Graphical Abstract

Synthesis and structure of a chiral areno-bridged [2.4]metacyclophane

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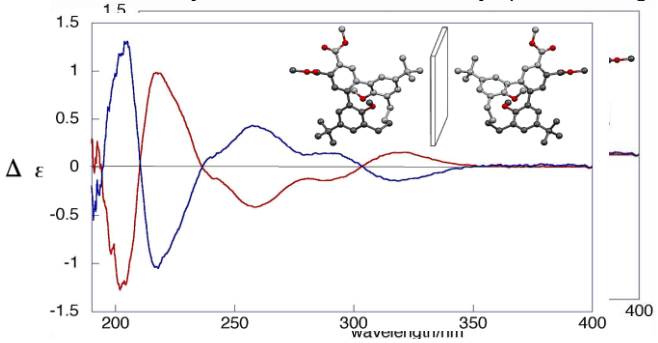


Synthesis and structure of a chiral areno-bridged [2.4]metacyclophane

Thamina Akther[a], Md. Monarul Islam[a,b], Taisuke Matsumoto[c], Junji Tanaka[c], Pierre Thuéry[d], Carl Redshaw[e] and Takehiko Yamato [a, *]

ABSTRACT

The reductive coupling reaction of 1,4-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)butane **3** was carried out using $TiCl_4$-Zn in pyridine followed by a McMurry coupling reaction to afford the compounds *anti* and *syn* 1,2-dimethyl[2.4]MCP-1-ene **4**. Bromination of **4** with BTMA-Br_3 in dry CH_2Cl_2 afforded the interesting compound 1,2-bis-(bromomethyl)-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-1-ene **6** and consecutive debromination with Zn and AcOH in CH_2Cl_2 solution afforded the stable solid 5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethylene[2.4]MCP **7** in 89% yield. Compound **7** was conveniently employed in a Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to provide 2-(3',6'-dihydrobenzo)-5,15-di-*tert*-butyl-8,18-dimethoxy [2.4]MCP-4',5'-dimethylcarboxylate **8** in good yield. Diels–Alder adduct **8** was converted into a novel and inherently chiral areno-bridged compound [2.4]MCP **9** by aromatization. The characterization and the reaction pathways to these products are discussed in detail.

1. Introduction

Cyclophanes, cyclic molecules containing both aromatic and aliphatic regions, are a class of compound that are captivating the imagination of chemists.[1] Metacyclophanes (= MCP) have been known for approximately 45 years and various derivatives have been prepared and found to exhibit unique properties.[2] The cyclophanes with shorter carbon chains (n = 4–6) have captivated the inspiration of chemists as exemplary compounds for the molecular strain and bending of benzene rings.[3] Synthetic and conformational analysis of this type of macrocyclic compounds was recently reported, with some researchers focusing on the formation of rigid structures by restricting the flexible conformations, thereby enabling these systems to act as platforms for diverse complexation experiments.[4] Our interest in this field stems from observations on cyclic diynes having two double bonds as a part of the aromatic ring system.[5]

Ramming and Gleiter reported the syntheses of [*n*]MCP-diynes and the conversion of propargylic into allenic moieties as well as reactions with strong bases.[6] The bromination–dehydrobromination reactions of the corresponding [2.*n*]MCP- enes to strained [2.*n*]MCP-ynes possessing bent triple bonds was reported by Kawase and co-workers.[7]

For over three decades, the McMurry reaction and other Ti based reductive couplings have been effectively applied to the synthesis of cyclophanes. A one-step route to alkene-containing cyclophanes is provided by the McMurry reaction which also allows for the generation of moderately strained cyclophanes.[8–12]

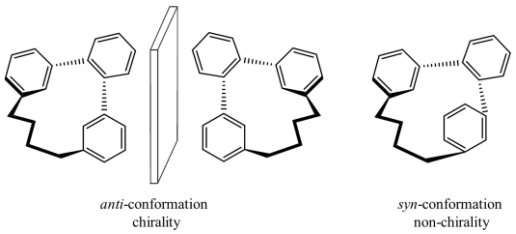


Fig. 1. Possible conformations of areno-bridged [2.4]MCPs.

