $CDBr_3$. These findings suggested that the introduction of two double bonds of the ethano-bridge might inhibit the *syn–syn* conformational flipping of 1,2-dimethylene[2.10]MCP **7** above this temperature which would exchange H_A and H_B of each CH_2 group. These perceptions suggested that the introduction of two double bonds of the ethano–bridge might restrict the *syn*-conformation of 1,2-dimethylene[2.10]MCP **7**.

Compound **7** is a stable solid and easy to purify. Compound **7** is conveniently employed in the reaction with dimethyl acetylenedicarboxylate (DMAD) to provide **8** in good yield. Diels-Alder adduct **8** was converted to areno–bridged [2.10]MCP **9** by aromatization with dichlorodicyano-*p*-benzoquinone (DDQ). The present Diels–Alder reaction of **7** with DMAD was completed within 24 h in toluene at reflux. Thus, the Diels–Alder reactivity of compound **7** exceeds that of 2,3-diphenyl-1,3-butadiene. This result suggests that the energy of the fixed s-*cis* conformation in**7** in the ground and transition state might lower the Diels–Alder barriers

due to the inflexibility of the MCP ring. The Diels–Alder reaction of **7** with suitable dienophiles followed by aromatization can be used to prepare a range of areno-bridged [2.*n*]MCPs.

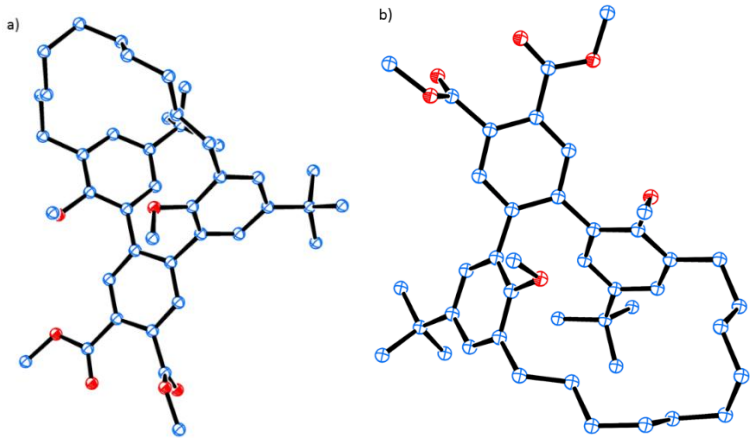


Figure 1. Single-crystal structure of **9** showing (a) the side view (b) the top view. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

Owing to the intrinsic structural features, we envisaged that MCP **9** would led to inherent chirality macrocycles due to intramolecular overcrowding like helicenes[28] or MCPs.[29] The synthesis and optical resolution of inherently chiral MCPs are challenging, but because of their potential uses in supramolecular chemistry, they remain attractive.[30] The design and synthesis of inherently chiral MCPs with novel structures therefore is a topic of great significance.

The structure of product **9** was determined by spectroscopic methods (^{1}H NMR and ^{13}C NMR), mass spectrometry and elemental analyses. The cyclic dimeric structure was confirmed by the mass spectral data for compound **9** (M^{+} = 657). The 300 MHz ^{1}H NMR spectrum of **9** in $CDCl_3$ exhibited a single peak at δ 3.68 ppm for the methoxy protons together with δ 6.84 and 7.05 (J = 2.4 Hz) ppm for the two aromatic protons. On the basis of the spectral data and the chemical conversion, compound **9** is assigned to the structure, 1,2-dibenzo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-4',5'-dimethylcarboxylate (**9**).

In anticipation of future investigations into the ability of MCPs to be employed as chiral catalysts and ligands, efforts were made to access the solid-state structures and the high-resolution NMR spectral data. Inherent chirality is a feature associated with some MCPs and

9 is predicted to have a plane of chirality. This is because it has two different types of substituents and bridged linkages which are fixed in a C_1 symmetrical structure and does not sustain a conformational change at or near ambient temperature.

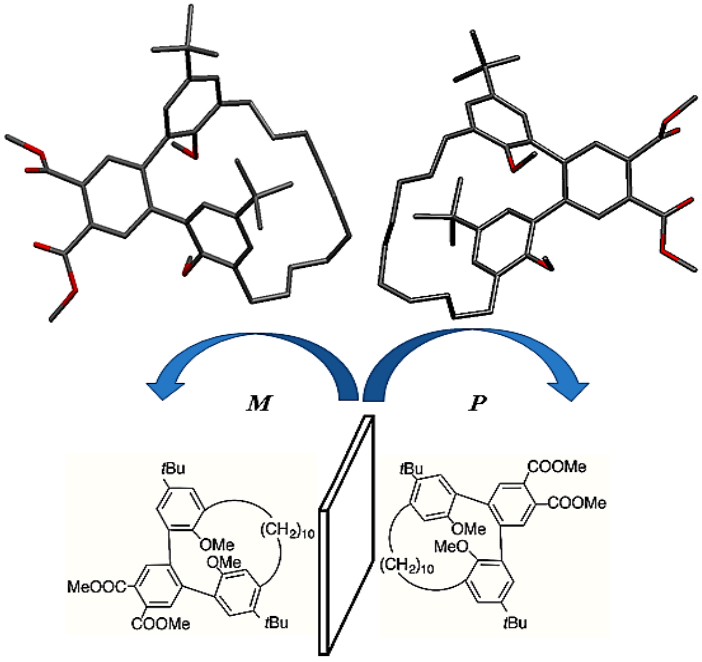
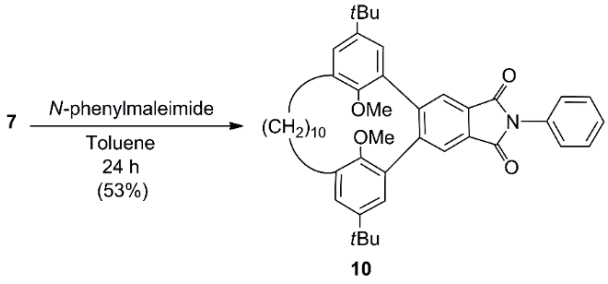


Figure 3. Schematic diagram of *M*-**9** (left side) and *P*-**9** (right side).

Compound **9** was crystallized by the slow, room temperature evaporation of a dichloromethane solution, into the space group *P-1*. Interestingly, the X-ray analysis disclosed that areno–bridged **9** adopts helical chirality, yet surprisingly, the dihedral angle of the arylenes connected by the phenyl unit is 33.98°. Consequently, the compound is chiral and the (*M*)- and (*P*)-isomers are packed alternatively in the crystal as depicted schematically in Figure 3 (CCDC no: 908368).



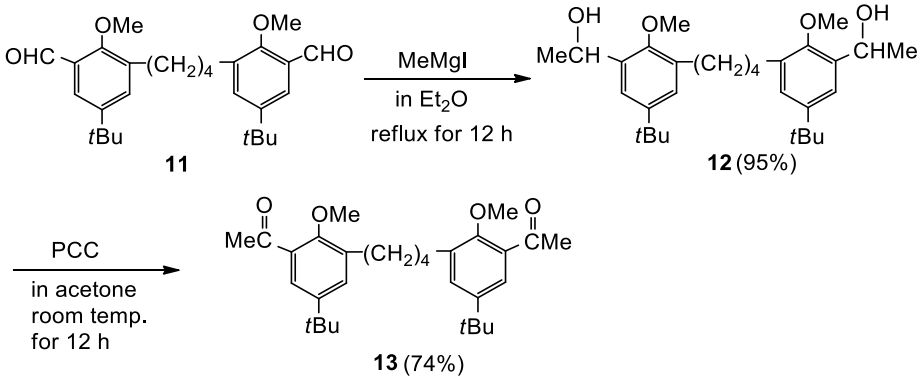
10

Scheme 4. Synthesis of 1,2-dibenzo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-4′,5′-*p*-dimethylbenzylamine **10**.

The removal of the external substituted COOMe group in compound **9** is preferable than that of the internal substituted OMe group. However, this process required very high temperatures and prolonged reaction times. In order to improve the reaction conditions to more suitable milder conditions, the reaction pathway was initiated from 1,2-dimethylene[2.10]MCP **7**. Compound **7** was treated with *N*-phenylmaleimide with toluene at 110 °C for 24 h to synthesized compound **10** (53% yield) as illustrated in Scheme 4.

The structure of **10** was characterized by ^{1}H and ^{13}C NMR, mass spectra and elemental analysis. The cyclic dimeric structure was strongly supported by the mass spectral data for compound **10** (M^{+} = 689). The ^{1}H NMR spectrum of **10** (300 MHz, $CDCl_3$) exhibits a single peak at δ 3.64 ppm for the methoxy protons together with six aromatic protons appeared as doublets at δ 6.69, 6.89 ppm and a singlet at δ 7.33 ppm, respectively, which are associated with the unsymmetrical structure of **10**.

Later we also described the shorter carbon chain [2.4]MCP and its properties concerning Diels–Alder reaction for the areno bridge structure through aromatization, which is slightly different from the longer carbon chain [2.10]MCP. The starting compound 1,4-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)butane **11** was easily prepared from 1,4-bis(5-*tert*-butyl-2-methoxyphenyl)butane according to our previously reported synthetic procedure.[23,24]

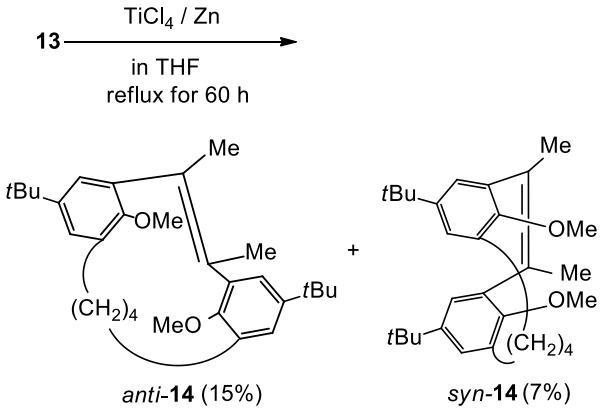


Scheme 5. Synthesis of 1,4-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)butane **13**.

In the presence of dichloromethyl ether and titanium tetrachloride ($TiCl_4$), a regioselective Friedel-Crafts acylation reaction[20,21] at the *meta* position of 1,4-bis(5-*tert*-butyl-2-methoxyphenyl)butane was achieved at room temperature to afford **11** in 68% yield. To a solution of methylmagnesium iodide in Et_2O was added dropwise a

solution of compound **11** in tetrahydrofuran (THF) under relatively mild conditions (refluxing for 12 h). The product afforded was 1,4-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)butane **12** in 95% yield.

Oxidation of compound **12** was carried out in acetone by dropwise addition to a solution of pyridinium chlorochromate (PCC) in acetone and stirring at room temperature for 24 h; 1,4-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)butane **13** was isolated in 74% yield as shown in Scheme 5.[23,24] Elemental analysis and spectral data were used to resolve the structures of compounds **12** and **13**. Furthermore, the ^{1}H NMR spectroscopic signals of **12** and **13** were also unambiguously assigned. Compound **13** was further subjected to reductive coupling by following McMurry reaction through the upgraded Grützmacher's procedure[16] (Scheme 6).



Scheme 6. Synthesis of *anti*- and *syn*-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]MCP-1-ene **14.**

Thus, the reductive coupling reaction of **13** was carried out by using $TiCl_4$-Zn in the presence of pyridine in refluxing THF under high dilution conditions to afford the required compounds *anti*- and *syn*-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]MCP-1-ene **14** in 15 and 7% yields, respectively. This result was different from that of the related McMurry cyclization of 1,3-bis(5-acetyl-2-methoxyphenyl)propane, which provided the identical [3.1]MCP by using $TiCl_4$ or acid induced pinacol rearrangement reaction.

The structure of **14** was elucidated based on elemental analyses and spectral data. The mass spectral data for **14** (M^+ = 434.65) fully support the cyclic structure. The conformation of **14** was clear from the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of

anti-**14** in $CDCl_3$ exhibits a singlet at δ 3.24 ppm for the methoxy protons, a singlet at δ 1.32 ppm for the *tert*-butyl protons and a pair of doublets at δ 6.72 and 7.01 (J = 2.6 Hz) ppm for the aromatic protons, which are in the deshielded region of the bridged double bond. Thus, the methoxy protons appear upfield because of the ring current of the opposite aromatic ring. The structure of the *syn*-conformer is even easily evaluated from the chemical shift of the methoxy protons at δ 3.68 ppm. Here, the *tert*-butyl proton of *syn*-**14** is observed at higher field, *viz* δ 1.11 ppm, due to the shielding effect of the aromatic ring. The aromatic protons of *syn*-**14** are reported at much higher field (δ 6.41 and 6.52 ppm) than those of the compound *anti*-**14**. This data confirms the assigned *anti*- and *syn*-structures for both the conformers of **14**.

The X-ray structure of *anti*-**14** (CCDC 1542177) in Fig. 4 clearly reveals that it is the *anti*-conformer in the solid state and that the two methoxy groups lie on the correlative side of the inner ring, which consists of a long bridging C27–C29 chain pointing outwards to minimize the steric repulsion with the bridge chain. The bond lengths of C1–C29 and C29–C28 in the trimethylene chains and C3–C12 and C16–C13 in the ethylenic chains have standard values at 1.51, 1.53, 1.49 and 1.51 Å, respectively. The length of the double bond in C12–C13 is 1.34 Å, which is alike of ethylene. The bond angles defined by C13–C12–C3 and C12–C13–C16 are 121.3(2)° and 121.6(2)°, showing that compound *anti*-[2.4]MCP-1-ene displays a non-distorted conformation. The two benzene rings of [2.4]MCP-1-ene slightly deviate from planarity. The intramolecular distances of C3–C16, C2–C17, C7–C22, C4–C21, C1–C18, C6–C19 are 2.93, 2.83, 9.37, 5.18, 3.20 and 5.14 Å, respectively.

The X-ray structure (CCDC no: 1541642) of *syn*-**14** (Figure 4) clearly demonstrates that **14** exists as the *syn*-conformer in the solid state and that the two methoxy groups lie on the correlative side of the 18–membered inner ring, which contains the long bridging C27–C30 chain pointing toward the outer direction thereby minimizing steric repulsion with the bridge chain. The selected bond lengths of C6–C30 and C30–C29 in the butamethylene chains and C2–C12 and C14–C17 in the ethylenic chains have typical values at 1.52, 1.53, 1.51 and 1.49 Å, respectively. The length of the double bond in C12–C13 is 1.36 Å, and is similar that of ethylene. The bond angles defined by C12–C14–C17 and C2–C13–C14 are 118.3(2)° and 119.2(2)°, reveal that

compound **14** displays a non–distorted conformation. The two benzene rings of *syn*-**14** slightly deviate from planarity. The intramolecular distances of C2–C17, C3–C18, C8–C23, C1–C16, C5–C20, C6–C21 are 2.80, 3.53, 5.35, 3.30, 4.69 and 4.05 Å, respectively.

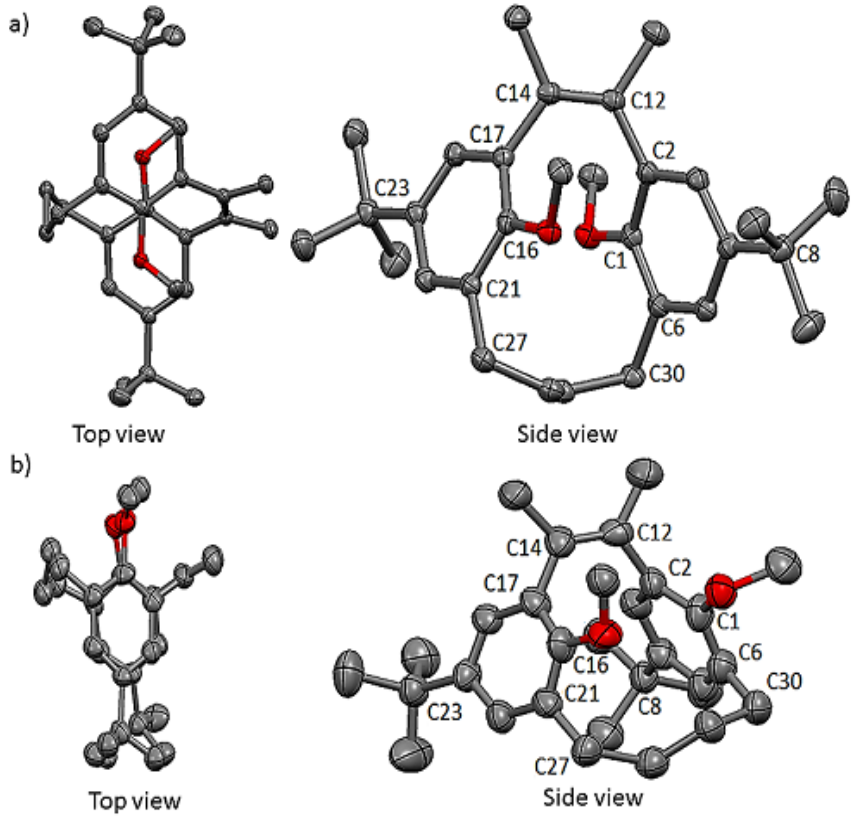
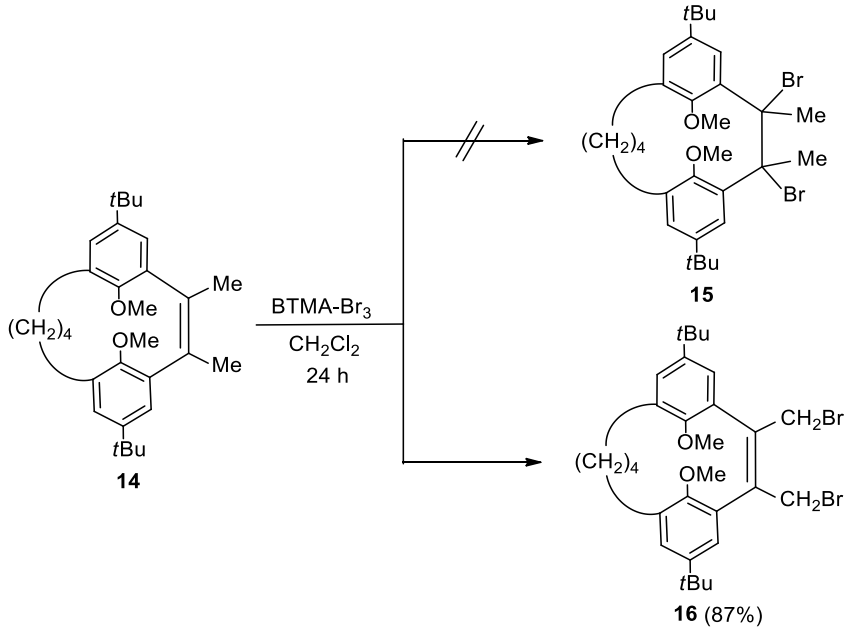


Figure 4. Single-crystal structures of a) *anti*-[2.4]MCP-1-ene **14** and b) *syn*-[2.4]MCP-1-ene **14** (side view and top view). Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

Bromination of **14** with 4.4 equiv. of benzyltrimethylammonium tribromide (BTMA-Br_3) in dry CH_2Cl_2 solution at room temperature for 24 h afforded the corresponding 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-bis(bromomethyl)[2.4]MCP-1-ene **16** in 87% yield (Scheme 7). Here, we use BTMA-Br_3 because it is easy to handle and a mild brominating reagent allowing us to control the reaction pathway. No bromination of compound **16** at the alkene bridge (double bond) was observed. This result is not similar with the bromination of the corresponding [2.4]MCP-1-ene which afforded the *cis*–addition product (to the bridging double bond).[25] The proposed mechanism presumably that, initially formation of bromonium ion and later consecutive deprotonation following HBr elimination to synthesis diene **12**.[26,27]

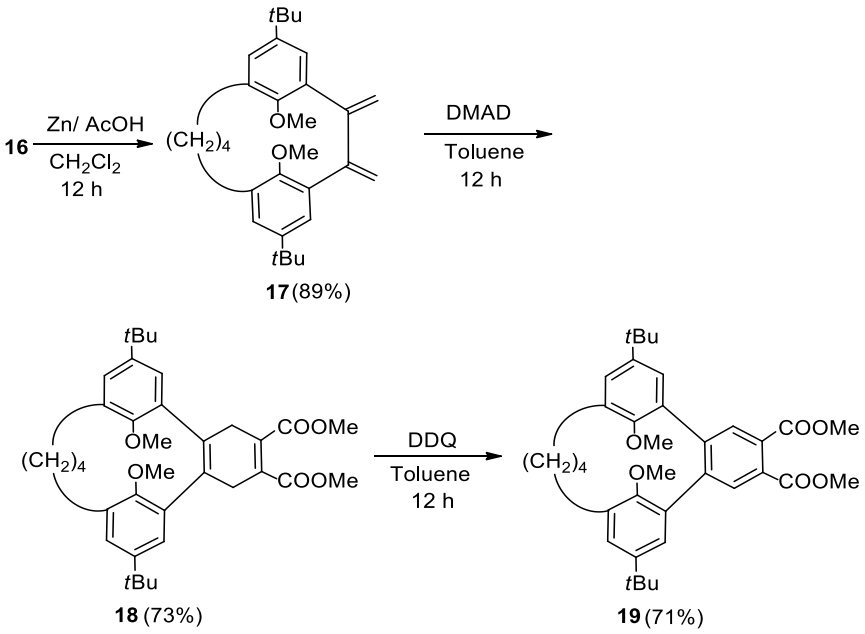


Scheme 7. Synthesis of 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-bis(bromomethyl)[2.4] MCP-1-ene **16**.

The structure of product **16** was proposed on the basis of elemental analyses and spectral data. The mass spectral data for diene **16** (M^+ = 676, 678 and 680) strongly supports a dibrominated structure. The ^{1}H NMR spectrum of compound **16** exhibited a singlet for the methoxy protons at δ 3.30 ppm as well as the resonances at δ 6.85 and 7.42 (J = 2.6 Hz) ppm for the two protons of the aromatic rings. The previously reported[17b] 1,2-bis(bromomethyl)[2.3]MCP-1-ene revealed a lower–field shift of the methoxy protons at δ 3.22 ppm along with δ 6.99 and 7.19 (J = 2.4 Hz) ppm for the two aromatic protons because of the short carbon chain length. The methylene protons of the bromomethyl group were observed as a doublet at δ 4.69 and 4.89 (J = 10.3 Hz) ppm. Thus, the introduction of a bromo group on the methyl group at the etheno bridge might restrict the rotation throughout the single bond of C–CH_2Br, which causes the methylene protons diasterotopic environment.

To synthesize the diene body from the brominated [2.4]MCP, the reduction of the double bonds does not proceed following the elimination reaction in presence of strong base alcoholic solvent. Interestingly, treatment of **16** with Zn followed by dropwise addition of AcOH in dry CH_2Cl_2 solution at room temperature for 24 h afforded the identical 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethylene[2.4] MCP **17** in 75% yield (Scheme 8). This type

of modified reaction has been widely endorsed to eliminate the bromine group to form a double bond.



Scheme 8. Synthesis of 1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate **19**.

The structure of the diene obtained in the present work was determined from elemental analyses and spectral data. The 300 MHz ^{1}H NMR spectrum of compound **17** in $CDCl_3$ revealed a doublet at δ 6.84 and 6.94 ppm for the two protons of the aromatic rings. The *exo*–methylene protons of the ethano-bridge were observed as broad singlets at δ 4.99 and 5.64 ppm, and the protons of the methoxy group were observed at δ 3.23 ppm. The butamethylene bridge protons gave rise to an abstruse signal pattern as predicted for a rigid [2.4]MCP. The protons of the benzylic CH_2 group were observed as two multiplets at δ 2.00–2.07 ppm and 2.70–2.77 ppm, which were additionally split by coupling with the protons of the central CH_2 groups. This central CH_2 groups was also observed as multiplets centered at δ 1.25–1.33 ppm. It was also found these methylene peaks were not merged up to 120 °C in $CDBr_3$. These findings suggested that the introduction of two double bonds of the ethano-bridge can inhibit the *syn–syn* conformational flipping of 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethylene[2.4]MCP **17** above this temperature which would exchange H_A and H_B protons of each CH_2 group. These perceptions suggested that the introduction of two

double bonds of the ethano-bridge might restraint the *syn*-conformation of 1,2-dimethylene[2.4]MCP **17**.

The Diels–Alder reaction of **7** with DMAD was completed within 24 h in toluene at reflux. Thus, the Diels–Alder reactivity of compound **17** exceeds that of 2,3-diphenyl-1,3-butadiene. This result suggests that the energy of the fixed s-*cis* conformation in **17** in the ground and transition state might lower the Diels–Alder barriers due to the inflexibility of the MCP ring. The Diels–Alder reaction of **17** with suitable dienophiles followed by aromatization can be used to prepare a range of areno-bridged [2.*n*]MCPs. Compound **17** is conveniently employed in the reaction with dimethyl acetylenedicarboxylate (DMAD) to provide **18** in good yield. Diels–Alder adduct **18** was converted to areno-bridged [2.4]MCP **19** by aromatization with dichlorodicyano-*p*-benzoquinone (DDQ).

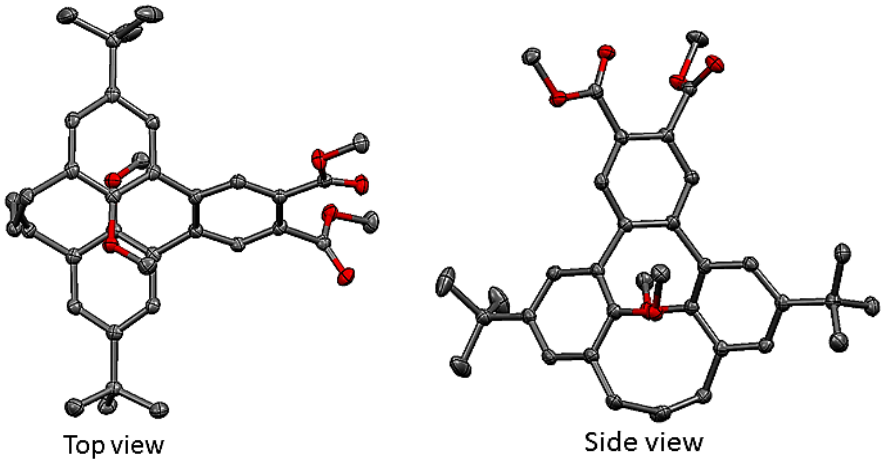


Figure 5. Drawing of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**19**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The structure of product **19** was elucidated by spectroscopic methods (^{1}H NMR and ^{13}C NMR), mass spectrometry and elemental analyses. The cyclic dimeric structure was consistent with the mass spectral data for compound **19** (M^{+} = 657). The 300 MHz ^{1}H NMR spectrum of **19** in $CDCl_3$ exhibited singlets at δ 3.00 and δ 3.68 ppm for the methoxy protons together with δ 6.92 and 7.05 (J = 2.4 Hz) ppm for the two aromatic protons. Based on the spectral data and the chemical conversion, compound **19** is assigned to the structure, *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-di-methoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**19**.

In anticipation of future investigations into the ability of MCPs to be employed as chiral catalysts and ligands, efforts were made to access the solid–state structures and the high–resolution NMR spectral data. Inherent chirality is a feature associated with some MCPs and compound *anti*-**19** is predicted to have a plane of chirality. This is because it has two different types of substituents and bridged linkages which are fixed in a C_1 symmetrical structure and does not sustain a conformational change at or near ambient temperature.

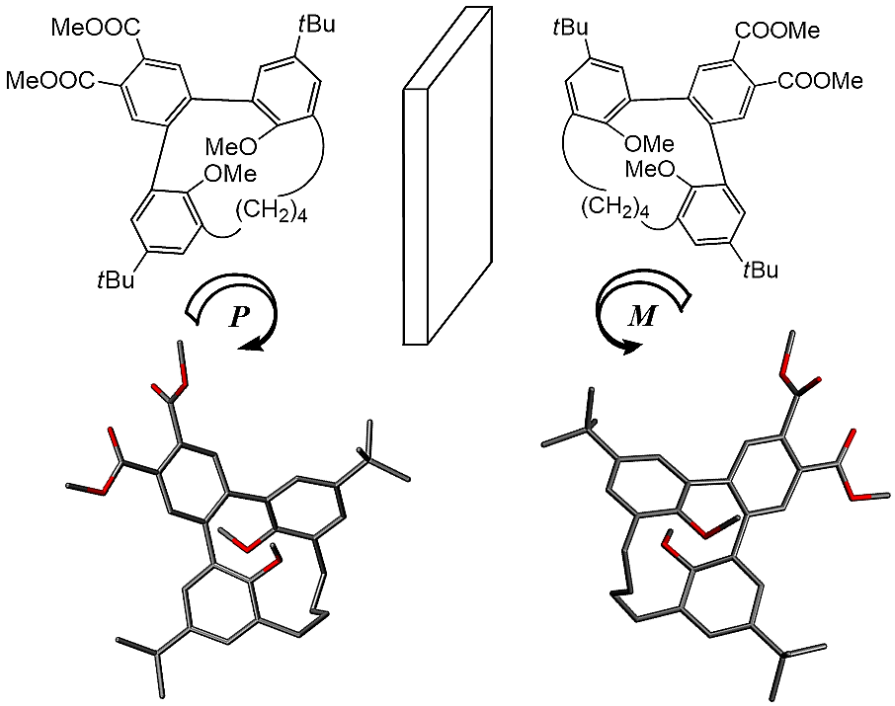


Figure 6. Schematic diagram of *M*-**19** (left side) and *P*-**19** (right side).

Compound *anti*-**19** was crystallized by the slow, room temperature evaporation of a dichloromethane solution, into the space group *P-1*. Interestingly, the X-ray analysis disclosed that areno-bridged [2.4]MCP *anti*-**19** adopts helical chirality, yet surprisingly, the dihedral angle of the arylenes connected by the phenyl unit is 33.98°. Therefore, the compound is chiral and the *M*- and *P*-isomers are packed alternatively in the crystal as depicted schematically in Figure 7 (CCDC no: 908369).

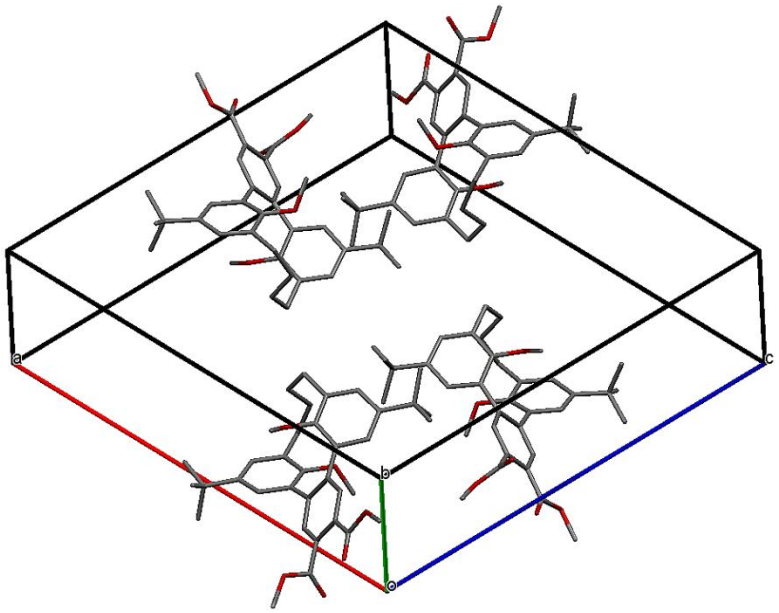


Figure 7. Packing drawing of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**19**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The chiral properties of the compound *anti*-**19** in solution were investigated by chromatographic resolution using a chiral column. Interestingly, *anti*-**19** exhibits two well resolved peaks in the ratio 50:50 for the *P*- and *M*-enantiomers. This finding strongly suggests that the resolution of racemic *anti*-**19** could be accomplished by chromatographic separation using a chiral column. In fact, we have succeeded in resolving each *P*- and *M*-enantiomers. The circular dichroism (CD) spectra of the separated enantiomer with precise mirror images are shown in Figure 8.

From Figure 8, we obtained the symmetrical shape of the retention time (3.843 min) and the retention time (4.862 min). It was confirmed that the compound *anti*-**9** had no enantiomer. First, one enantiomer which was optically resolved with a chiral column was left at room temperature for 3 weeks. In the solution at room temperature, no peak of the after-distillate was observed after 3 weeks. It was found that compound *anti*-**9** did not undergo racemization. Only one peak was observed and it turned out that racemization did not occur. Since it was found that racemization did not occur at room temperature, compound *anti*-**9** was dissolved at 100 °C.

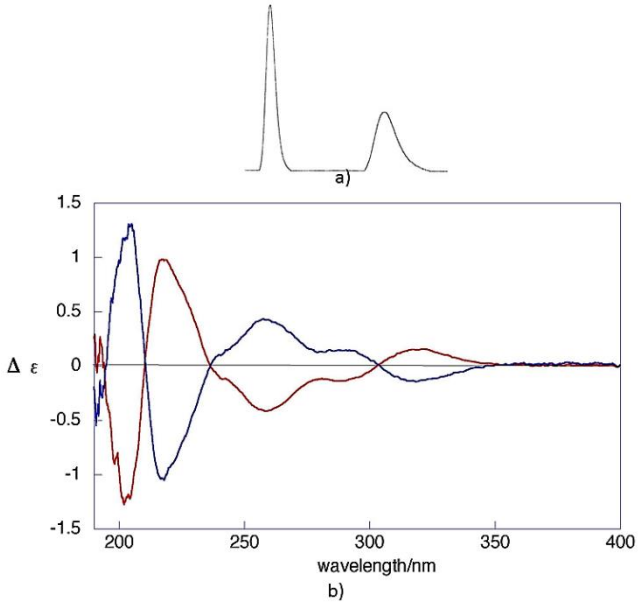


Figure 8. (a) Chromatogram of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**19** (HPLC on chiral column). Daicel chiralpak ADeH. Eluent: hexanes. (b) CD spectra of *P*- and *M*-enantiomers of inherently chiral *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**19**.

It was left for 1 day to investigate whether racemization occurred. Since no peak of the after-distillate was observed even after leaving at 100 °C for 1 day, it turned out not to be racemized. The pre-distillate of the *anti*-**19** was dissolved in a solution of CH_2Cl_2 and the specific rotation measurement was carried out. The specific rotation of compound *anti*-**19** was $[\alpha]_D$ = + 72 (faster-moving enantiomer on Daicel Chiralpac AD-H with 1 v/v % ethanol in hexane as the eluent) in 240 nm. Specific expected rotation was small because compound *anti*-**19** had a shorter carbon crosslinking chain of 4, so it was a flexible compound.

3.3 Conclusions

We have described a simple and effective method for the synthesis of areno-bridged [2.*n*]MCP by successive Diels-Alder reaction from 1,2-dimethylene[2.*n*]MCP, and also its chiral conformation. To explore the rates of conformational behaviour of the described [2.*n*]MCPs, a series of electrophilic substitution reactions such as bromination, acylation and hydroxylation reactions of [2.*n*]MCPs were studied. Further mechanistic details of [2.*n*]MCP

derivatives are being explored (by introducing different groups) and will be reported in due course.

3.4 Experimental Section

3.4.1 General

All melting points (Yanagimoto MP-S1) are uncorrected. NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 spectrometer with Me_4Si as an internal reference: *J* values are given in Hz. IR spectra were measured for samples as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC. Elemental analyses were performed by Yanaco MT-5. G.L.C. analyses were performed with a Shimadzu gas chromatograph, GC-14A; silicone O V-1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}.

3.4.2 Materials

Synthesis of 5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene **1** and 1,4-bis(5-*tert*-butyl-2-methoxylphenyl)butane **11** were prepared from anisole according to the reported procedure.[17,18]

3.4.2.1. Bromination of 1 with BTMA-Br_3

To a solution of **1** (100 mg, 0.193 mmol) in CH_2Cl_2 (10 mL) was added BTMA-Br_3 (331 mg, 0.848 mmol) at room temp. After the reaction mixture was stirred at room temperature for 5 min, it was poured into a large amount of ice/water (50 mL) and extracted with CH_2Cl_2 (20 mL × 2). The combined extracts were washed with water, dried with $MgSO_4$ and concentrated. The residue was washed with hexane to give a colorless solid (129 mg), which was recrystallized from hexane to afford 1,2-bis(bromomethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]metacyclophan-1-ene **2** (103 mg, 80%) as colorless prisms. M.p. 138–139 °C. IR: υ_{max} (KBr): 2954, 2929, 2856, 1476, 1218 and 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (18H, s), 1.05–1.38 (16H, m), 2.05–2.16 (2H, m), 2.68–2.78 (2H, m) 3.65

(6H, s), 4.52 (2H, d, *J* = 10.0 Hz), 4.84 (2H, d, *J* = 10.0 Hz), 6.67 (2H, d, *J* = 2.4 Hz) and 6.91 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.54, 25.98, 27.15, 27.20, 29.24, 30.23, 31.58, 32.43, 34.11, 58.64, 61.39, 126.41, 127.40, 131.70, 135.05, 139.22, 145.47 and 153.95 ppm. EI-MS: *m/z*: 676, 678 and 680 [M^+]. $C_{36}H_{52}O_2Br_2$ (678.62): calcd C 63.72, H 8.02; found: C 63.75, H 7.92.

3.4.2.2. Acetalization of 2 with silver acetate

A solution of **2** (100 mg, 0.148 mmol) and silver acetate (93 mg, 0.568 mmol) in acetic acid (4 mL) were stirred at room temperature for 24 h. After the addition, the reaction mixture was concentrated and the residue was extracted with CH_2Cl_2 (200 mL × 2). The CH_2Cl_2 extract was concentrated and the residue was chromatographed on silica gel with benzene as eluent to give a colorless solid. Recrystallization from hexane gave 1,2-bis (methylacetate)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]metacyclophan-1-ene **4** (98 mg, 78%) as colourless prisms. M.p. 144–145 °C. IR: υ_{max} (KBr): 2929, 2848, 1754, 1730, 1476, 1369, 1358, 1240, 1015 and 956 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–1.45 (16H, m), 1.11 (18H, s), 1.98 (6H, s), 2.14–2.23 (2H, m), 2.74–2.82 (2H, m) 3.68 (6H, s), 5.14 (2H, d, *J* = 12.6 Hz), 5.20 (2H, d, *J* = 12.6 Hz), 6.79 (2H, d, *J* = 2.4 Hz) and 6.95 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.34, 31.41, 31.54, 34.00, 60.64, 60.84, 64.50, 126.04, 126.08, 126.49, 131.93, 134.62, 136.21, 144.97, 153.66 and 170.74 ppm. FABMS: calcd. for $C_{40}H_{58}O_6$ ([M^+] *m/z* = 634.4233), found 634.4235 [M^+].

3.4.2.3. Hydrolysis of 2 with potassium hydroxide

A solution of **4** (100 mg, 0.157 mmol) and potassium hydroxide (93 mg, 1.66 mmol) in ethanol (8 mL) were stirred at room temperature for 2 h. After the addition, the reaction mixture was concentrated and the residue was extracted with CH_2Cl_2 (200 mL × 2). The CH_2Cl_2 extract was concentrated and the residue was chromatographed on silica gel with benzene as eluent to give a colorless solid. Recrystallization from hexane gave 1,2-bis (hydroxymethyl)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]metacyclophan-1-ene **5** (101 mg, 72%) as colorless prisms. M.p. 162–163 °C. IR: υ_{max} (KBr): 3394, 2929, 1863, 1476, 1354, 1211 and 1008 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (18H, s), 1.10–1.44 (16H, m), 2.17–2.26 (2H, m), 2.71–2.80 (2H, m) 3.74 (6H, s), 4.48 (1H, s), 4.51 (2H, d, *J* = 12.6 Hz),

4.77 (1H, s), 4.80 (2H, d, *J* = 12.6 Hz), 6.77 (2H, d, *J* = 2.4 Hz) and 6.95 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.36, 30.02, 31.33, 31.42, 33.96, 61.34, 64.47, 125.55, 126.07, 126.14, 133.73, 134.50, 140.35, 145.31 and 153.46 ppm. FABMS: calcd. for $C_{40}H_{54}O_6$ ([M^+] *m/z* = 550.4022), found 550.1024 [M^+].

3.4.2.4. Debromination of 2 with zinc powder

To a solution of **2** (100 mg, 0.148 mmol) in CH_2Cl_2 (10 mL) and acetic acid was gradually added Zn powder (193 mg, 2.96 mmol) and the system was stirred at room temperature for 24 h. The reaction mixture was filtered and washed with CH_2Cl_2 (10 mL × 3). The filtrate was condensed under reduced pressure to leave a residue. The residue was column chromatographed over silica gel with $CHCl_3$ as eluent to give a colorless solid. Recrystallization from ethanol afforded 5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethylene[2.10] metacyclophane **7** (148 mg, 75%) as colorless needles. M.p. 146–148 °C. IR: υ_{max} (KBr): 1722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–1.15 (16H, m), 1.20 (18H, s), 2.11–2.38 (2H, m), 2.73–2.90 (2H, m), 3.64 (6H, s), 5.53 (2H, bs), 5.69 (2H, bs), 6.92 (2H, d, *J* = 2.4 Hz) and 7.05 (2H, bs) ppm. EI-MS: *m/z*: 516 [M^+]. $C_{36}H_{52}O_2$ (516.81): calcd C 83.67 H 10.14; found: C 83.51, H 10.21.