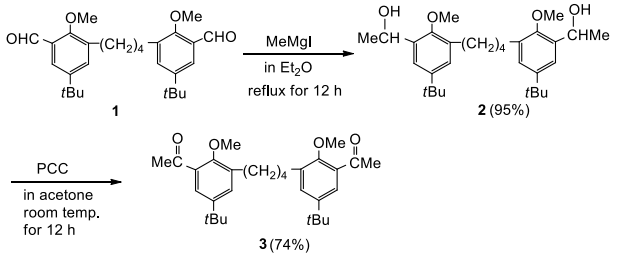
Our research group has published a series of [2.*n*]MCPs utilizing McMurry coupling reactions, in which the aliphatic chain length ranged from 2 to 10.[13] Reports on the synthesis of chiral [2.*n*]MCPs which contain long carbon chains have

Very recently, we reported the synthesis and a conformational study of the areno-bridged [2.10]MCP together with its chiral yet to be published. Helical chirality is one type of chiral system that does not contain any stereogenic centers. [14–17]

properties, but we have not yet succeeded in the resolution of each enantiomer, which we think is due to the flexible structure.[13f] In this paper, conformational studies of a number of shorter methylene bridged [2.4]MCPs which can adopt *anti*- and *syn*-conformations (as represented in Fig. 1), both in solution and the solid state, are described. We also report the first successful synthesis and resolution of each enantiomer of the novel chiral [2.4]MCP containing an areno-bridge and a brief discussion about the inherently chiral properties.

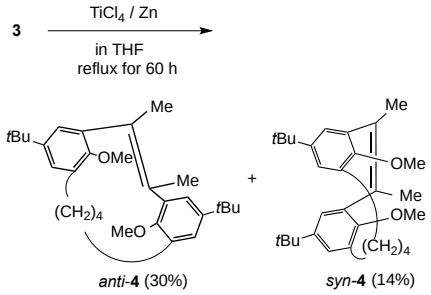
2. Results and discussion

The starting compound 1,4-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)butane **1** was easily prepared from 1,4-bis(5-*tert*-butyl-2-methoxyphenyl)butane according to our previously reported synthetic procedure.[13,18,19] 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 **1** in 68% yield. To a solution of methylmagnesium iodide in Et_2O was added dropwise a solution of compound **1** 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 **2** in 95% yield.



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

Oxidation[22] of compound **2** 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 **3** was isolated in 74% yield as shown in Scheme 1.[23–29] Elemental analysis and spectral data were used to resolve the structures of compounds **2** and **3**. Furthermore, the ^{1}H NMR spectroscopic signals of **2** and **3** were also unambiguously assigned.



Scheme 2 Synthesis of *anti*- and *syn*-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]MCP-1-ene **4**.

Compound **3** was further subjected to reductive coupling by following the McMurry reaction through the upgraded Grützmacher's procedure (Scheme 2).[30] 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*-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4]MCP-1-ene **4** in 30 and 14% yields, respectively. This result was different from that of the related McMurry cyclization of 1,3-bis(5-acetyl-2-methoxyphenyl)propane **3**, which provided the identical [3.1]MCP when using $TiCl_4$ or an acid induced pinacol rearrangement reaction.[31]

The structure of **4** was elucidated based on elemental analyses and spectral data. The mass spectral data for **4** (M^+ = 434.65) fully support the cyclic structure. The conformation of **4** was clear from the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of *anti*-**4** 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*-**4** is observed at higher field, *viz* δ 1.11 ppm, due to the shielding effect of the aromatic ring. The aromatic protons of *syn*-**4** are reported at much higher field (δ 6.41 and 6.52 ppm) than those of the compound *anti*-**4**. These data confirm the assigned *anti*- and *syn*-structures for both the conformers of **4**.