3.4.2.5. Deals-Alder reaction of 7 with dimethyl acetylenedicarboxylate

A solution of compound **7** (20 mg, 0.0387 mmol) and dimethylacetylenedicarboxylate (10 mg, 0.0423 mmol) in toluene (2 mL) was heated at 100 °C for 12 h. After the reaction mixture was cooled to room temperature, the solvent was condensed under the reduced pressure to leave a residue. The residue was column chromatographed over silica gel with toluene-$CHCl_3$ (1:1) as eluent to give 1,2-(3',6'-dihydrobenzo)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]metacyclophane-4',5'-dimethylcarboxylate **8** (18 mg, 73%) as colourless prisms (hexane). M.p. 146–148 °C. IR: υ_{max} (KBr): 1722 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–1.40 (16H, m), 1.11 (18H, s), 2.07–2.22 (2H, m), 2.72–2.85 (2H, m), 3.32 (6H, s), 3.7–4.0 (4H, m), 3.86 (6H, s), 6.78 (2H, d, *J* = 2.4 Hz) and 6.97 (2H, d, *J* = 2.4 Hz) ppm. EI-MS: *m/z*: 658 [M^+]. $C_{42}H_{58}O_6$ (658.91): calcd C 76.35 H 8.87; found: C 76.51, H 8.75.

3.4.2.6. Oxidation of 8 with DDQ

A solution of **8** (40 mg, 0.067 mmol) and DDQ (17 mg, 0.0728 mmol) in toluene (4 mL) was heated at 50 °C for 12 h. After the reaction mixture was cooled to room temperature, the solvent was condensed under the reduced pressure to leave a residue. The residue was column chromatographed over silica gel with $CHCl_3$ as eluent to give a colourless solid. Recrystallization from methanol afforded of 1,2-dibenzo-5,21-di-*tert*-butyl-8,24-dimethoxy [2.10]metacyclophane-4',5'-dimethylcarboxylate **9** (28 mg, 70%) as colourless prisms (hexane). M.p. 143–144 °C. IR: υ_{max} (KBr): 2929, 2848, 1741, 1727, 1464, 1432, 1277, 1225, 1129, 1004, 875 and 787 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88–0.98 (2H, m), 1.06 (18H, s), 1.12–1.25 (12H, m), 1.32–1.47 (2H, m), 2.18–2.26 (2H, m), 2.81–2.88 (2H, m), 3.40 (6H, s), 3.93 (6H, s), 6.84 (2H, d, *J* = 2.4 Hz), 7.05 (2H, d, *J* = 2.4 Hz) and 7.98 (2H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.38, 30.19, 31.44, 34.06, 52.57, 60.55, 126.50, 127.03, 130.08, 131.45, 131.91, 134.92, 141.89, 145.57, 153.32 and 168.07 ppm. FABMS: calcd. for $C_{42}H_{56}O_6$ ([M^+] *m/z* = 656.4077), found 656.4044 [M^+].

3.4.2.6. Diels-Alder reaction of 7 with N-phenylmaleimide

A solution of **7** (30 mg, 0.058 mmol) and *N*-phenylmaleimide (12.1 mg, 0.070 mmol) in dry toluene (5 mL) was heated at 110 °C for 24 h. After the reaction mixture was cooled to room temperature, the solvent was condensed under the reduced pressure to leave a residue. The residue was column chromatographed over silica gel with ethyl acetate as eluent to give 1,2-(3',4',5',6'-tetrahydrobenzo)-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10] metacyclophane-4',5'-*N*-phenyl-maleimide **10** (84.1 mg, 53%) as colorless prisms (hexane). M.p. 184–185 °C. IR: υ_{max} (KBr): 2952, 2929, 2856, 1716, 1502, 1380, 1222, 1196, 1174, 1011 and 879 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (18H, s), 1.12–1.38 (16H, m), 2.14–2.23 (2H, m), 2.69–2.80 (2H, m), 2.90 (2H, dd, *J* = 2.4 Hz, *J* = 12 Hz), 3.24 (2H, d, *J* = 12 Hz), 3.46 (2H, d, *J* = 2.4 Hz), 3.64 (6H, s), 6.69 (2H, d, *J* = 2.4 Hz), 6.89 (2H, d, *J* = 2.4 Hz) and 7.33–7.45 (5H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.39, 30.12, 31.33, 32.24, 33.95, 40.52, 60.95, 125.01, 126.02, 126.56, 128.45, 128.94, 132.25, 133.52, 134.07, 134.49, 145.27, 153.61 and 179.07 ppm. FABMS: calcd. for $C_{46}H_{59}NO_4$ ([M^+] *m/z* = 689.4444), found 689.4444 [M^+].

3.4.2.7. Synthesis of 1,4-bis(5-tert-butyl-3-(1-hydroxyethyl)-2-methoxylphenyl)butane

To a solution of methylmagnesium bromide [prepared from methyl iodide (14.4 g, 101 mmol) and magnesium (2.05 g, 84.3 mmol)] in Et_2O (45 mL) was added a solution of **11** (8.85 g, 20.9 mmol) in tetrahydrofuran (100 mL) dropwise under the conditions of gentle refluxing. After the reaction mixture was refluxed for an additional 5 h, it was quenched with 10% ammonium chloride (100 mL) and extracted with Et_2O (100 mL × 3). The extract was washed with water (100 mL × 2), dried over $MgSO_4$, and concentrated *in-vacuo*. The residue was recrystallized from hexane to afford 1,4-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)butane **12** in 95% yield as colorless prisms. M.p. 110–112 °C. IR: υ_{max} (KBr): 3328, 2965, 2857, 2827, 2359, 2344, 1481, 1463, 1363, 1294 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.30 (18H, s), 1.53 (6H, d, *J* = 6.4 Hz), 1.67–1.76 (4H, m), 2.36 (2H, s), 2.63–2.73 (4H, m), 3.77 (6H, s), 5.15–5.23 (2H, q, *J* = 6.4 Hz, *J* = 6.2 Hz), 7.13 (2H, d, *J* = 2.6 Hz) and 7.28 (2H, d, *J* = 2.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.89, 29.80, 29.83, 30.84, 30.88, 31.47, 34.45, 61.73, 65.51, 120.75, 126.36, 134.60, 137.32, 146.99 and 153.07 ppm. EI-MS: *m/z* 471 [M^+]. $C_{30}H_{46}O_4$ (470.68): calcd C 76.55, H 9.85; found: C 76.23, H 9.90.

3.4.2.8. Synthesis of 1,4-bis(3-acetyl-5-tert-butyl-2-methoxylphenyl)butane

To a solution of $C_5H_5NH^+CrO_3Cl^-$ (31.0 g, 144 mmol) in acetone (300 mL) was added a solution of 1,3-bis(5-*tert*-butyl-3-(1'-hydroxyethyl)-2-methylphenyl)propane **12** (10.62 g, 23.3 mmol) in acetone (100 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated *in-vacuo*. The residue was subjected to silica-gel (Wako, C-300; 500 g) column chromatography using as eluent $CHCl_3$ to afford 1,4-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)butane **13** in 74% yield as colorless prisms (MeOH). M.p. 112–113 °C. IR: υ_{max} (KBr): 2966, 1671, 1572, 1469, 1458, 1222, 1004, 890 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.30 (18H, s), 1.71–1.75 (4H, m), 2.64 (6H, s), 2.69–2.71 (4H, m), 3.73 (6H, s), 7.34 (2H, d, *J* = 2.4 Hz) and 7.42 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.72, 30.21, 30.38, 30.81, 31.29, 34.39, 62.73, 124.25, 130.98, 132.91, 135.65, 146.75, 155.13 and 201.82 ppm. FAB-MS: *m/z* 467.6131 [M^+]. $C_{30}H_{42}O_4$ (467.6690): calcd C 77.21, H 9.07; found: C 76.95, H 9.16.

3.4.2.9. McMurry coupling reaction

The McMurry reagent was prepared from $TiCl_4$ (13.75 cm^3, 125 mmol) and Zn powder (18 g, 275 mmol) in dry THF (500 mL), under nitrogen. A solution of 1,4-bis(3-acetyl-5-*tert*-butyl-2-methoxylphenyl)butane **13** (3.4 g, 7.5 mmol) and pyridine (22.8 mL, 0.2 mol) in dry THF (250 mL) was added over 60 h to the black mixture of the McMurry reagent by using a high-dilution technique with continuous refluxing and stirring. The reaction mixture was refluxed for an additional 8 h, cooled to room temperature, and hydrolyzed with aqueous 10% K_2CO_3 (200 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were washed with water, dried with $MgSO_4$ and concentrated *in-vacuo*. The residue was chromatographed over silica gel (Wako C-300, 300 g) with hexane–toluene (1:1) and toluene as eluents to give *anti*-**14** and *syn*-**14** as a colorless solid. Each eluents were recrystallized from hexane to afford *anti*-**14** (537 mg, 15%) and *syn*-**14** (411 mg, 7%), respectively.

anti-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]metacyclophan-1-ene (*anti*-**14**) was obtained in 15% yield as colorless prisms (MeOH). M.p. 174–175 °C. IR: υ_{max} (KBr): 2966, 1476, 1450, 1229, 1019, 875 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.10–1.21 (4H, m), 1.32 (18H, s), 1.91–1.99 (2H, m), 2.27 (6H, s), 2.71–2.80 (2H, m), 3.24 (6H, s), 6.72 (2H, d, *J* = 2.6 Hz) and 7.01 (2H, d, *J* = 2.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.05, 21.41, 31.58, 31.68, 32.48, 33.91, 59.40, 124.02, 127.15, 129.97, 132.58, 134.48, 143.80 and 153.31 ppm. FAB-MS: *m/z* 434.6185 [M^+]. $C_{30}H_{42}O_2$ (434.6533): calcd C 82.90, H 9.74; found: C 82.81, H 9.73.

syn-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]metacyclophan-1-ene (*syn*-**14**) was obtained in 7% yield as colorless prisms (hexane). M.p. 174–175 °C. IR: υ_{max} (KBr): 2952, 1454, 1472, 1362, 1218, 1015, 868 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.87–1.00 (4H, m), 1.11 (18H, s), 1.91–2.16 (2H, m), 2.21 (6H, s), 2.68–2.82 (2H, m), 3.68 (6H, s), 6.41 (2H, d, *J* = 2.3 Hz) and 6.52 (2H, d, *J* = 2.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.01, 27.81, 31.48, 32.19, 32.38, 33.62, 60.61, 123.59, 124.29, 126.17, 133.26, 133.41, 134.70 and 142.84 ppm. FAB-MS: *m/z* 434.32 [M^+]. $C_{30}H_{42}O_2$ (434.65): calcd C 82.90, H 9.74; found: C 82.58, H 9.70.

3.4.2.10. Bromination of anti-14 with BTMA–Br_3 in CH_2Cl_2

To a solution of *anti*-**14** (185 mg, 0.44 mmol) in CH_2Cl_2 (24 mL) was added BTMA-Br_3 (170.3 mg, 0.44 mmol) at room temperature. After the reaction mixture was stirred for 24 h, it was poured into water (20 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 3). The extract was washed with 10% aqueous sodium thiosulfate (10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated *in-vacuo*. The residue was column chromatographed over silica gel with hexane and hexane–toluene (1:1) as eluents. Recrystallization of the former eluents from hexane gave *anti*-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-bis(bromomethyl)[2.4]metacyclophan-1-ene *anti*-**16** in 87% yield as colourless prisms (hexane). M.p. 148–149 °C. IR: υ_{max} (KBr): 2966, 2900, 2856, 1649, 1553, 1476, 1454, 1354, 1262, 1203, 1170, 1107, 1019, 923, 879, 857, 805, 639, 573, 529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.05–1.26 (4H, m), 1.34 (18H, s), 1.93–2.00 (2H, m), 2.69–2.79 (2H, m), 3.30 (6H, s), 4.69 (2H, d, *J* = 10.3 Hz), 4.89 (2H, d, *J* = 10.3 Hz), 6.85 (2H, d, *J* = 2.6 Hz) and 7.42 (2H, d, *J* = 2.6 Hz) ppm. EI-MS: *m/z* 592 [M^+]. $C_{30}H_{40}Br_2O_2$ (592.45): calcd C 82.90, H 9.74; found: C 82.81, H 9.73.

3.4.2.11. Debromination of 16 with zinc powder

To a solution of *anti*-**16** (100 mg, 0.148 mmol) in CH_2Cl_2 (10 mL) and acetic acid was gradually added Zn powder (193 mg, 2.96 mmol) and the system was stirred at room temperature for 24 h. The reaction mixture was filtered and washed with CH_2Cl_2 (10 mL × 3). The filtrate was condensed under the reduced pressure to leave the residue. The residue was column chromatographed over silica gel with $CHCl_3$ as eluent to give a colourless solid. Recrystallization from hexane afforded 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethylene [2.4]metacyclophane (*anti*-**17**) in 89% yield as colourless prisms (hexane). M.p. 148–149 °C. IR: υ_{max} (KBr): 2966, 2900, 2856, 1649, 1553, 1476, 1454, 1354, 1262, 1203, 1170, 1107, 1019, 923, 879, 857, 805, 639, 573, 529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ =1.25–1.33 (4H, m), 1.31 (18H, s), 2.00–2.07 (2H, m), 2.70–2.77 (2H, m), 3.23 (6H, s), 4.99 (2H, d, *J* = 2.4 Hz), 5.64 (2H, d, *J* = 2.4 Hz), 6.84 (2H, d, *J* = 2.6 Hz) and 6.94 (2H, d, *J* = 2.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.85, 31.55, 31.64, 32.70, 33.43, 33.73, 60.13, 112.50, 126.45, 128.46, 128.66, 131.50, 132.54 and 133.60 ppm. FAB-MS: *m/z* 432.6028 [M^+]. $C_{30}H_{40}O_2$ (432.6464): calcd C 83.21, H 9.15; found: C 83.36, H 9.21.

3.4.2.12. Deals-Alder Reaction of 17 with dimethyl acetylenedicarboxylate

A solution of compound *anti*-**17** (70 mg, 0.17 mmol) and dimethylacetylene-dicarboxylate (28.5 mg, 0.20 mmol) in toluene (5 mL) was heated at 100 °C for 12 h. After the reaction mixture was cooled to room temperature, the solvent was condensed under the reduced pressure to leave the residue. The residue was column chromatographed over silica gel with toluene–$CHCl_3$ (1:1) as eluent to give 1,2-(3',6'-dihydrobenzo)-5,15-di-*tert*-butyl-8, 18-dimethoxy[2.4]metacyclophane-4',5'-dimethylcarboxylate *anti*-**18** in 97% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25–1.27 (4H, m), 1.31 (18H, s), 1.90–1.93 (2H, m), 2.66–2.70 (2H, m), 3.26–3.49 (4H, m), 3.24 (6H, s), 3.86 (6H, s), 6.79 (2H, d, *J* = 2.4 Hz) and 7.05 (2H, d, *J* = 2.4 Hz) ppm. EI-MS: *m/z* 574 [M^+]. $C_{36}H_{46}O_6$ (574.75): calcd C 83.21, H 9.15; found: C 83.36, H 9.21.

3.4.2.13. Oxidation of 18 with DDQ

A solution of *anti*-**18** (51.5 mg, 0.092 mmol) and DDQ (27.2 mg, 0.12 mmol) in toluene (5 mL) was heated at 50 °C for 24 h. After the reaction mixture was cooled to room temperature, the solvent was condensed under the reduced pressure to leave the residue. The residue was column chromatographed over silica gel with $CHCl_3$ as eluent to give a colorless solid. Recrystallization from methanol afforded 1,2-dibenzo-5,15-di-*tert*-butyl-8, 18-dimethoxy[2.4]metacyclophane-4',5'-dimethylcarboxylate *anti*-**19** in 71% yield as colorless prisms (methanol). M.p. 205–207 °C. IR: υ_{max} (KBr): 2856, 1730 (C=O), 1477, 1219, 1019 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.29 (4H, m), 1.33 (18H, s), 2.01–2.12 (2H, m), 2.75–2.85 (2H, m), 3.00 (6H, s), 3.98 (6H, s), 6.92 (2H, d, *J* = 2.4 Hz), 7.05 (2H, d, *J* = 2.4 Hz) and 7.90 (2H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.11, 31.54, 32.42, 33.73, 34.10, 52.68, 60.32, 127.26, 129.22, 129.70, 130.09, 131.51, 133.30, 144.18, 145.61, 153.66 and 167.76 ppm. EI-MS: *m/z* 572 [M^+]. $C_{36}H_{44}O_6$ (572.73): calcd C 75.50, H 7.74; found: C 75.71, H 7.69.

3.4.2.14. X-ray Crystallography

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation for *anti*-**1**, *anti*-**9**, *anti*-**14**, *syn*-**14** and *anti*-**19**. Data were corrected for Lorentz and polarisation effects and for absorption. The structures

were solved by charge flipping or direct methods algorithms and refined by full-matrix least-squares methods, on F^2.

Table 2. Summary of crystal data of compounds *anti*-**1**, *anti*-**9**, *anti*-**14**, *syn*-**14** and *anti*-**19**.

Parameter	*anti*-**1**	*anti*-**9**	*anti*-**14**	*syn*-**14**	**19**
Empirical formula	$C_{36}H_{54}O_2$	$C_{42}H_{56}O_6$	$C_{30}H_{42}O_2$	$C_{30}H_{42}O_2$	$C_{42}H_{56}O_6$
Formula weight	518.7	656.87	434.66	434.66	572.71
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	*P 2₁/n*	*P -1*	P *-1*	P *-1*	P *21/c*
a[Å]	10.9255(5)	11.1383(12)	12.566(2)	10.186(3)	20.9875(11)
b[Å]	16.8025(10)	14.1866(15)	14.492(2)	10.193(2)	7.4420(4)
c[Å]	17.2729(10)	24.7618(15)	15.599(2)	15.068(5)	20.5477(13)
α[°]	90.0000	83.210(6)	90.3443(15)	72.06(6)	90.0000
β[°]	90.142(3)	77.532(6)	107.876(3)	70.73(5)	102.870(4)
γ[°]	90.0000	78.155(5)	105.177(3)	64.60(5)	90.0000
Volume[Å^3]	3170.9(3)	3727.9(6)	2597.9(7)	1308.3(9)	3128.7(3)
Z	4	4	4	2	4
Dcalcd[Mg/m^3]	1.087	1.170	1.111	1.103	1.216
Temperature [K]	100	100	123	123	100
Unique reflns	4340	13864	11790	5804	5877
Obsd reflns	3982	8115	9460	3736	4196
Parameters	353	915	597	299	389
R(int)	0.1007	0.1379	0.0577	0.1005	0.0971
$R[I > 2\sigma(I)]$[a]	0.0638	0.0804	0.0761	0.1327	0.0612
*wR*2[all data][b]	0.1496	0.2391	0.1652	0.3411	0.1470
GOF on F^2	1.074	1.020	1.106	1.169	1.070

[a] Conventional *R* on F_{hkl}: $\Sigma||F_o| - |F_c||/\sigma|F_o|$. [b] Weighted *R* on $|F_{hkl}|^2$: $\Sigma[w(F_o^2 - F_c^2)_2]/\Sigma[w(F_o^2)^2]^{1/2}$

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 908365, 908368, 1542177, 1541642 & 908369. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc. cam.ac.uk].

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Chapter 4

Synthesis and conformations of [2.*n*]metacyclophan-1-ene epoxides and their conversion to [*n*.1]metacyclophanes

A series of syn- and anti-[2.n]metacyclophan-1-enes have been prepared in good yields by McMurry cyclizations of 1,n-bis(5-tert-butyl-3-formyl-2-methoxyphenyl)alkanes. Significantly, acid catalyzed rearrangements of [2.n]metacyclophan-1-enes afforded [n.1]metacyclophanes in good yield. The ratios of the products are strongly regulated by the number of methylene bridges present. The percentages of the rearrangement products increase with increasing length of the carbon bridges.

4.1 Introduction

Cyclophanes[1] have been well-studied in organic chemistry and have been found to adopt unusual chemical conformations due to the build-up of strain. Although the parent [2.2]metacyclophane (MCP = metacyclophane) was first reported as early as 1899 by Pellegrin,[2] the synthesis of *syn*-[2.2]MCP was only realized 85 year later. Mitchell et al.[3] efficiently prepared *syn*-[2.2]MCP at low temperature using (arene)chromiumcarbonyl complexation to influence the stereochemistry. Later, Itô et al.[4] also isolated and characterized *syn*-[2.2]MCP, and it can be noted that *syn*-[2.2]MCP isomerizes conveniently to its *anti*-isomer above 0 °C. On the other hand, Boekelheide[5] and Staab[6] successfully synthesized the intra-annularly substituted *syn*-[2.2]MCPs. However, reports on the synthesis and reaction chemistry of *syn*-[2.*n*]MCP have not thus far been published.

On the other hand, Merz et al.[7] reported the stereospecific epoxidation of (*E*)- and (*Z*)-stilbene crown ethers with *m*-chloroperbenzoic acid to afford the epoxy crown ethers. Oda et al.[8] also published the epoxidation of *trans*-diethylstilbestrol with *m*-chloroperbenzoic acid to afford the racemic *trans*-diethylstilbestrol oxide. Thus, there is considerable interest in synthesizing the [2.*n*]MCP-1-enes and their conversion to 1,2-epoxy[2.*n*]MCP, which can enforce the *syn*-conformation, whilst restricting the flexibility resulting from ring inversion.

Although [*n*.1]MCPs have been prepared by various workers, these previous synthetic routes were too tedious for practical application. Vögtle[9] reported the first synthesis of both [4.1] and [5.1]MCP by the application of a new method, namely sulfone pyrolysis. Later, Lin et al.[10] succeeded in preparing the lower [3.1]homologue by implementing a photochemical method. However, it was quite difficult to obtain sufficient amounts of the products for any subsequent studies by following such a route.

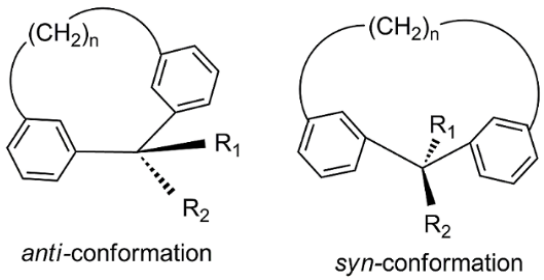


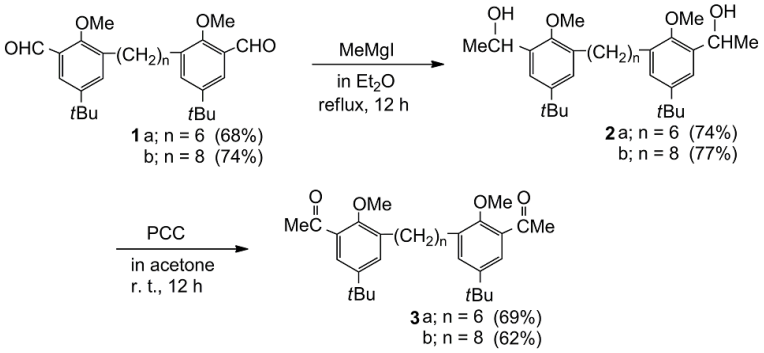
Figure 1. Possible configurations of [*n*.1]MCPs.

Recently, we have reported the formation of 1,2-dimethyl[2.*n*]MCP-1-enes[11] by employing the reductive coupling of carbonyl compounds by low-valent titanium, i.e. deploying the McMurry reaction[12–16] as a key step. In this paper, we report the synthesis of [2.*n*]MCP-ene using the McMurry cyclization reaction and subsequent conversion to 1,2-epoxy[2.*n*]MCP. The latter compounds were further modified to [*n*.1]MCPs by an acid catalyzed rearrangement. Conformational studies of these MCPs which can adopt *anti*- and/ *syn*-conformations (as represented in Figure 1), both in solution and the solid state are also described.

4.2 Results and Discussion

The starting compounds 1,6-bis(5-*tert*-butyl-3-formyl-2-methoxy phenyl)hexane **1a** and 1,8-bis(5-*tert*-butyl-3-formyl-2-methoxy phenyl)octane **1b** are easily prepared from 1,6-bis(5-*tert*-butyl-2-methoxyphenyl)hexane and 1,8-bis(5-*tert*-butyl-2-methoxyphenyl)octane, respectively according to our previous synthetic route.[17–19] In the presence of dichloromethyl ether and titanium tetrachloride ($TiCl_4$), a regioselective Friedel-Crafts acylation reaction[20, 21] at the *meta* positions of 1,6-bis(5-*tert*-butyl-2-methoxyphenyl)hexane and 1,8-bis(5-*tert*-butyl-2-methoxyphenyl) octane was achieved at room temperature to afford the required **1a** and **1b** in 68 and 74% yield, respectively. To a solution of methylmagnesium iodide (MeMgI) in Et_2O was added a solution of compounds **1a** and **1b** in tetrahydrofuran (THF) dropwise under relatively mild conditions (refluxing for 12 h) to afford 1,6-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)hexane **2a** and 1,8-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)octane **2b** in 74 and 77% yield, respectively.

Oxidations[22] of **2a** and **2b** were carried out in acetone by adding them dropwise to a solution of pyridinium chlorochromate (PCC) in acetone and stirring at room temperature for 24 h; 1,6-bis(3-acetyl-5-*tert*-butyl-2-methoxy phenyl)hexane **3a** and 1,8-bis(3-acetyl-5-*tert*-butyl-2-methoxy phenyl)octane **3b** in 69 and 62% yields, were produced respectively as shown in Scheme 1.[23–29]

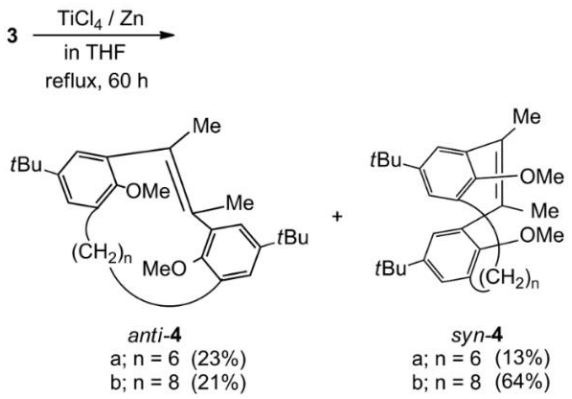


Scheme 1. Synthesis of 1,6-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)hexane **3a** and 1,8-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)octane **3b**.

Elemental analysis and spectral data were used to resolve the structures of compounds **2** and **3**. Furthermore, the ^{1}H NMR signals of **2** and **3** were also unambiguously assigned. The compounds **3a** and **3b** were subjected to reductive coupling by the McMurry reaction following the upgraded Grützmacher's procedure[30] (Scheme 2).

Thus, the reductive coupling reaction of **3** was carried out by using $TiCl_4$-Zn in the presence of pyridine in refluxing THF under high dilution conditions to afford the required compounds *anti*- and *syn*-5,17-di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl [2.6]MCP-1-ene **4a** in 23 and 13% yields, respectively also *anti*- and *syn*-5,19-di-*tert*-butyl-8,22-dimethoxy-1,2-dimethyl[2.8]MCP-1-ene **4b** in 21 and 64% yields, respectively. This result was different from that of the related McMurry cyclization of 1,3-bis(5-acetyl-2-methoxy-phenyl)propane, which afforded the corresponding [3.1]MCP by $TiCl_4$ or acid induced pinacol rearrangement.[31]

The structures of **4a** and **4b** were elucidated on the basis of their elemental analyses and spectral data. In particular, the mass spectral data for **4a** and **4b** (M^+ = 462.4 for **4a** and 490.4 for **4b**) fully support the cyclic structure. The conformations of **4a** and **4b** were readily apparent from their ^{1}H NMR spectrum. The ^{1}H NMR spectrum of *anti*-**4a** in $CDCl_3$ exhibits a singlet at δ 3.34 ppm for the methoxy protons, a singlet at δ 1.31 ppm for the *tert*-butyl protons and a pair of doublets at δ 6.89 and 7.04 (J = 2.7 Hz) ppm for the aromatic protons, which are in the deshielded region of the bridged double bond.



Scheme 2. Synthesis of 5,17-di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl[2.6]MCP-1-ene **4a** and 5, 19-di-*tert*-butyl-8,22-dimethoxy-1,2-dimethyl[2.8]MCP-1-ene **4b**.

Thus, the methoxy protons appear upfield because of the ring current of the opposite aromatic ring. The structure of the *syn*-conformer is also easily evaluated from the chemical shift of the methoxy protons at δ 3.67 ppm. Here, the *tert*-butyl proton of *syn*-**4a** is observed at higher field, viz δ 1.11 ppm, due to the shielding effect of the aromatic ring. The aromatic protons of *syn*-**4a** are reported at much higher field (δ 6.64 and 6.77 ppm) than those of compound *anti*-**4a**. These data confirm the assigned *anti*- and *syn*-structures for both two **4a** conformers.

The X-ray structure of *anti*-**4a** (CCDC 1526807) in Figure 2 clearly reveals that it is the *anti*-conformer in the solid state and that the two methoxy groups lie on the correlative side of the inner ring, which consists of a long bridging C16–C21 chain pointing outwards to minimize the steric repulsion with the bridge chain. The bond lengths of C21–C20 and C22–C21 in the hexamethylene chains and C2–C24 and C1–C5 in the ethylenic chains have standard values at 1.53, 1.50, 1.50 and 1.49 Å, respectively. The length of the double bond in C1–C2 is 1.34 Å, which is like that of ethylene. The bond angles defined by C1–C2–C24 and C2–C1–C5 are 123.3(2)° and 122.7(2)°, showing that compound *anti*-**4a** displays a non-distorted conformation. The two benzene rings of **4a** slightly deviate from planarity. The intramolecular distances of C5–C24, C6–C23, C9–C29, C10–C25, C7–C22, C8–C27 are 2.97, 3.45, 8.08, 5.18, 4.69 and 6.11 Å.

The ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of *anti*-**4b** possesses a singlet at δ 3.52 ppm for the methoxy protons, and a singlet at δ 1.28 ppm for the *tert*-butyl protons. For the

aromatic protons, a pair of doublets was observed at δ 6.86 and 7.01 (J = 2.4 Hz) ppm which are in the deshielding region of the bridged double bond. Thus, the methoxy protons

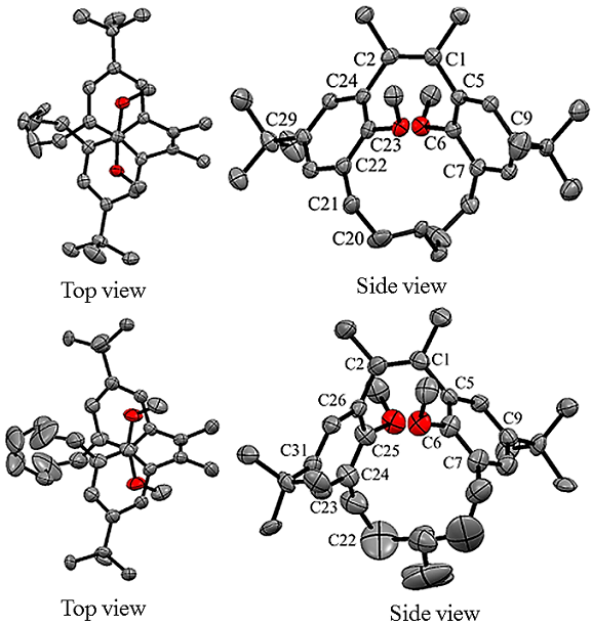
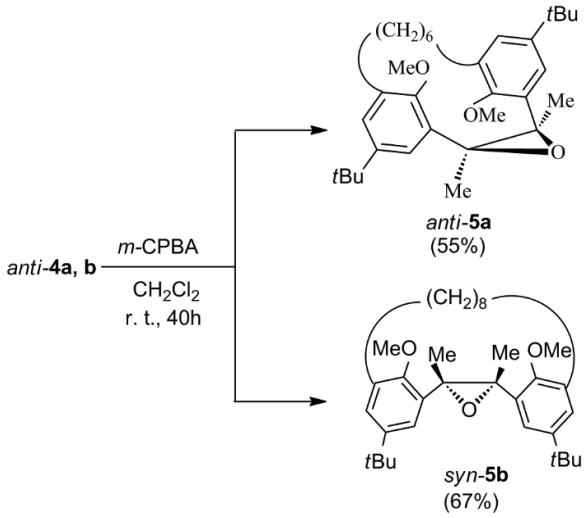


Figure 2. ORTEP drawings of Top: *anti*-5,17-di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl[2.6]MCP-1-ene **4a**; and Bottom: *anti*-5,19-di-*tert*-butyl8,22-dimethoxy-1,2-dimethyl[2.8]MCP-1-ene **4b**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

experience an upfield shift due to the ring current of the opposite aromatic ring. From the chemical shift of the methoxy protons at δ 3.69 ppm, the structure of the *syn*-conformer is confirmed. Also, the *tert*-butyl proton of *syn*-**4b** occurs to higher field, i.e. δ 1.12 ppm, due to the shielding effect of the benzene ring. The aromatic protons of *syn*-**4b** are observed at much higher field (δ 6.74 and 6.82 ppm) than those of *anti*-**4b**. These data allow for the assignment of the *anti* and *syn* structures of the two conformers of **4b**.

The X-ray structure of *anti*-**4b** (CCDC 1526816) in Figure 2 clearly demonstrates that the *anti*-conformer is adopted in the solid state and that the two methoxy groups lie on the correlative side of the inner ring, which contains the long bridging C16–C23 chain pointing outwards to keep the steric repulsion with the bridge chain to a minimum. The bond lengths of C23–C22 and C24–C23 in the octamethylene chains and C2–C26 and C1– C5 in the ethylenic chains have standard values at 1.44, 1.43, 1.45 and 1.45 Å, respectively. The length of the double bond in C1–C2 is 1.34 Å, which is similar to that of ethylene. The bond angles

defined by C1–C2–C26 and C2–C1–C5 are 121.4(2)° and 121.3(2)°, showing that compound **4b** displays a non-distorted conformation. The two benzene rings of **4b** moderately deviate from planarity. The intramolecular distances of C5–C26, C6–C25, C9–C31, C10–C27, C7–C24, C8–C29 are 2.86, 3.70, 6.29, 5.80, 4.89 and 4.85 Å.



Scheme 3. Synthesis of 5,17-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,20-dimethoxy[2.6]MCP **5a** and 5,19-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,22-dimethoxy[2.8]MCP **5b**.

The epoxidation[32] of **4a** and **4b** with *m*-chloroperbenzoic acid in the presence of dichloromethane at room temperature for 40 h afforded the desired 1,2-epoxy[2.*n*]MCP **5a** and **5b** in 55 and 67% yields, respectively, as colourless prisms (Scheme 3). The ^{1}H NMR for the benzene proton at δ 7.38 (J = 2.4 Hz) ppm in addition to resonances at δ 6.95 and 7.29 ppm for the other two protons of the aromatic rings. These observations strongly suggest that the structure corresponds exclusively to the *anti*-conformation. These findings strongly suggest that the *exo*-epoxide structure of **5a** and the *syn*-epoxidation resulting from *exo*-attack at the double bond of *syn*-**5a** formed during the ring inversion of *anti*-**5a** might be sterically favourable (Table 1). However, several attempts of preparing *syn*-**5a** by epoxidation of *anti*-**4a** failed and only an intractable mixture of products resulted.

Table 1. Conformational analysis of [*n*.2]MCP-enes **5a, b**.

Compound	Number of methylene units [*n*]	Products yield [%][a]	
		anti-**5**	*syn*-**5**
anti-**4a**	6	55	0
anti-**4b**	8	0	67

[a] Isolated yields are shown in parentheses.

The protons of the hexamethylene bridge gave rise to a complicated signal pattern, as would be expected for a rigid *syn*-[2.6]MCP. The protons of the benzylic CH_2 group were observed as two multiplets cantered at δ 2.28 and 2.49 ppm which were further split by coupling with the protons of the other CH_2 groups. The peak pattern ascribed to twelve chemically distinct protons of the alkane bridge was evidence for the absence of *anti*-*anti* interconversion which would exchange the H_A and H_B protons of each CH_2 group.

The ^{1}H NMR spectrum of *syn*-**5b** revealed a doublet for the aromatic proton at δ 7.11 (J = 2.4 Hz) ppm in addition to the resonances at δ 6.84 ppm for the other two protons of the aromatic rings. These observations suggest that the structure consists exclusively of the *syn*-conformation. These estimations strongly suggest that the *exo*-epoxide structure of *syn*-**5b** and *syn*-epoxidation from *exo*-attack at the double bond of *syn*-**4** which is formed at the time of the ring inversion of *syn*-**4b** might be sterically favourable.

The protons of the octamethylene bridge gave rise to a complex signal pattern, again as expected for a rigid *syn*-[2.8]MCP. The protons of the benzylic CH_2 group were observed as two multiplets centered at δ 2.21 and 2.91 ppm which were further split by coupling with the protons of the CH_2 groups. The peak pattern ascribed to sixteen chemically distinct protons of the alkane bridge proved the absence of *syn*-*syn* inter-conversion which would exchange H_A and H_B of each CH_2 group. These findings suggest a rigid structure for *syn*-**4b** at this temperature. This result suggests that the introduction of an oxirane ring into the ethano bridge can strongly reduce the flexibility arising from ring inversion.

Compound *anti*-5,17-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,20-dimethoxy[2.6] MCP **5a** crystallized in the centrosymmetric space group $P2_1/a$ (CCDC 1526819). There are independent molecules (Z = 4) at general positions in the asymmetric unit of the crystal structure. It is clear that *anti*-**5a** adopt the *anti*-conformation in which two benzene rings are in a non-planar chain form (Figure 3).

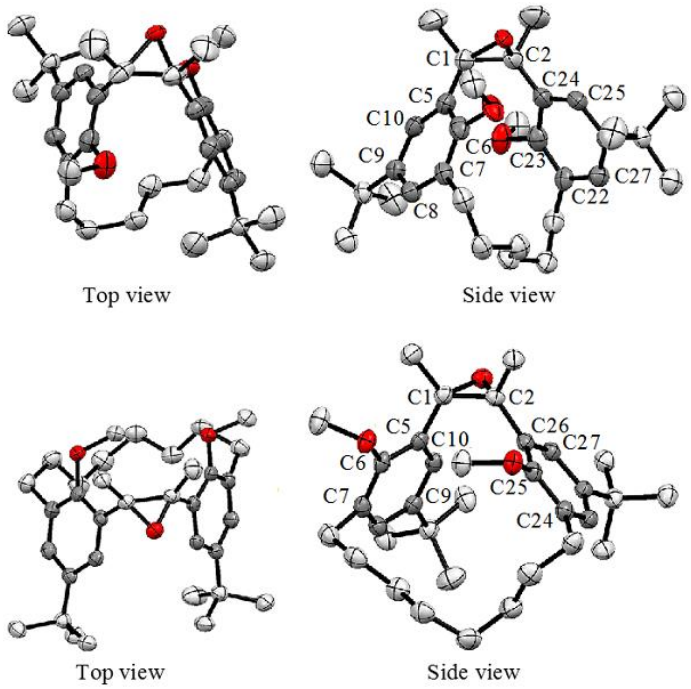
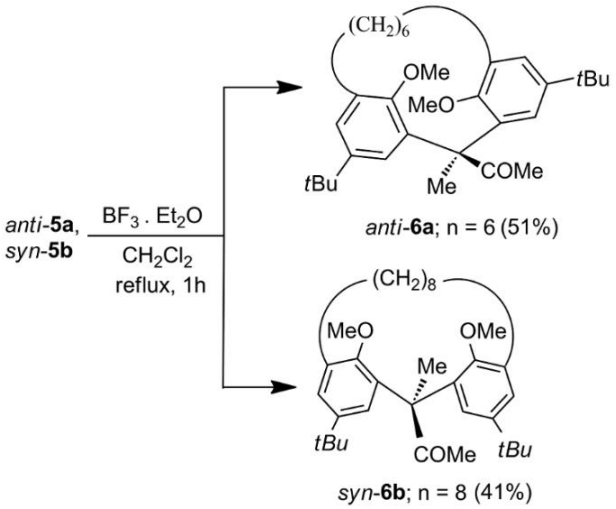


Figure 3. ORTEP drawings of Top: *anti*-5,17-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,20-dimethoxy [2.6]MCP **5a**; and Bottom: *syn*-5,19-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,22-dimethoxy[2.8]MCP **5b**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The measured torsional angles between the planes C6–C8–C10–C7, C4–C5–C6 and C8–C3–C7 planes, and those of C22–C27–C25–C24 with C27–C28–C29 and C24–C25–C26 are 116.9°, 121.1°, 117.1° and 120.9°, respectively, showing that this molecule has an asymmetrical strain between the 'top' and 'bottom' rings, and that the amount of strain is much greater at the internal carbons than at the external carbons. The C6–C5–C1–C3 and C4–C2–C26–C25 planes are twisted out of coplanarity and have a dihedral angle of 5.2°, and thus the two carbonyl groups, C6–O2 and C25–O3 do not lie in the same plane where the adjacent two carbon atoms are included.

The crystal structure (CCDC 1526822) shows that the conformation adopted by *syn*-5,19-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,22-dimethoxy[2.8]MCP **5b** is the *syn*-conformation, in which two aromatic rings are part of a non-planar chain (Figure 3). Here, the bond lengths of C16–C17 and C16–C7 in the octamethylene chains and C5–C1 and C26–C2 in the ethylenic chains have typical values at 1.54, 1.51, 1.50 and 1.51 Å, respectively. The bond angles defined by C25–C26–C2 and C1–C5–C6 are 121.6 and 122.8 Å, showing that **5b** displays a slightly distorted conformation. The two

benzene rings of **5b** slightly deviate from planarity. The intramolecular distances of C5–C26, C1–C6, C7–C24, C9–C28 are 3.08, 4.41, 5.88 and 4.95 Å.