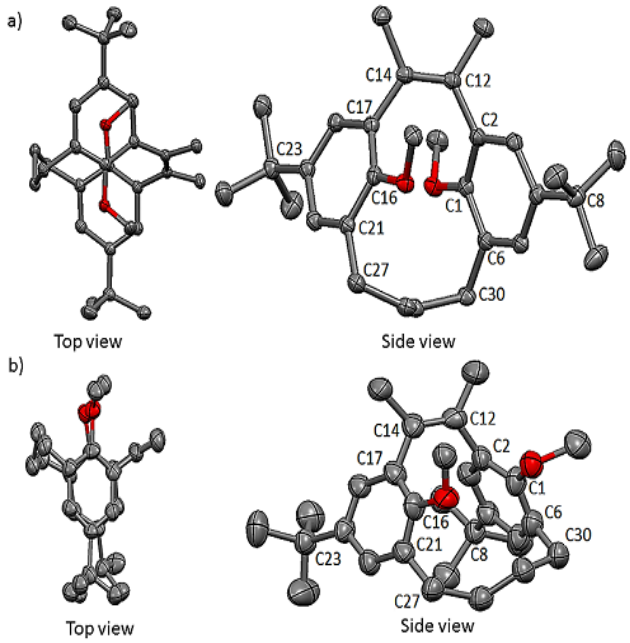
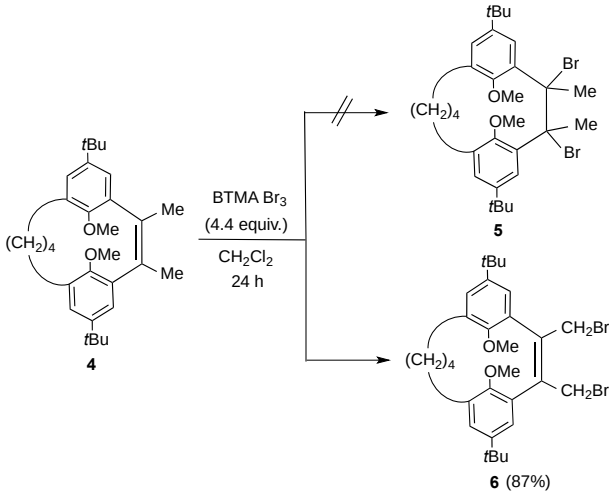


Fig. 2. Single-crystal structures of a) *anti*-[2.4]MCP-1-ene *anti*-**4** and b) *syn*-[2.4]MCP-1-ene *syn*-**4** (side view and top view). Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The X-ray structure of *anti*-**4** (CCDC 1542177) in Fig. 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 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 similar to that 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.

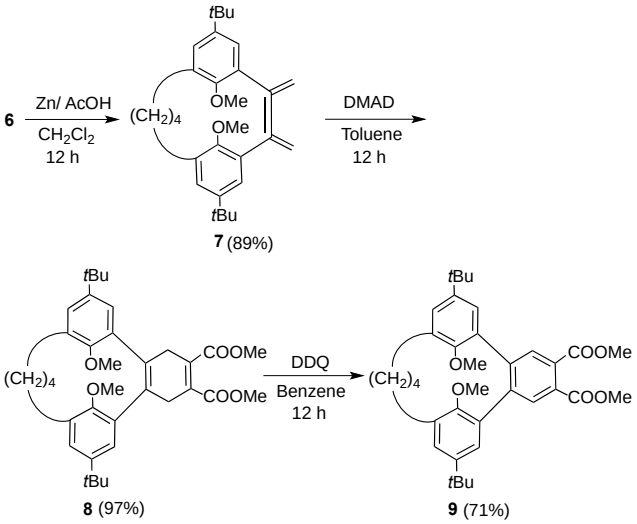
The X-ray structure (CCDC 1541642) of *syn*-**4** (Figure 2) clearly demonstrates that **4** exists as the *syn*-conformer in the solid state and that the two methoxy groups lie on the correlative side of the 18–membered inner ring, which contains the long bridging C27–C30 chain pointing toward the outer 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 to that of ethylene. The bond angles defined by C12–C14–C17 and C2–C13–C14 are 118.3(2)° and 119.2(2)°, and reveal that compound **4** displays a non–distorted conformation. The two benzene rings of *syn*-**4** 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.