Scheme 3. Synthesis of 13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl[6.1]MCP **6a** and 15-acetyl-11,18-di-*tert*-butyl-14,21-dimethoxy-15-methyl[8.1]MCP **6b**.

Both methoxy groups on the benzene rings of **5b** point outwards, away from the decamethylene bridge chain. This contributes to the lack of steric crowding with the hydrogens and carbons of the bridge chains. Thus, it is a *meso* compound.

In the case of the treatment of compounds **5a** and **5b** with BF_3-Et_2O as catalyst in CH_2Cl_2, the desired acid catalysed rearrangement[33] products [6.1]MCP **6a** and [8.1]MCP **6b** were obtained as the main products in 51 and 41% yields, respectively (Table 2). No formation of dehydration product(s) or ring-cleavage product(s) was observed. The yields of the rearrangement products **6** decrease with the number of the methylene bridges. This result might be attributed to the decrease of carbon ring strain in the [*n*.1]MCPs.

Table 2. Conformational analysis of [*n*.1]MCP-enes **6a, b**.

Compound	Number of methylene units [*n*]	Products yield [%][a]	
		anti-**6**	*syn*-**6**
anti-**5a**	6	51	0
syn-**5b**	8	0	41

[a] Isolated yields are shown in parentheses.

Similarly, the conformation of the [*n*.1]MCPs **6a** and **6b** were readily apparent from their ^{1}H NMR spectra. For example, in the ^{1}H NMR spectrum of [6.1]MCP **6a** in $CDCl_3$ upfield shifts and different chemical shifts for the internal aromatic protons at δ 7.25 and 7.28 ppm due to the ring current of the opposite aromatic ring were observed. This data strongly suggests that the structure of **6a** is the *anti*-conformer.

Furthermore, the two methoxy groups exhibit different chemical shifts at δ 3.29 and 3.41 ppm, each as a singlet. The four external aromatic protons were also observed as different chemical shifts at δ 7.05 (J = 2.4 Hz) and 7.12 (J = 2.4 Hz) ppm; the latter proton is in a strongly deshielding region of the oxygen atom of the acetyl group on the methylene bridge. The compound **6a** exhibits a splitting pattern for the benzyl protons as two multiplets centred at δ 2.25 and 2.41 ppm. The central CH_2 groups were also observed as two multiplets centred at δ 0.88 and 1.32 ppm. These findings suggest a regio-selective formation of [6.1]MCP **6a** at this temperature. In the ^{1}H NMR spectrum of [8.1]MCP **6b** in $CDCl_3$ upfield shifts and different chemical shifts for the aromatic protons at δ 6.86 and 6.87 ppm strongly suggest that the structure of **6b** is the *syn*-conformer. Furthermore, the two methoxy groups appear as a singlet with chemical shift δ 3.71 ppm. A splitting pattern for the benzyl protons as two multiplets centred at δ 2.30 and 2.89 ppm was exhibited for this compound. The CH_2 groups were also observed as two multiplets centred at δ 0.78 and 1.59 ppm. These findings suggest a rigid structure of [8.1]MCP **6b** at this temperature and this one is a *meso* compound.

The chiral properties of the compound *anti*-**6a** in solution were investigated by chromatographic resolution using a chiral column. Interestingly, *anti*-**6a** exhibits two well resolved peaks in the ratio of 50:50 for the *P*- and *M*-enantiomers. This finding strongly suggests that the resolution of racemic *anti*-**6a** could be accomplished by chromatographic separation using a chiral column. In fact, we have succeeded in resolving each *P*- and *M*-enantiomers. The circular dichroism (CD) spectra of the separated enantiomer with precise mirror images are shown in Figure 4. Indeed, we have succeeded in generating inherent chirality in the metacyclophane system containing two aromatic rings by the regio-selective rearrangement of [6.1]metacyclophane **6a**.

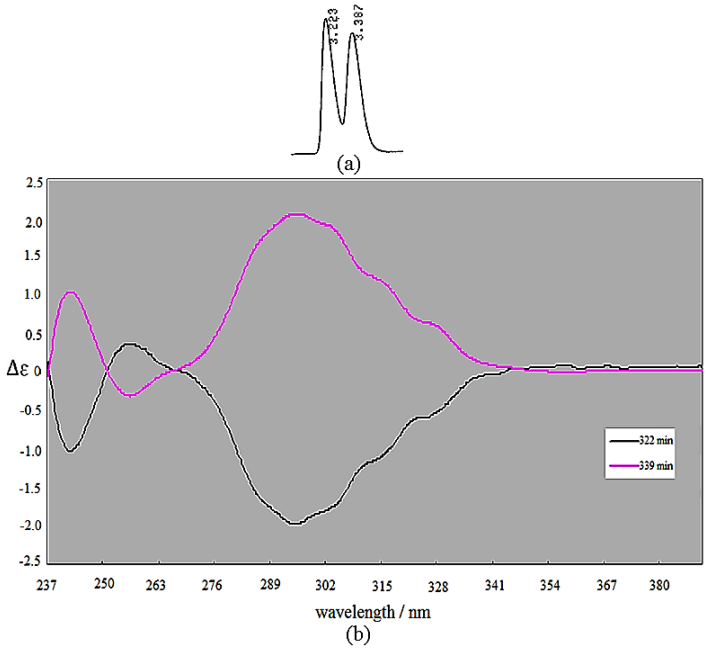


Figure 4. (a) Chromatogram of *anti*-13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl[6.1]MCP **6a** (HPLC on chiral column). Daicel chiralpak ADeH. Eluent: hexanes. (b) CD spectra of *P*- and *M*-enantiomers of inherently chiral MCP *anti*-13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl [6.1]MCP **6a**.

Density functional theory (DFT) computational studies were carried out to demonstrate the geometry-optimized energies of compounds **5**–**6**. The starting structures were generated with the initial geometries based upon their own X-ray crystal structures. The DFT level of theory using the prominent B3LYP (Becke, three-parameter, Lee-Yang-Parr)[34] exchange-correlation functional with the 6-31G(d) basis set. By using Gaussian-09, the individual geometry-optimized structures of these molecules were first conducted in the gas phase and after that in solvent (chloroform) with the B3LYP/6-31G(d) basis set.[35] The DFT-geometry optimized B3LYP/6-31G(d) energies in both the gas-phase or with the solvent correction term for all four compound **6a**, **6b**, **5a**, **5b** is given in Figure 5.

The trend for the stabilities of **6** and **5** could tentatively be rationalized based on the *anti*-conformations of **6a** and **5a** *vs* the *syn*-conformations of **6b** and **5b**. However, the geometry-optimized energy of the *syn*-structure is sufficiently higher than that of the *anti*-structure. Both the single crystal and DFT-optimized structures of **5a** indicate that it adopts an *anti*-conformation and that the methoxy groups are positioned opposite to the benzene rings (Figure 3 and 5).

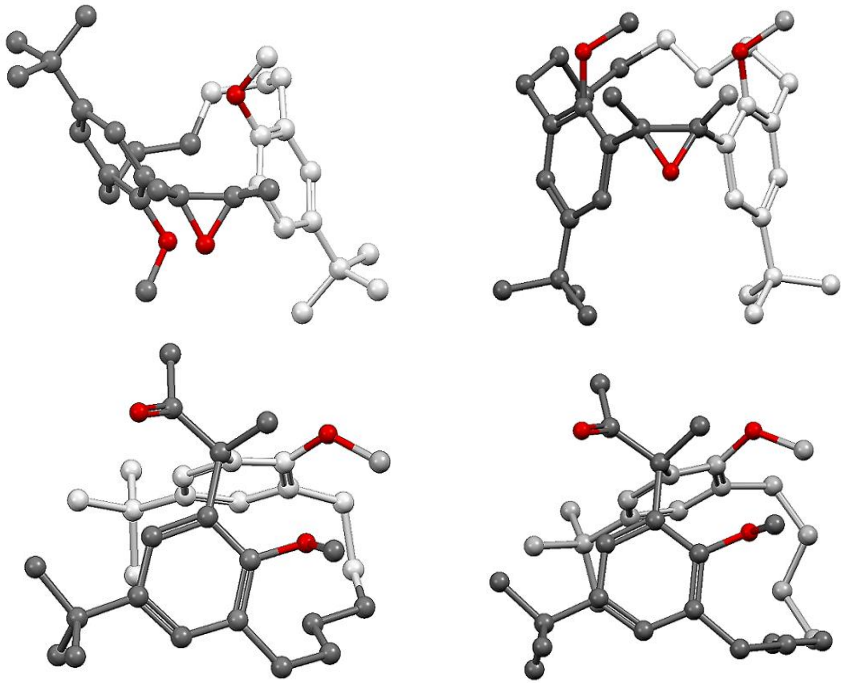


Figure 5. a) DFT geometry-optimized structures of *anti*-**5a** (top left), *syn*-**5b** (top right), *anti*-**6a** (bottom left) and *syn*-**6b** (bottom right). Color code: carbon = dark and light grey, and oxygen = red. Hydrogen atoms omitted for clarity.

Table 3. DFT geometry-optimized computed energies for the compounds **5**–**6** generated from the solid-state X-ray coordinates.

Compound	Energy (kJ mol^{-1})			
	Gas-phase	HOMO	LUMO	Δ*E*
anti-**5a**	-3866698.72	-553.98	5.25	548.73
syn-**5b**	-3866688.48	-545.05	7.04	538.01
anti-**6a**	-4073149.44	-15.75	2.63	13.12
syn-**6b**	-4073145.22	-13.13	2.63	10.50

[a] Based on DFT using the B3LYP/6-31G(d) basis set-up.

The greater activity may be attributed to the higher solubility of the compounds. We have calculated the energies of the HOMO and LUMO orbitals in Table 3. The difference between the energy levels of the HOMO and LUMO (the HOMO–LUMO gap, Δ*E*) shows the stability or reactivity of the molecules, such as, pointing out the possible electron-rich or electron-deficient regions in the structures.

4.2.5. X-ray Crystallography

Diffraction data were collected on a Bruker APEX2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation for *anti*-**4a**, *anti*-**4b**, *anti*-**5a** and *syn*-**5b**. Data were corrected for Lorentz and polarisation effects and for absorption. The structures were solved by charge flipping or direct methods algorithms and refined by full-matrix least-squares methods, on F^2.

Table 4. X-ray crystal structure of compounds *anti*-**4a**, *anti*-**4b**, *anti*-**5a** and *syn*-**5b**.

Parameter	*anti*-**4a**	*anti*-**4b**	*anti*-**5a**	*syn*-**5b**
Empirical formula	$C_{32}H_{46}O_2$	$C_{34}H_{50}O_2$	$C_{32}H_{46}O_3$	$C_{34}H_{50}O_3$
Formula weight	462.71	490.77	478.71	506.76
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
Space group	*P 2₁/n*	*C 2/c*	*C 2/c*	*P 2₁/n*
a[Å]	10.8892(5)	18.5100(18)	18.0647(12)	9.879(3)
b[Å]	14.5980(6)	11.9741(12)	10.9779(8)	36.171(5)
c[Å]	17.6382(8)	14.7028(15)	15.0137(10)	17.228(4)
α[°]	90.0000	90.0000	90.0000	90.0000
β[°]	91.421(6)	113.069(8)	109.868(8)	89.9800(2)
γ[°]	90.0000	90.0000	90.0000	90.0000
Volume[Å^3]	2802.9(2)	2998.1(6)	2800.2(4)	6156(2)
Z	4	4	4	10
Dcalcd[Mg/m^3]	1.096	1.087	1.135	1.367
Temperature [K]	100	100	100	123
Unique reflns	5100	2748	2566	5711
Obsd reflns	2895	1242	1445	5711
Parameters	335	192	168	385
R(int)	0.1036	0.1471	0.1450	0.0300
$R[I> 2\sigma(I)]$[a]	0.0655	0.0757	0.0649	0.0427
*wR*2[all data][b]	0.2843	0.3461	0.4263	0.5100
GOF on F^2	1.033	1.371	1.417	1.519

[a] Conventional R on F_{hkl}: $\Sigma||F_o| - |F_c||/\sigma|F_o|$. [b] Weighted R on $|F_{hkl}|^2$: $\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1526807, 1526816, 1526819 & 1526822. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc. cam.ac.uk].

4.3 Conclusions

In conclusion, a new synthesis of [2.*n*]MCP-1-enes **4a** and **4b** by McMurry cyclization has been developed. Acid catalysed rearrangements of **5a** and **5b** the corresponding epoxides formed with *m*-CPBA can be applied toward the synthesis of [*n*.1]MCPs **6a** and **6b**, respectively. ^{1}H NMR spectroscopy and X-ray analysis of compounds **5** and **6** confirmed that they adopted different *anti*- and *syn*-conformation both in solution and in the solid state. The results from DFT calculations were consistent with the observed experimental results. Further studies based on this type of novel ring contraction of [2.*n*]cyclophanes is being extended with glycol units at the ethylene bridge to afford [*n*.1]cyclophanes, are now in progress.

4.4 Experimental Section

4.4.1 General methods:

All melting points were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Nippon Denshi JEOL FT-300 spectrometer and Varian-400MR-vnmrs 400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. The IR spectra were obtained as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed with a Yanaco MT-5 analyser. Elemental analyses were performed by Yanaco MT-5. Gas–liquid chromatograph (GLC) analyses were performed by Shimadzu gas chromatograph, GC-14A; silicone OV-1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}.

4.4.2 Materials

1,6-Bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)hexane **1a** and 1,8-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)octane **1b** were prepared according to the literature procedures.[17]

4.4.2.1. *Preparation of 1,6-bis(5-tert-butyl-3-(1-hydroxyethyl)-2-methoxylphenyl) hexane (2a)*

To a solution of methylmagnesium iodide [prepared from methyl iodide (14.40 g, 101 mmol) and magnesium (2.05 g, 84.3 mmol)] in Et_2O (45 mL) was added a solution of **1a** (8.85 g, 20.9 mmol) in tetrahydrofuran (100 mL) dropwise under the conditions of gentle reflux. After the reaction mixture was refluxed for an additional 5 h, it was quenched with 10% ammonium chloride (100 mL) and extracted with Et_2O (100 × 3mL). The extract was washed with water (100 mL × 2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from hexane to afford 1,6-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)hexane **2a** (7.71 g, 74%) as colorless prisms. M.p. 125–126 °C. IR (KBr): υ_{max} = 3308, 2963, 2856, 2827, 1480, 1463, 1429, 1363, 1282, 1231, 1202, 1172, 1119, 1074, 1011 and 879 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s), 1.51–1.70 (6H, m), 1.52 (6H, d, *J* = 6.6 Hz), 2.26–2.36 (4H, m), 2.58–2.68 (4H, m), 3.77 (6H, s), 5.16–5.25 (2H, bs), 7.11 (2H, d, *J* = 2.4 Hz) and 7.27 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.94, 29.77, 30.07, 31.11, 34.31, 61.76, 65.76, 120.74, 126.29, 134.58, 137.50, 146.81 and 153.25 ppm. MS (EI): m/z found 499 [M^+]. Anal. calcd. for $C_{32}H_{50}O_4$ (498.7) C, 77.06; H, 10.10, found C, 77.23; H, 10.41.

4.4.2.2. *Preparation of 1,8-bis(5-tert-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)octane (2b)*

Compound **2b** was synthesized in the same manner as described above for **2a** and obtained (8.48 g, 77%) as colorless prisms. M.p. 107–108 °C. IR (KBr): υ_{max} = 3313, 2915, 1469, 1295, 1174, 1115, 1000 and 879 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s), 1.36–1.45 (4H, m), 1.52 (6H, d, *J* = 6.6 Hz), 1.58–1.69 (6H, m), 2.33 (4H, s), 2.59–2.63 (4H, m), 3.77 (6H, s), 5.20 (2H, broad s), 7.12 (2H, d, *J* = 2.4 Hz)

and 7.27 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.51, 28.87, 29.65, 30.49, 31.03, 34.16, 61.22, 65.12, 120.03, 125.91, 134.58, 136.84, 146.55 and 152.69 ppm. MS (EI): m/z found 527 [M^+]. Anal. calcd. for $C_{34}H_{54}O_4$ (526.9) C, 77.52; H, 10.33, found C, 76.17; H, 10.29.

4.4.2.3. *Preparation of 1,6-bis(3-acetyl-5-tert-butyl-2-methoxy phenyl)hexane (3a)*

To a solution of pyridinium chlorochromate, $C_5H_5NH^+CrO_3Cl^-$ (31.0 g, 144 mmol) in acetone (300 mL) was added a solution of 1,6-bis(5-*tert*-butyl-3-(1'-hydroxyethyl)-2-methylphenyl)- hexane **2a** (10.62 g, 21.3 mmol) in acetone (100 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was subjected to silica-gel (Wako, C-300; 500 g) column chromatography using as eluent $CHCl_3$ to afford 1,6-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl) hexane **3a** (7.27 g, 69%) as colorless prisms (Hexane). M.p. 127–128 °C. IR (KBr): υ_{max} = 2848, 1676, 1472, 1362, 1222, 1126 and 1004 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s), 1.42–1.50 (4H, m), 1.45 (4H, s), 1.61–1.72 (4H, m), 2.63 (6H, s), 3.73 (6H, s), 7.33 (2H, d, *J* = 2.4 Hz) and 7.41 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.65, 30.08, 30.50, 30.98, 31.43, 34.51, 62.81, 124.30, 131.13, 133.06, 136.04, 146.84, 155.27 and 201.92 ppm. MS (EI): m/z found 495 [M^+]. Anal. calcd. for $C_{32}H_{46}O_4$ (494.7) C, 77.69; H, 9.37, found C, 77.91; H, 9.36.

4.4.2.4. *Preparation of 1,8-bis(3-acetyl-5-tert-butyl-2-methoxyphenyl)octane (3b)*

Compound **3b** was synthesized in the same manner as described above for **3a** and obtained (6.91 g, 62%) as colorless prisms (MeOH). M.p. 58–59 °C. IR (KBr): υ_{max} = 2944, 2848, 1682 (C=O), 1476, 1369, 1266, 1222 and 1008 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s), 1.37–1.46 (12H, m), 1.55–1.68 (4H, m), 2.63 (6H, s), 3.73 (6H, s), 7.34 (2H, d, *J* = 2.4 Hz) and 7.41 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.49, 29.75, 29.96, 30.43, 30.91, 31.35, 34.44, 62.72, 124.17, 131.04, 132.97, 136.04, 146.74, 155.18 and 201.88 ppm. MS (EI): m/z found 522 [M^+]. Anal. calcd. for $C_{34}H_{50}O_4$ (522.7) C, 78.12; H, 6.94, found C, 77.88; H, 9.60.

4.4.2.5 *McMurry coupling reaction of 3*

The McMurry reagent was prepared from $TiCl_4$ (13.75 mL, 125 mmol) and Zn powder (18.0 g, 275 mmol) in dry THF (500 mL), under nitrogen. A solution of 1,6-bis(3-acetyl-5-*tert*-butyl-2-methoxylphenyl)hexane **3a** (3.4 g, 6.8 mmol) and pyridine (22.8 mL, 0.20 mol) in dry THF (250 mL) was added within 60 h to the black mixture of the McMurry reagent by using a high-dilution technique with continuous refluxing and stirring. The reaction mixture was refluxed for additional 8 h, cooled to room temperature, and hydrized with aqueous 10% K_2CO_3 (200 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were washed with water, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wako C-300, 300 g) with hexane–toluene (1:1) and toluene as eluents to give *anti*-**4a** and *syn*-**4a** as a colorless solid. Each eluent was recrystallized from hexane to afford *anti*-**4a** (724 mg, 23%) and *syn*-**4a** (410 mg, 13%), respectively. *anti*-5,17-Di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl[2.6]metacyclophan-1-ene (*anti*-**4a**) was obtained as colorless prisms (MeOH). M.p. 183–184 °C. IR (KBr): υ_{max} = 2944, 2856, 1469, 1358, 1233, 1107, 1023, 875, 805 and 654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.50 (2H, m), 0.83 (2H, m), 1.26 (4H, m), 1.31 (18H, s), 2.10 (2H, m), 2.22 (6H, s), 2.52 (2H, m), 3.34 (6H, s) 6.89 (2H, d, *J* = 2.7 Hz) and 7.04 (2H, d, *J* = 2.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.13, 26.56, 27.94, 29.13, 31.30, 33.90, 59.37, 124.29, 124.36, 129.44, 133.39, 135.98, 144.19 and 152.03 ppm. MS (EI): m/z found 462.4 [M^+]. Anal. calcd. for $C_{32}H_{46}O_2$ (462.7) C, 83.06; H, 10.02, found C, 82.87; H, 9.99.

syn-5,17-Di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl[2.6]-metacyclophan-1-ene (*syn*-**4a**) was obtained as colorless prisms (MeOH). M.p. 90–91 °C. IR (KBr): υ_{max} = 2961, 2923, 1476, 1235 and 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.59 (2H, m), 0.85 (2H, m), 1.11 (18H, s), 1.30 (4H, m), 2.18 (6H, s), 2.28 (2H, m), 2.80 (2H, m), 3.67 (6H, s), 6.64 (2H, d, *J* = 2.4 Hz) and 6.77 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 31.2, 32.8, 33.9, 34.3, 64.5, 70.7, 122.1, 126.9, 127.2, 127.4, 128.0, 128.6, 128.9, 129.3, 129.5, 137.3, 143.6, 146.8, 146.9, 156.2 and 156.6 ppm. MS (EI): m/z found 462 [M^+]. Anal. calcd. for $C_{32}H_{46}O_2$ (462.7) C, 83.06; H, 10.02, found C, 82.59; H, 10.01.

4.4.2.6 *Preparation of 5,19-di-tert-butyl-8,22-dimethoxy-1,2-dimethyl[2.8] metacyclophan-1-ene (4b)*

Compound *anti*-**4b** was synthesized in the same manner as described above for *anti*-**4a** and obtained (701 mg, 21%) as colourless prisms (MeOH). M.p. 178–179 °C. IR (KBr): υ_{max} = 2959, 2856, 1472, 1458, 1262, 1233 and 1104 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.95 (6H, m), 1.12–1.33 (6H, m), 1.28 (18H, s), 2.01–2.11 (2H, m), 2.15 (6H, s), 2.59–2.70 (2H, m), 3.52 (6H, s), 6.86 (2H, d, *J* = 2.4 Hz) and 7.01 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.25, 24.41, 25.89, 27.45, 28.96, 31.44, 34.02, 59.76, 124.93, 125.59, 129.90, 132.92, 136.42, 143.74 and 152.44 ppm. MS (EI): m/z found 490.4 [M^+]. Anal. calcd. for $C_{34}H_{50}O_2$ (490.8) C, 83.21; H, 10.27, found C, 83.52; H, 10.18.

Compound *syn*-**4b** was synthesized in the same manner as described above for *syn*-**4a** and obtained (2.14 g, 64%) as colourless prisms (MeOH). M.p. 104–105 °C. IR (KBr): υ_{max} = 2944, 2856, 1472, 1454, 1362, 1214, 1015, 875 and 801 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94–1.12 (6H, m), 1.12 (18H, s), 1.27–1.36 (6H, m), 2.13–2.23 (2H, m), 2.20 (6H, s), 2.73–2.85 (2H, m), 3.69 (6H, s), 6.74 (2H, d, *J* = 2.4 Hz) and 6.82 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.62, 26.92, 27.62, 29.24, 30.40, 31.57, 33.93, 60.02, 125.58, 126.14, 131.40, 134.06, 136.16, 144.25 and 153.48 ppm. MS (EI): m/z found 490 [M^+]. Anal. calcd. for $C_{34}H_{50}O_2$ (490.8) C, 83.21; H, 10.27, found C, 83.82; H, 10.18.

4.4.2.7 *General procedure for epoxydation of 4 with m-CPBA*

To a suspension of *anti*-**4a** (20 mg, 0.044 mmol) and $NaHCO_3$ (6 mg, 0.082 mmol) in toluene (2 mL) was added *m*-CPBA (20.5 mg, 0.082 mmol) and the mixture was stirred for 40 h. The reaction mixture was diluted with water (20 mL), and extracted with CH_2Cl_2 (10 mL × 2). The combined extracts were washed with water (10 mL × 2), dried with $MgSO_4$ and concentrated. The residue was recrystallized from methanol to give (11 mg, 55%) *anti*-5,17-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,20-dimethoxy [2.6]metacyclophane (*anti*-**5a**) as colorless prisms (MeOH). M.p. 192–193 °C. IR (KBr): υ_{max} = 2944, 2856, 1472, 1450, 1352, 1229, 1085, 1019, 875 and 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25–0.35 (4H, m), 0.70–0.81 (4H, m), 1.30 (9H, s),

1.31 (9H, s), 1.73 (3H, s), 1.95 (3H, s), 2.21–2.35 (2H, m), 2.44–2.53 (2H, m), 3.39 (3H, s), 3.49 (3H, s), 6.94 (1H, d, *J* = 2.4 Hz), 6.95 (1H, d, *J* = 2.4 Hz), 7.29 (1H, d, *J* = 2.4 Hz) and 7.38 (1H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.13, 27.67, 29.70, 31.79, 33.87, 60.21, 61.91, 66.77, 125.91, 126.43, 132.48, 134.94, 145.30 and 153.58 ppm. MS (EI): m/z found 478.4 [M^+]. Anal. calcd. for $C_{32}H_{46}O_3$ (478.7) C, 80.29; H, 9.69, found C, 79.90; H, 9.62.

However, several attempted epoxidations of *syn*-**5a** failed. Only an intractable mixture of products resulted.

4.4.2.8 *Preparation of syn-5,19-di-tert-butyl-1,2-epoxy-1,2-dimethyl-8,22-dimethoxy[2.8] metacyclophane (syn-5b)*

Compound *syn*-**5b** was synthesized in the same manner as described above for *anti*-**5a** and obtained (15 mg, 67%) as colourless prisms (MeOH). M.p. 152–153 °C. IR (KBr): υ_{max} = 2959, 2922, 2856, 1480, 1362, 1258, 1203 1111, 1011 and 801 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71–0.97 (4H, m), 1.16 (18H, s), 1.31–1.42 (4H, m), 1.48–1.59 (4H, m), 1.88 (6H, s), 2.16–2.26 (2H, m), 2.87–2.94 (2H, m), 3.80 (6H, s), 6.84 (2H, d, *J* = 2.4 Hz) and 7.11 (2H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.88, 26.03, 27.35, 28.18, 30.55, 31.44, 34.06, 60.63, 67.84, 122.93, 127.20, 131.92, 133.05, 144.36 and 153.87 ppm. FABMS: m/z found 506.4 [M^+]. Anal. calcd. for $C_{34}H_{50}O_3$ (506.7) C, 80.58; H, 9.94, found C, 80.58; H, 9.86.

4.4.2.9 *General procedure for the acid catalysed rearrangement of epoxy metacyclophane (anti-5a)*

To a suspension of *anti*-**5a** (30 mg, 0.062 mmol) in CH_2Cl_2 (3 mL) was added BF_3-Et_2O (8.4 mg, 0.059 mmol) and the mixture was heated to reflux for 1 h. The cooled solution was quenched by water (5 mL), and extracted with CH_2Cl_2 (10 mL × 2). The combined extracts were washed with 5% aqueous $NaHCO_3$ (10 mL), water (10 mL × 2), dried with $MgSO_4$ and concentrated to give *syn*-13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl[6.1]metacyclophane (*anti*-**6a**) (15 mg, 51%) as colorless prisms (MeOH). M.p. 111–112 °C. IR (KBr): υ_{max} = 2966, 2915, 2863, 1690 (C=O), 1476, 1454, 1358, 1222, 1107, 1004, 879 and 643 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ =

0.53–0.70 (2H, m), 0.80–0.95 (2H, m), 1.30 (9H, s), 1.32 (9H, s), 1.26–1.37 (4H, m), 1.71 (3H, s), 1.76 (3H, s), 2.20–2.30 (2H, m), 2.34–2.47 (2H, m), 3.29 (3H, s), 3.41 (3H, s), 7.05 (1H, d, *J* = 2.4 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 7.25 (1H, d, *J* = 2.4 Hz) and 7.28 (1H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.12, 26.29, 27.16, 28.72, 28.85, 29.17, 31.39, 31.55, 34.28, 61.08, 61.89, 123.67, 125.36, 125.40, 128.52, 133.27, 144.55, 144.85 and 210.26 ppm. FABMS: m/z found 478.3 [M^+]. Anal. calcd. for $C_{32}H_{46}O_3$ (478.7) C, 80.29; H, 9.69, found C, 80.33; H, 9.67.

4.4.2.10 *Preparation of syn-15-acetyl-11,18-di-tert-butyl-14,21-dimethoxy-15-methyl [8.1]metacyclophane (syn-6b)*

Compound *syn*-**6b** was synthesized in the same manner as described above for *anti*-**6a** and obtained (13 mg, 41%) as colorless prisms (MeOH). M.p. 118–119 °C. IR (KBr): υ_{max} = 2937, 2856, 1690 (C=O), 1568, 1476, 1476, 1362, 1211, 1008, 894, 750 and 717 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70–0.86 (4H, m), 1.16 (18H, s), 1.24–1.34 (4H, s), 1.54–1.64 (4H, m), 2.25–2.35 (2H, m), 2.37 (3H, s), 2.42 (3H, s), 2.82–2.95 (2H, m), 3.71 (6H, s) and 6.87 (4H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.45, 25.21, 27.67, 28.72, 29.02, 29.39, 30.06, 31.44, 31.77, 34.23, 61.91, 63.61, 110.31, 125.90, 126.31, 126.58, 135.60, 144.92, 156.34 and 210.70 ppm. FABMS: m/z found 506.3 [M^+]. Anal. calcd. for $C_{34}H_{50}O_3$ (506.7) C, 80.58; H, 9.94, found C, 80.66; H, 9.88.

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Chapter 5

Demethylation of 5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]metacyclophane-1-ynes with BBr_3 to afford novel [*n*]benzofuranophanes

Novel [n]benzofuranophane (n = 8 & 10) 2a–b have been prepared by successive intramolecular cyclization from 5,19-di-tert-butyl-8,22-dimethoxy[n]metacyclophane-1-yne (syn-1a–b) by treatment with BBr_3 in CH_2Cl_2 at room temperature for 8 h. [2.n]Benzofuranophanes 2a–b were also obtained by treatment of 1,2-di-endo-bromo-5,19-di-tert-butyl-8,22-dimethoxy[n]metacyclophane (meso-3a–b) with BBr_3 in CH_2Cl_2 by using same reaction condition.

4.1 Introduction

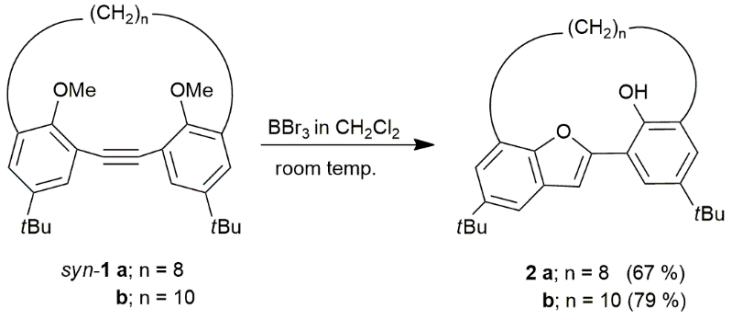
Cyclophanes have been gathered much attention on physical and chemical properties due to theirs regid structure with intriguing geometry.[1–5] To study the molecular functions based on the novel structures, several macrocyclic cyclophanes with strained acetylenic bonds have been synthesized by using the McMurry coupling as a key step.[6–8] The strained cyclophynes was synthesized as an intermediate by a trapping method.[9–12] [*n*]MCP-diynes (MCP = metacyclophane) easily reacts with strong bases to achive allenic and olefinic isomers which changes the basic characteristics of cyclic diynes.[13] Fallis with his co-workers have reported the synthetic route of novel acetylenic cyclophanes by Pd- and Cu-mediated coupling reactions.[14,15] On the other hand, we have succeeded to prepare dimethoxy[2.*n*]MCP-1-ynes with bent triple bonds[16] by the bromination-dehydrobromination of the corresponding [2.*n*]MCP-1-enes.[17–19] These latter intermediates 1,2-dibromo-4,22-dimethoxy[2.10]MCPs can afford convenient starting materials for the preparation of 4b,9b-dihydro[10]benzofuro[3,2-*b*] benzofuranophane by double intramolecular cyclization in presence of BBr_3 in CH_2Cl_2 at room temperature.[18]

Yamaguchi and co-workers released a series of fully ring-fused ladder π-conjugated skeletons by the double intramolecular cyclizations of diaryl acetylenes.[20–24] A highly efficient and atom-economical construction of 2 substituted 5-hydroxybenzofurans featuring the dienone-phenol rearrangement reaction of quinols containing an alkyne moiety.[25–27] Recently, our group has illuslated an efficient synthetic route to achieve arene-based macrocyclic [3.3.1]MCPs containing a benzofuran ring. Treatment of [3.3.1]MCP-2,11-dione with TMSCl (trimethyl silyl chloride) can afford dihydrobenzofuran and benzofuran rings by simple intramolecular nucleophilic cyclization.[28] Due to the innate structural aspects, we anticipated that 5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]MCP-1-ynes would provide a unique platform for the framework of unsymmetrical benzofuranophane and inspired us to attempt the synthesis of cyclophane containing benzofuran analogues. The mainly purpose of this research is present an efficient approach to synthesize unsymmetrical benzofuranophanes, furthermore, the relationship between structure with their properties have been investigated details.

5.2 Results and Discussion

According to our previous reported, the starting compound 5,19-di-*tert*-butyl-8,22-dimethoxy[2.8]MCP-1-yne (*syn*-**1a**) was synthesized by dehydrobromination reaction of *syn*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-dimethoxy[2.8]MCP in presence of HOBu^t at 80 °C for 12 h, 48% yield.[17,30] Subsequently, demethaylation reaction of *syn*-**1a** with BBr_3, a commercially available, excellent demethylating or dealkylating agent for the cleavage of ethers also with subsequent cyclization, in CH_2Cl_2 solution at room temperature for 8 h (Scheme 1) afford the expected [8]benzofuranophane **2a** in 67% yield. So, this example inspired us to further investigate the effect of the increase of carbon chain in MCP skeleton structure for BBr_3-induced cyclization reaction. The length of the cross-linking chain can be increased up to a certain level to form benzofuranophane. Therefore, [2.10]MCP is treated with BBr_3 for synthesis of benzofuranophane.

At higher temperature and prolonged reaction time 17,18-di-*endo*-bromo-13,21-di-*tert*-butyl-16,24-dimethoxy[2.10]MCP was treated with potassium *tert*-butoxide in refluxing HOBu^t at 80 °C for 3 h and synthesized 5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-yne (*syn*-**1b**) in 93% yield, along with 7% monodehydrobrominated product as reported procedure.[17,30] Bromination of *syn*-**1b** with BBr_3 carried out in a CH_2Cl_2 solution at room temperature for 0.5 h generates [10]benzofuranophane **2b** in 79% yield. In this case, reaction occurred within a very short time (3 h) than that of *syn*-**1a**.



Scheme 1. Reaction of *syn*-**1** with BBr_3 in CH_2Cl_2.

The structure of **2a** was characterized by ^{1}H and ^{13}C NMR, mass spectra and elemental analysis, as well as single crystal X-ray diffraction. The ^{1}H NMR spectrum of **2a** (300 MHz,

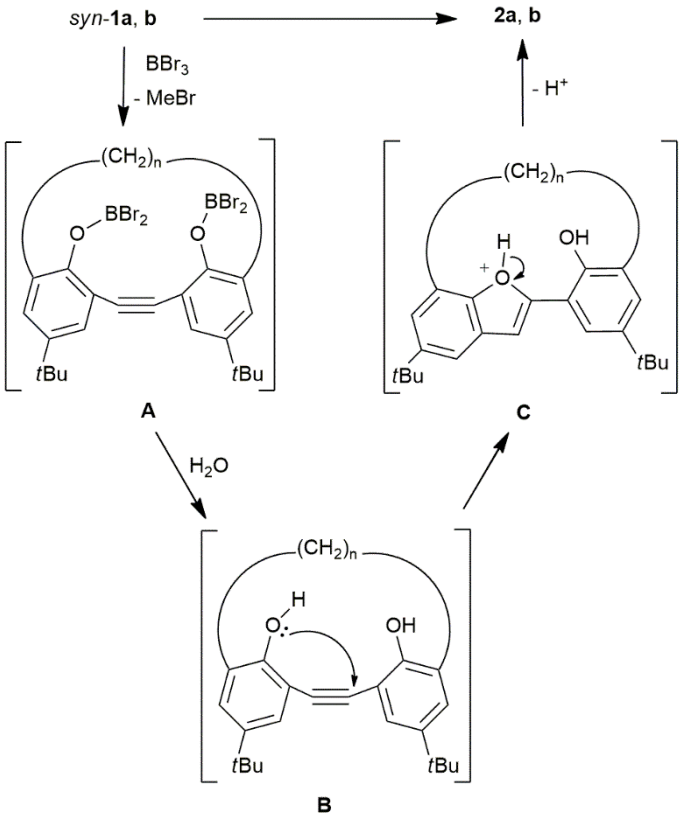
$CDCl_3$) shows five aromatic protons are observed as a singlet at δ 6.91 ppm and doublets at δ 7.11, 7.13, 7.23, 7.45 ppm, respeactively, which are clearly associated with the unsymmetrical structure of **2a**. The ^1H NMR (300 MHz, $CDCl_3$) spectrum also exhibits the signal for one hydroxyl group in the lower magnetic field δ 7.18 ppm, which is exchanged by D_2O. This data is consistent with the existence of intramolecular hydrogen bonding between the hydroxyl group and the oxygen of the benzofuran ring. A peak for O–H band was observed at 3527 cm^{-1} in the IR spectrum. On the basis of the spectral data and the chemical conversion, compound **2a** is assigned to the structure, 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[8](7,3*'*)benzofuranophane.

The ^1H NMR (300 MHz, $CDCl_3$) spectrum exhibits the signal for one hydroxyl group in the lower magnetic field δ 7.67 ppm, which is exchanged by D_2O strongly suggested the highly formation of an intramolecular hydrogen bond. The IR spectrum of **2b** also shows the absorption of the hydroxyl stretching vibration around 3511 cm^{-1}. On the basis of the spectral data and the chemical analysis, compound **2b** is assigned to the structure, 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[10](7,3*'*)benzofuranophane.

Despite the fact that the detailed reaction mechanism of generation of [*n*]benzofuranophane from 5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]MCP-1-ynes is not clear at this time, it can be considered to have progressed as follows in Scheme 2. The mechanism of BBr_3 reaction of starting material *syn* apparently proceeds via the formation of a complex **A** followed by elimination of an alkyl bromide. **A** can undergo hydrolysis to give a hydroxyl group based product **B** from which the electrophilic attack to the triple bond to initiate the cation intermediate **C** provided final compound [*n*]benzofuranophane by dehydrobromination. In this reaction, BBr_3 as excellent demethylating or dealkylating agent, play an significant role to activate the cyclization reaction. The detail mechanism of the BBr_3-induced cyclization reaction will discuss in below.

Bromination of *anti*- and *syn*-5,10-di-*tert*-butyl-8,22-dimethoxy[2.8]MCP-1-ene with 1.1 equiv. of benzyltrimethylammonium tribromide ($BTMABr_3$), which was found to be a convenient solid brominating agent,[29] in CH_2Cl_2 solution at room temperature for 1 h and 2 h led to the *trans* and *cis* adduct *anti*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-dimethoxy[2.8]MCP (*dl*-**5a**) and *syn*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-

dimethoxy[2.8]MCP (*meso*-**3a**), respectively following previous report.[17,30] Both *meso*-**3a** and *dl*-**5a** react with BBr_3 in CH_2Cl_2 as former reaction conditions (Scheme 3) to afford compound **2a**. Extension of reaction time to 8 h will give more percentage of the product.

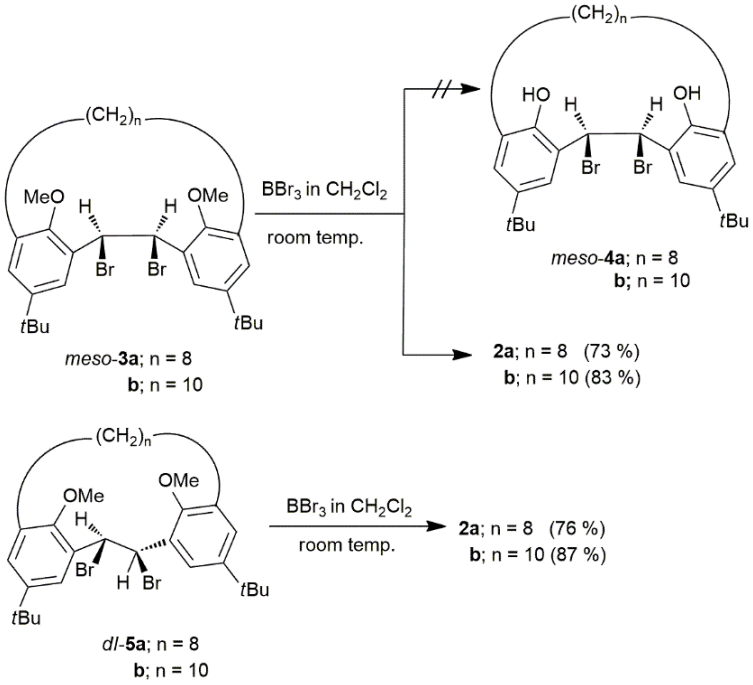


Scheme 2. Proposed reaction mechanism of formation of [*n*]benzofuranophanes *syn*-**2** from 5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]MCP-1-ynes *syn*-**1**.

Similarly, 1,2-di-*endo*-bromo-(*meso*-**3b**) and 1-*endo*,2-*exo*-dibromo-5,21-di-*tert*-butyl-8, 24-dimethoxy[2.10]MCP (*dl*-**5b**) were prepared by bromination of *(Z)*- and *(E)*-5,2-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene with 1.1 equiv. of $BTMABr_3$ in CH_2Cl_2 at room temperature for 5 min in 54 and 88% yields, respectively, according to the reported procedure.[17,30,31] Under different conditions for demethylation of *meso*-**3b** to afford *meso*-**4b** with trimethylsilyl iodide in acetonitrile solution[32–34] was not succieed. Only an awkward mixture of products was obtained. Interestingly, treatment of *meso*-**3b** with BBr_3 in CH_2Cl_2 at room temperature for 0.5 h divergent outcomes were procured.

However, the formation of the corresponding demethylation product, 1,2-di-*endo*-bromo-8,24-dihydroxy[2.10]MCP (*meso*-**4b**) was not observed during the reaction. Similar reaction

to afford [10]benzofuranophane **2b** was resulted in the treatment of *dl*-**5b** with BBr_3 in CH_2Cl_2 under the same conditions described above in 87% yield (Scheme 3).

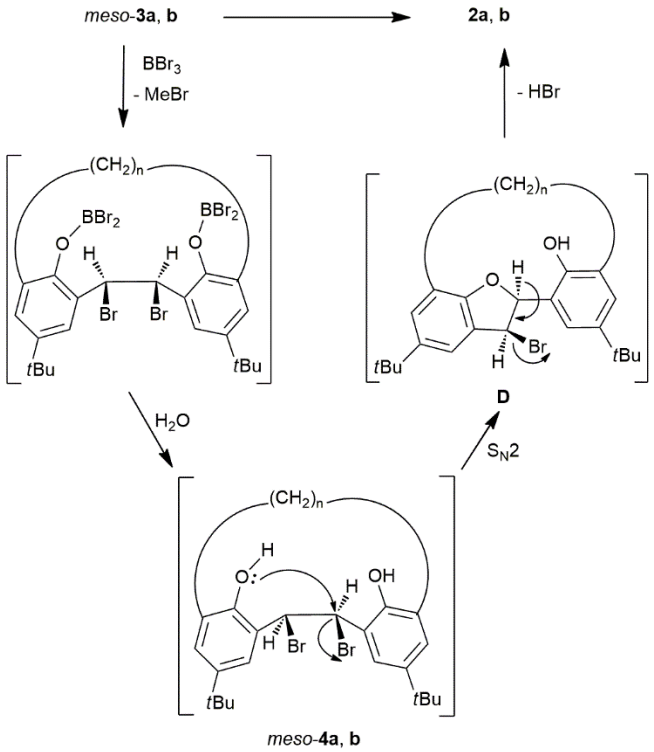


Scheme 3. Reaction of *meso*-**3a** and *dl*-**5a** with BBr_3 in CH_2Cl_2.

The mechanism of formation of [*n*]benzofuranophane from *meso* compound in presence of BBr_3 is based on speculation as shown in Scheme 4. The present BBr_3 induced conversion from 1,2-di-*endo*-bromo-5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]MCP to desired [*n*]benzofuranophane possibly raised by demethylation of methoxy groups to provide the corresponding phenol derivatives *meso*-**4a**,**b** followed by the nucleophilic substitution at the C_2 carbon to afford five membered dihydrofuran skeleton (**D**) from which the final product [*n*]benzofuranophane was formed by dehydrobromination reaction.

Intramolecular hydrogen bonding in compound **2** has been investigated in solution by NMR as a major tool. The evidence of hydrogen bonding can be provided by ^1H and heteronuclear chemical shifts, coupling constants, solvent and deuterium isotope effects on chemical shifts. The use of hydroxyl protons in hydrogen bonding and conformational NMR studies in solution, displays experimental challenges because of rapid chemical exchange between hydroxyl groups and protic solvents. Proton exchange rates in alcohol –OH groups can be weakened by dissolving in DMSO-d_6 or acetone-d_6 or by using organic co-solvents and thus, have already been promoted in structural analysis of benzofuranophane. For

compound **2a**, in DMSO-d_6 a very sharp peak for hydroxyl group observed at δ 8.71 ppm. In acetone-d_6 the hydroxyl peak shifted to lower frequency at δ 7.97 ppm. In $CDCl_3$, the signal, this is further shifted to lowest frequency at δ 7.18 ppm. For compound **2b**, in DMSO-d_6 a very sharp peak for hydroxyl group observed at δ 8.35 ppm. In acetone-d_6 the hydroxyl peak shifted to lower frequency at δ 7.91 ppm. In $CDCl_3$ the peak shifted to lowest frequency at δ 7.67 ppm. The phenolic hydroxyl proton form intramolecular hydrogen bond with the oxygen in benzofuran unit.



Scheme 4. Proposed reaction mechanism of formation of [*n*]benzofuranophanes *syn*-**2** from *meso*-**3a**,**b**.

The ^{1}H NMR of **2a**–**b** (400 MHz) in DMSO-d_6 and acetone-d_6 lead to shift the hydroxyl peak at low field region indicating that the intramolecular hydrogen bonding is disrupted in polar solvent and formation of intermolecular hydrogen bonding with solvent (Figure 1 & Figure 2). For compound **2a** OH peak shifted to lower field than that of compound **2b**. This is because of the shorter number of carbon chain length, which causes more steric hindrance into the cyclophane system.

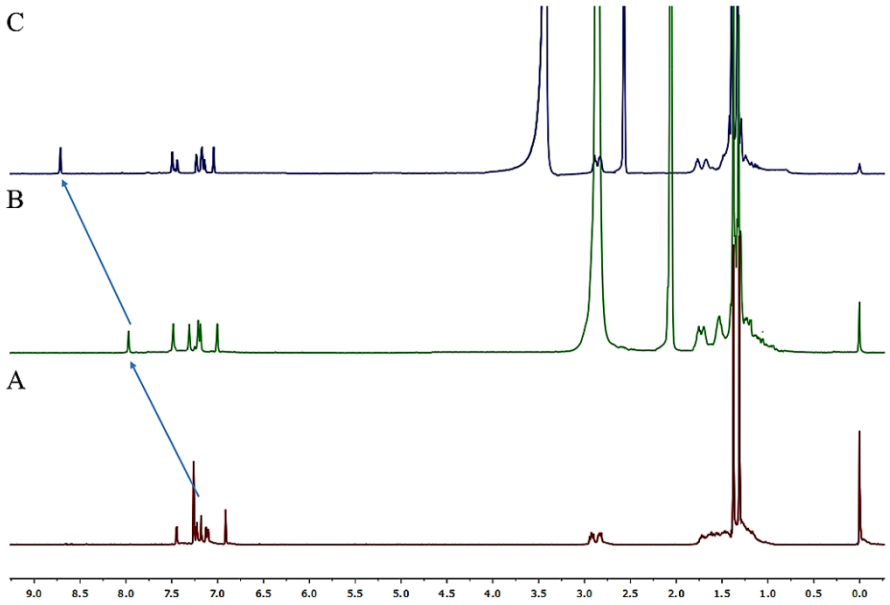


Figure 1. ^{1}H NMR spectra of **2a** (100 MHz, 293 K); (A) $CDCl_3$, (B) $(CD_3)_2CO$, (C) $(CD_3)_2SO$.

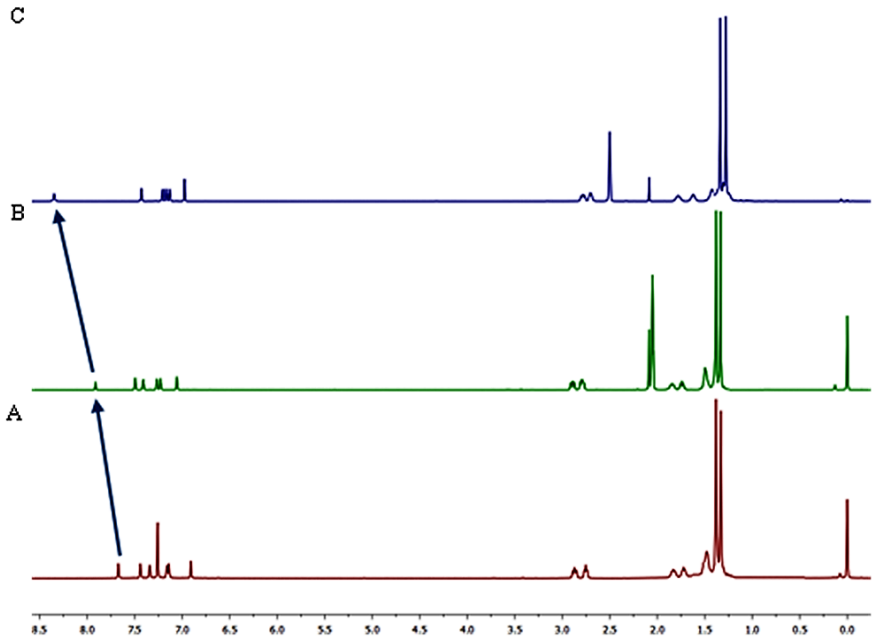


Figure 2. ^{1}H NMR spectra of **2b** (100 MHz, 293 K); (A) $CDCl_3$, (B) $(CD_3)_2CO$, (C) $(CD_3)_2SO$.

The suitable crystals **2a** and **2b** for single crystal X-ray analysis were cultivated from a hexane-chloroform (V_{hexane}:$V_{Chloroform}$ = 1:1) by slow evaporation process at room temperature. Compound **2a** crystallizes in the orthorhombic crystal system with space group *P bca*, whereas compound **2b** in the monoclinic crystal system with space group *Cc*. The key

crystallographic data is summarized and each crystal structure **2a** and **2b** are shown in Figure 3.

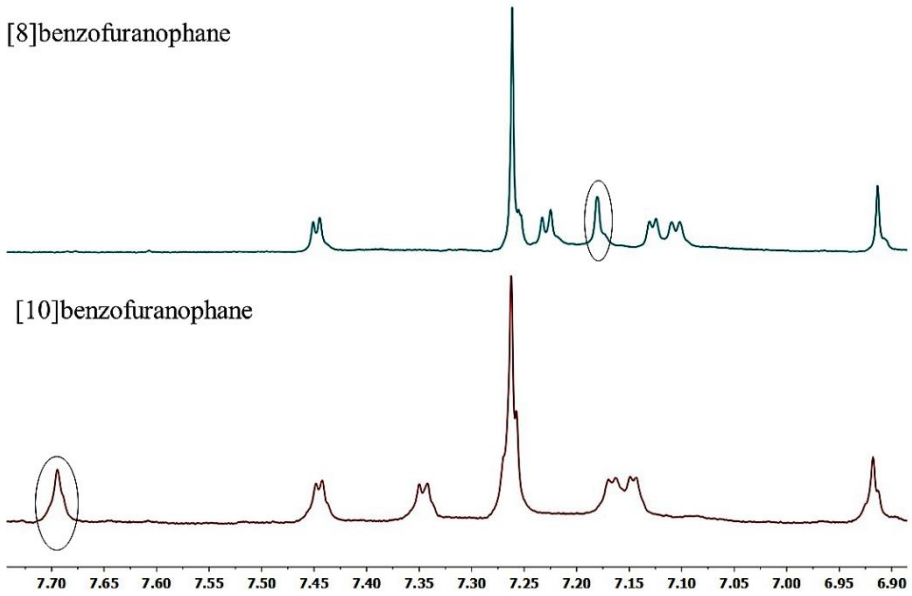


Figure 3. The chemical shift for hydroxyl group between [8]benzofuranophane **2a** and [10]benzofuranophane **2b** in ^{1}H NMR.

The X-ray structure of novel [8]benzofuranophane **2a** and [10]benzofuranophane **2b** were displayed in Figure 3. In **2a**, the benzofuran ring is not co-plane with phenyl ring with a torsion angle of 34.2^{o}, the hydroxy (OH) at the 2-position of benzene has formed intramolecular hydrogen bonding with adjacent oxygen atom (O2), and the distance of O2-H2…O1 is 1.98 Å. Similarly, in compound **2b** with 10 carbon line alkyl, the torsion angle (23.5^{o}) is less than **2a** between benzofuran ring and phenyl ring, which indicated the length of alkyl would affect the molecular conformation; for example, hydroxyl (OH) in **2a** are strongly affected by steric effects of the neighbor carbon line alkyl, however, the compound **2b** with longer line alkyl would release the strain. Indeed, as our speculation, some methylene group are involved in a strong intermolecular interaction and disorder with occupancy ratio 0.5:0.5 for C23, C24 and C25 in X-ray structure, respectively. However, no disordered structure was observed in compound **2b**.

In case of compound **2b** the present conformational rigidity might be attributed to the strong intramolecular hydrogen bond among the hydroxyl group and the oxygen atom on the

benzofuran ring which strongly reduce the conformational ring flipping. The hydrogen bond O2-H2…O1 was 1.82 Å, which is a reasonable distance for intramolecular hydrogen bonding.

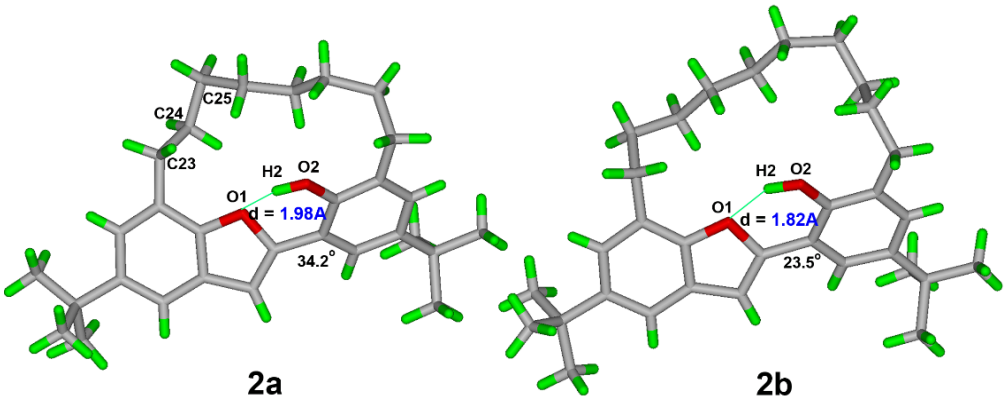
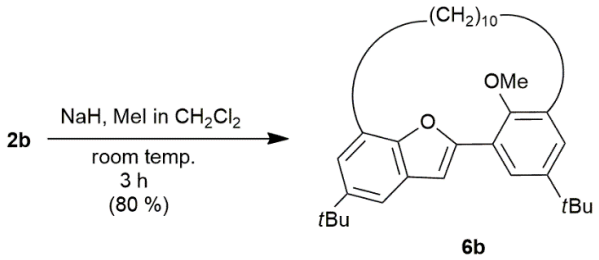


Figure 3. Ortep drawing of compound **2a** and **2b**. Thermal ellipsoids are drawn at the 50% probability level.

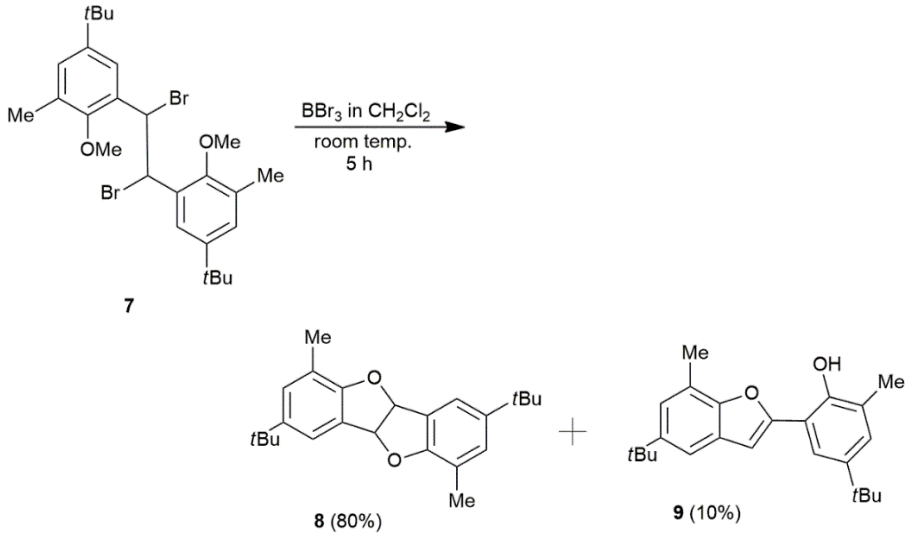
In addition, the intramolecular hydrogen bonds were further confirmed by the Temperature-dependent NMR. The conformation of this compound in solution is rigid and the signals of the benzylic methylene protons do not coalesce below 150 °C in DMSO. This finding strongly suggest the restricted rotation around the diaryl linkage of [10]benzofuranophane **2b**. Both ^{1}H NMR and X-ray results strongly suggest that compound **2b** have stronger intramolecular hydrogen bonding in comparison with compound **2a**.

To gain a deep insight into the synergistic effect of the steric effects and intramolecular hydrogen bonding for molecular conformation in benzofuranophane derivatives, the hydroxyl group in **2b** was replaced by methyl group as followed Scheme 5. After that compound **2b** was treated with Methane iodide in the presence of NaH in anhydrous THF solution at room temperature for 3 h, the corresponding methoxy derivative **6b** was obtained in 64% yield. The hydroxyl group of compound **2b** is converted into the larger methoxy group. The ^{1}H-NMR peak of OH disappears from the spectrum and conducts internal methoxy proton as a singlet at δ 3.41 ppm and H proton of benzofuran ring as a singlet at δ 6.91 ppm (relative intensity 3:1).



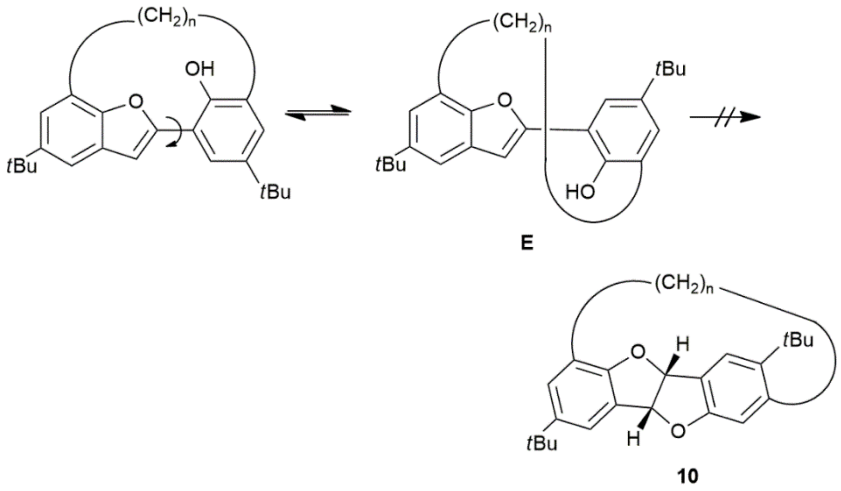
Scheme 5. O-Methylation of **2b** with methyl iodide in the presence of NaH.

In fact, 1,2-dibromo-1,2-bis(5-*tert*-butyl-2-methoxy-3-methyl-phenyl)ethane **7** as reference compound, was treated with BBr_3 in CH_2Cl_2 under the same conditions as those in *meso*-**3b**, but only the recovery of the starting compound resulted (Scheme 6). When the reaction time was extended to 5 h instead of 0.5 h, resulted the corresponding 2-(2-hydroxy phenyl)benzofuran **9** in 10% yield along with the further cyclisation product, *cis*-4b,9b-dihydrobenzofuro[3,2-b]benzofuran **8** in 80% yield.[35–37] Prolonged the reaction time to 24 h resulted in the exclusive formation of the compound **8**. These results strongly support the reaction mechanism for the formation of the benzofuran skeleton as described above.



Scheme 6. Reaction of **7** with BBr_3 in CH_2Cl_2.

The much faster reaction was observed in *meso*-**3b** than that of **7** under the same reaction conditions for treatment of BBr_3 in CH_2Cl_2 at room temperature. The enhanced reactivity towards the nucleophilic attack of phenolic oxygen in the C_2 carbon may be attributable to the cyclophane structure of *meso*-**5b** in which the reaction site can be sterically much closer than that in compound **7**.



Scheme 7. Possible cyclization of [*n*]benzofuranophanes **2** to form compound **10**.

Second cyclization of **9** to **8** might be attributable to the conformational flexibility of **9** around the diaryl linkage of 2-arylbenzofuran. However, in the case of [*n*]benzofuranophane, formation of compound **10** was not observed by prolonging the reaction time (Scheme 7). The rotation around the diaryl linkage to form conformer **E** might be restricted due to its cyclophane structure containing sterically hindered tertiary butyl group.

5.4.2.5. X-ray Crystallography

Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation for **2a** and **2b**. Data were corrected for Lorentz and polarisation effects and for absorption. The structures were solved by charge flipping or direct methods algorithms and refined by full-matrix least-squares methods, on F^2.

Table 1. Summary of crystal data of **2a** and **2b**.

Complex	**2a**	**2b**
Empirical formula	C_{30} H_{40} O_2	C_{32} H_{44} O_2
Formula weight	432.64	460.67
Crystal system	orthorhombic	monoclinic
Space group	*Pbca*	*C c*
a[Å]	28.1308(5)	14.6104(12)
b[Å]	18.0592(3)	21.5562(19)
c[Å]	9.9558(18)	9.0564(4)
α[º]	90.0000	90.0000

β[°]	90.0000	100.897(4)
γ[°]	90.0000	90.0000
Volume[Å^3]	5057.77(16)	2800.8(4)
Z	8	4
Dcalcd[Mg/m^3]	1.136	1.092
temperature [K]	123	100
unique reflns	4616	2512
obsd reflns	3514	2235
parameters	326	314
R(int)	0.0408	0.0270
R[I> 2σ(I)][a]	0.0628	0.0822
wR_2[all data][b]	0.1691	0.2292
GOF on F^2	1.039	0.963

[a] Conventional R on Fhkl: Σ||Fo| – |Fc||/σ|Fo|. [b] Weighted R on |Fhkl|2: Σ[w(Fo2 – Fc2)2]/Σ[w (Fo2)2]1/2

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 908365 & 908368. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

5.3 Conclusions

We have denoted an expedient preparation procedure of novel [8]benzofuranophane **2a** and [10]benzofuranophane **2b** by treatment of 5,19-di-*tert*-butyl-8,22-dimethoxy[2.8]MCP-1-yne (*syn*-**1a**) and 5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-yne (*syn*-**1b**) with BBr_3 in CH_2Cl_2 at room temperature, respectively by intramolecular cyclization reaction. Enthrallingly, *meso*-**3a**, *dl*-**5a**, *meso*-**3a** and *dl*-**5b** under the same reaction conditions with BBr_3 in CH_2Cl_2 rendered compound **2a** and **2b** in good yield. Further studies on the synthesis, reactions and chemical properties of different [n]benzofuranophanes are now in progress will be reported in due time.

5.4 Experimental Section

5.4.1 General methods

All reagents used were procured from commercial sources and were used without further purification. All the solvents used were dried and distilled by the usual procedures before use. ^{1}H and ^{13}C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and Varian-400MR-vnmrs400 and referenced to 7.26 and 77.0 ppm respectively for chloroform-D solvent with $SiMe_4$ as an internal reference: *J*-values are given in Hz. Infrared (IR) spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by a Yanaco MT-5. All melting points (Yanagimoto MP-S1) are uncorrected. Silica gel columns were prepared by use of Merk silica gel 60 (63-200 μm).

5.4.2 Materials

The starting materials 5,19-di-*tert*-butyl-8,22-dimethoxy[2.8]MCP-1-yne (*syn*-**1a**) and 5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-yne (*syn*-**1b**) were synthesized by dehydrobromination reaction in presence of $HOBu^t$ as published report.[17,30] *anti*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-dimethoxy[2.8]MCP (*dl*- **5a**) and *syn*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-dimethoxy[2.8]MCP (*meso*-**3a**) were prepared according to the literatures.[17,30] 1,2-di-*endo*-bromo-(*meso*-**3b**) and 1-*endo*,2-*exo*-dibromo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP (*dl*-**5b**) were processed according to the reported procedure.[17,30,31]

5.4.2.1. *Synthesis of 5-tert-butyl-1-(5'-tert-butyl-2'-hydroxyphenyl)[8](7,3') benzofuranophane (2a)*

To a solution of 5,19-di-*tert*-butyl-8,22-dimethoxy[2.8]MCP-1-yne (*syn*-**1a**) (60 mg, 0.13 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.14 mL, 1.32 mmol) in CH_2Cl_2 (0.1 mL). After the reaction mixture, has been stirred at room temperature for 8 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The

combined extracts were washed with water (10 mL × 3), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-chloroform (3:1) as eluent to give the crude compound **2a** as a colorless solid. Recrystallization from hexane gave 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[8](7,3*'*)benzofuranophane **2a** (35 mg, 73%) as colorless prisms, M.p. 173–174 °C. IR (KBr): ν = 3427 (OH), 2959, 2856, 1476, 1362, 1203 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17–1.77 (12H, m), 1.31 (9H, s), 1.37 (9H, s), 2.80–2.86 (2H, m), 2.89–2.96 (2H, m), 6.91 (1H, s), 7.11 (1H, d, *J* = 2.4 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 7.18 (1H, s, *J* = 2.4 Hz), 7.22 (1H, d, *J* = 2.4 Hz) and 7.44 (1H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.15, 29.17, 29.70, 29.80, 29.85, 29.93, 30.06, 30.28, 31.51, 31.91, 34.04, 34.77, 102.01, 115.02, 116.00, 122.68, 123.29, 125.70, 127.98, 128.67, 131.77, 142.93, 146.89, 150.78, 151.33 and 155.32 ppm. EI-MS: *m*/*z* 432 [M^+]. $C_{30}H_{40}O_2$ (432.65): calcd. C 83.28, H 9.32. Found: C 83.72, H 8.32.

5.4.2.2. *Synthesis of 5-tert-butyl-1-(5'-tert-butyl-2'-hydroxyphenyl)[10](7,3') benzofuranophane (2b)*

To a solution of 5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-yne (*syn*-**1b**) (60 mg, 0.12 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.12 mL, 1.23 mmol) in CH_2Cl_2 (0.10 mL). After the reaction mixture, has been stirred at room temperature for 0.5 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (10 mL × 2), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-chloroform (2:1) as eluent to give the crude compound **2b** as a colorless solid. Recrystallization from ethanol gave 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[10](7,3*'*)benzofuranophane **2b** (44 mg, 79%) as colorless prisms, M.p. 127–128 °C. IR (KBr): ν = 3529, 3514 (OH), 2955, 2933, 2857, 1481, 1459, 1365, 1261, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.48 (12H, m), 1.33 (9H, s), 1.38 (9H, s), 1.68–1.74 (2H, m), 1.78–1.88 (2H, m), 2.74–2.77 (2H, m), 2.84–2.89 (2H, m), 6.91 (1H, s), 7.14 (1H, d, *J* = 2.4 Hz), 7.16 (1H, d, *J* = 2.4 Hz), 7.34 (1H, d, *J* = 2.4 Hz), 7.44 (1H, d, *J* = 2.4 Hz) and 7.67 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.61, 27.57, 27.95, 28.52, 28.77,

28.96, 29.16, 29.32, 29.90, 31.26, 31.51, 31.89, 34.06, 34.74, 102.54, 114.87, 115.04, 121.75, 122.91, 125.57, 127.95, 129.09, 130.99, 142.78, 146.89, 150.10, 151.15 and 155.72 ppm. EI-MS: *m*/*z* 460 [M^+]. $C_{32}H_{44}O_2$ (460.70): calcd. C 83.43, H 9.63. Found: C 83.36, H 9.63.

5.4.2.3. *Synthesis of 5-tert-butyl-1-(5'-tert-butyl-2'-hydroxyphenyl)[8](7,3') benzofuranophane (2a)*

To a solution of *syn*-15,16-di-*endo*-bromo-11,19-di-*tert*-butyl-14,22-dimethoxy[2.8] MCP (*meso*-**3a**) (80 mg, 0.13 mmol) in CH_2Cl_2 (8 mL) at 0 °C was gradually added a solution of BBr_3 (0.12 mL, 1.29 mmol) in CH_2Cl_2 (0.2 mL). After the reaction mixture, has been stirred at room temperature for 8 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (10 mL × 3), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-chloroform (3:1) as eluent to give crude compound **2a** as a colorless solid. Recrystallization from hexane gave 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[10](7,3*'*)benzofuranophane **2a** (35 mg, 73%) as colorless prisms.

Similarly, compound *dl*-**5a** was treated with BBr_3 in CH_2Cl_2 at room temperature for 8 h to afford **2a** in 73% yield as colourless prisms.

5.4.2.4. *Synthesis of 5-tert-butyl-1-(5'-tert-butyl-2'-hydroxyphenyl)[10](7,3') benzofuranophane (2b)*

To a solution of 1,2-di-*endo*-bromo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP (*meso*-**3b**) (60 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.09 mL, 0.92 mmol) in CH_2Cl_2 (0.1 mL). After the reaction mixture, has been stirred at room temperature for 0.5 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (10 mL × 2), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-chloroform (4:1) as eluent to give crude compound **2b** as a colorless solid. Recrystallization from ethanol gave 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[10](7,3*'*)benzofuranophane **2b** (35 mg, 83%) as colorless prisms.

Similarly, compound 1-*endo*,2-*exo*-dibromo-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10] MCP (*dl*-**5b**) was treated with BBr_3 in CH_2Cl_2 at room temperature for 0.5 h to afford **2b** in 87% yield as colorless prisms.

5.4.2.5 *Synthesis of 5-tert-butyl-1-(5'-tert-butyl-2'-methoxyphenyl)[10](7,3') benzofuranophane (6b)*

A mixture of 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-hydroxyphenyl)[10](7,3*'*)benzofuranophane **2b** (40 mg, 0.09 mmol) and NaH (29 mg, 1.22 mmol, 60%) in dry tetrahydrofuran (4 mL) was heated at reflux for 1 h under N_2. Then methyl iodide (0.05 mL, 0.87 mmol) was added and the mixture heated at reflux for an additional 3 h. After cooling the reaction mixture to room temperature, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (10 mL × 2), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane as eluent to give 5-*tert*-butyl-1-(5*'*-*tert*-butyl-2*'*-methoxyphenyl)[10](7,3*'*)benzofuranophane **6b** (26 mg, 64%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18–1.39 (12H, m), 1.33 (9H, s), 1.39 (9H, s), 1.44–1.60 (2H, m), 1.68-1.85 (2H, m), 2.01–2.17 (1H, m), 2.37–2.49 (1H, m), 2.67–2.83 (1H, m), 2.86–3.07 (1H, m), 3.42 (3H, s), 6.82 (1H, s), 7.12 (1H, d, *J* = 2.4 Hz), 7.20 (1H, d, *J* = 2.4 Hz), 7.31 (1H, d, *J* = 2.4 Hz) and 7.44 (1H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.68, 27.25, 27.88, 28.05, 28.10, 28.71, 28.84, 29.20, 30.74, 31.47, 31.79, 31.95, 34.24, 34.67, 59.67, 103.02, 114.39, 122.19, 122.81, 125.23, 126.25, 128.15, 128.45, 135.86, 145.62, 145.80, 152.35, 154.97 and 155.71 ppm. EI-MS: *m*/*z* 474 [M^+]. $C_{33}H_{46}O_2$ (474.72): calcd. C 83.49, H 9.77. Found: C 83.37, H 9.61.

5.4.2.6 *Synthesis of 3,8-di-tert-butyl-1,6-dimethyl-cis-4b,9b-dihydrobenzofuro[3,2-b] benzofuran (8)*

To a solution of (*E*)-1,2-bis(5-*tert*-butyl-2-methoxy-3-methylphenyl)ethane **7** (60 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.09 mL, 0.92 mmol) in CH_2Cl_2 (0.1 mL). After the reaction mixture, has been stirred at room temperature for 5 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (10 mL × 3), dried over $MgSO_4$ and then

concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-$CHCl_3$ (4:1) as eluent to give crude **8** (80%) as a colourless solid. 3,8-di-*tert*-butyl-1,6-dimethyl-*cis*-4b,9b-dihydrobenzofuro[3,2-b] benzofuran **8** was obtained as colourless prisms (hexane), M.p. 184–185 °C. IR (KBr): ν = 2944, 1616, 1487, 1362, 1181 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (18H, s), 2.21 (6H, s), 6.23 (2H, s), 7.12 (1H, d, *J* = 2.4 Hz) and 7.40 (1H, d, *J* = 2.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.67, 31.73, 34.32, 87.13, 119.96, 120.44, 123.64, 129.54, 144.10 and 156.55 ppm. EI-MS: *m*/*z* 350 [M^+]. $C_{24}H_{30}O_2$ (350.51): calcd. C 82.24, H 8.63. Found: C 82.03, H 8.63.

5.4.2.7 *Synthesis of 2-(5-tert-butyl-7-methylbenzofuran-2-yl)-4-tert-butyl-6-methylphenol (9)*

To a solution of (*E*)-1,2-bis(5-*tert*-butyl-2-methoxy-3-methylphenyl)ethane **7** (60 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.09 mL, 0.92 mmol) in CH_2Cl_2 (0.1 mL). After the reaction mixture, has been stirred at room temperature for 5 h, it was poured into ice-water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (2 × 10 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane-$CHCl_3$ (1:4) as eluent to give crude **9** (10%) as a colorless solid. 2-(5-*tert*-butyl-7-methylbenzofuran-2-yl)-4-*tert*-butyl-6-methylphenol **9** was obtained as colorless prisms (hexane), M.p. 143–145 °C. IR (KBr): ν = 3425 (OH), 2956, 2853, 1452, 1280 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (9H, s), 1.38 (9H, s), 2.21 (3H, s), 2.55 (3H, s), 6.98 (1H, s), 7.12 (1H, d, *J* = 2.4 Hz), 7.16 (1H, d, *J* = 2.4 Hz), 7.43 (1H, d, *J* = 2.4 Hz), 7.46 (1H, d, *J* = 2.4 Hz) and 7.79 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.37, 14.89, 15.41, 28.68, 30.79, 33.50, 101.98, 113.64, 118.93, 119.21, 120.03, 122.36, 124.50, 126.91, 128.51, 141.80, 142.82, 145.75, 148.69 and 155.58 ppm. EI-MS: *m*/*z* 352 [M^+]. $C_{29}H_{32}O_2$ (352.52): calcd. C 81.77, H 9.15. Found: C 81.73, H 9.16.

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Summary

Cyclophanes are well-studied in organic chemistry because they adopt unusual chemical conformations due to build-up of strain. Ever since the cyclophane chemistry has been developed continuously especially due to the various important applications which they present in divers domains such as host molecules for different cations or small neutral molecules, chiral ligand or industrial applications. The ability to place certain groups (i.e. two aromatic systems) within proximity of each other often results in interesting geometries and chemical properties. They are fundamentally interesting compounds, which exhibit interesting properties which make them particularly useful for industrially purposes. Being typically rigid structures they found use in material science, surface chemistry, polymer chemistry and having a potential useful application for different catalysis and medical purposes. The chemical behavior of the molecular bridges in cyclophanes has not been studied to the same extent as the reactivity of the aromatic subunits.

Starting from chapter 1, a brief introduction of metacyclophane with the different types of synthetic routes with their interesting properties were discussed. Some examples for chiral metacyclophane assign the structure both in solid and liquid state also described in details. In this thesis, we mainly focus on the synthesis and crystal structures of 1,2-dimethyl[2.*n*] metacyclophan-1-enes which exhibited different properties due to different substituted groups.

In chapter 2, A series of 1,2-dimethyl[2.10]metacyclophan-1-enes (MCP-1-enes) containing different substituent groups has been synthesized to illustrate there conformational behavior. 4,22-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene **3** was synthesized by a Grignard coupling reaction, Friedel-Crafts acylation reactions and McMurry coupling reaction from 1,10-dibromodecane. The formation of 4,22-dihydroxy-1,2-dimethyl[2.10] MCP-1-ene **4** was carried out by demethylation of compound **3** with boron tribromide and the *syn* type conformation of **4** was characterized by X-ray diffraction, and was found to form both intramolecular and intermolecular hydrogen bonds between the two hydroxyl groups. From this reaction an interesting compound [10]tetrahydrobenzo-furanophane **5** was afforded on prolonging the reaction time. 5,21-diformyl-4,22-dihydroxy-1,2-dimethyl [2.10]MCP-1-ene **6** has been prepared from compound **4** by using the Duff method in the

presence of hexamethylenetetramine. Structural analysis by ^{1}H NMR spectroscopy and X-ray diffraction confirmed that both the solution and the crystalline state of compound **6** adopts an *anti*-conformation which forms an intramolecular hydrogen bond between the formyl group and the hydroxyl group, which is an interesting finding for long carbon chain MCP compounds.

Following this results, in chapter 3, Bromination of 5,21-di-tert-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene (MCP-1-ene; **1** with benzyltrimethylammonium tribromide exclusively afforded 1,2-bis(bromomethyl)-5,21-di-tert-butyl-8,24-dimethoxy [2.10]MCP-1-ene **2**. Debromination of **2** with Zn and AcOH in CH_2Cl_2 solution produced dimethylene[2.10]MCP **7** which was treated with DMAD to provide 1,2-(3′,6′-dihydrobenzo)-5,21-di-tert-butyl-8,24-dimethoxy[2.10] MCP-4′,5′-dimethylcarboxylate **8** in good yield. Diels–Alder adduct **8** was converted into a novel and inherently chiral areno-bridged dimethoxy[2.10]MCP-4′,5′-dimethylcarboxylate **9**, possessing *C1* symmetry, by aromatization with DDQ. A new type of *N*-phenyl-maleimide substituted 1,2-(3′,6′-dihydrobenzo)-5,21-di-tert-butyl-8,24-dimethoxy[2.10]MCP-4′,5′-*N*phenylmaleimide **10** was also synthesized from **7** through treatment with *N*-phenylmaleimide in toluene followed by aromatization with DDQ. Single-crystal X-ray analysis of **9** revealed the formation of a *syn*-isomer.

In continuation with the same interest, in chapter 4, A series of *syn*- and *anti*-[2.*n*]metacyclophan-1-enes have been prepared in good yields by McMurry cyclizations of 1,*n*-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)alkanes. Significantly, acid catalyzed rearrangements of [2.*n*]metacyclophan-1-enes afforded [*n*.1]metacyclophanes in good yield. The ratios of the products are strongly regulated by the number of methylene bridges present. The percentages of the rearrangement products increase with increasing length of the carbon bridges. Characterization and the conformational studies of these products are described. Single crystal X-ray analysis revealed the adoption of *syn*- and *anti*-conformations. The results from DFT calculations were consistent with the observed experimental results.

In chapter 5, Novel [*n*]benzofuranophanes (n = 8 & 10) have been prepared by successive intramolecular cyclization from 5,19-di-tert-butyl-8,22-dimethoxy[*n*] metacyclophane-1-yne (*syn*) by treatment with BBr_3 in CH_2Cl_2. [2.*n*]Benzofuranophanes were also obtained by treatment of 1,2-di-endo-bromo-5,19-di-*tert*-butyl-8,22-dimethoxy [*n*]metacyclophane

(*meso*) with BBr_3 in CH_2Cl_2 by using the same reaction conditions. ^1H NMR spectra of [*n*]benzofuranophanes reveals the formation of intramolecular hydrogen bonding between hydroxyl proton with the oxygen of the furan moiety and X-ray analysis shows that the lengths between H (OH) and O (furan) are 1.981 and 1.823 Å, respectively. The conformation of [8]benzofuranophane in solution is rigid with restricted rotation around the diaryl linkage rather than [10]benzofuranophane because of weak intramolecular hydrogen bonding and the short length of the cross-linking chain.

In summary, several kinds of [2.*n*]metacyclophan-1-enes were designed and synthesized varied with the many types of substituted groups. We presume that the present strategy and the remarkable chiral properties of these [2.*n*]metacyclophan-1-enes will help us to extend the potential applications of cyclophanes.

Publications

1. Demethylation of 5,*n*-di-*tert*-butyl-8,*n*-dimethoxy[2.*n*]metacyclophane-1-ynes with BBr_3 to afford novel [*n*]benzofuranophanes
   T. Akther, M. M. Islam, T. Matsumoto, J. Tanaka, X. Feng, C. Redshaw and T. Yamato
   Journal of Molecular Structur., **2016**, 1122, 247–255.

2. Synthesis, structural properties, electrophilic substitution reactions and DFT computational studies of 1,2-dimethyl[2.10]metacyclophane-1-enes
   T. Akther, M. M. Islam, S. Rahman, P. E. Georghiou, T. Matsumoto, J. Tanaka, P. Thuéry, C. Redshaw and T. Yamato
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3. Synthesis and Structure of 1,2-Dimethylene[2.10]metacyclophane and Its Conversion to Chiral [10]Benzenometacyclophanes
   T. Akther, M. M. Islam, T. Matsumoto, J. Tanaka, P. Thuéry, C. Redshaw and T. Yamato
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4. Synthesis and conformations of [2.*n*]metacyclophan-1-ene epoxides and their conversion to [*n*.1]metacyclophanes
   T. Akther, M. M. Islam, S. Rahman, P. E. Georghiou, T. Matsumoto, J. Tanaka, C. Redshaw and T. Yamato
   Org. Biomol. Chem., 2017, **15**, 3519–3527.