Scheme 3 Synthesis of bis(bromomethyl)-5,15-di-*tert*-butyl-8,18-dimethoxy-1,2- [2.4]MCP-1-ene **6**.

Bromination of **4** with 4.4 equiv. of benzyltrimethylammonium tribromide (BTMA-Br_3)[29] in CH_2Cl_2 solution at room temperature for 24 h afforded the corresponding 1,2-bis(bromomethyl)-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]-MCP-1-ene **6** in 87% yield (Scheme 3). No bromination product **5** at the alkene bridge (double bond) was observed under the reaction conditions used. This result is quite different from the bromination of the corresponding [2.4]MCP-1-ene which afforded the *cis*–addition product (to the bridging double bond).[29] When **4** was treated with 1.2 equiv. BTMA-Br_3 at room temperature for 24 h, **6** was formed in 30% yield with 70% recovery of **4**. In the case of 2.4 equiv. BTMA-Br_3, the yield of **6** increased to 70 % yield. These results strongly suggest that the present transformation probably occurred by addition of bromine to the bridged double bond of **4** followed by a two-fold dehydrobromination to give the corresponding 1,2-dimethylene[2.4]MCP **7**, from which 1,4-bromine addition occurred to afford 1,2-bis(bromomethyl)[2.4]-MCP-1-ene **6** .[30–31]

The structure of product **6** was proposed on the basis of elemental analyses and spectral data. The mass spectral data for diene **6** (M^+ = 676, 678 and 680) strongly supports a dibrominated structure. The ^{1}H NMR spectrum of compound **6** exhibited a singlet for the methoxy protons at δ 3.30 ppm as well as the resonances at δ 6.85 and 7.42 ppm (J = 2.6 Hz) 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.



Scheme 4 Synthesis of 1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy-[2.4]MCP-4',5'-dimethylcarboxylate **9**.

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 the presence of a strong basic alcoholic solvent. Interestingly, treatment of **6** 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 **7** in 75% yield (Scheme 4). This type of modified reaction has been widely utilized to eliminate the bromine group to form a double bond.

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 **7** 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 **7** 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 **7**. The Diels–Alder reaction of **7** with DMAD was completed within 12 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. 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 [2.4]MCP **9** by aromatization with dichlorodicyano-*p*-benzoquinone (DDQ).

The structure of product **9** 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 **9** (M^+ = 657). The 300 MHz ^{1}H NMR spectrum of **9** 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 ppm (J = 2.4 Hz) for the two aromatic protons. Based on the spectral data and the chemical conversion, compound **9** 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*-**9**.

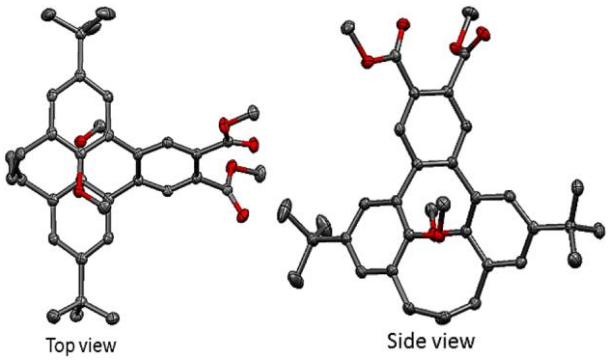


Fig. 3. Drawing of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy [2.4]MCP-4',5'-dimethylcarboxylate *anti*-**9**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

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*-**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.

Compound *anti*-**9** was crystallized by the slow, room temperature evaporation of a dichloromethane solution, and was found to possess the space group *P-1*. Interestingly, the X-ray analysis disclosed that the areno-bridged [2.4]MCP *anti*-**9** adopts helical chirality, yet surprisingly, the dihedral angle of the arylenes connected by the phenyl unit is 33.98°.

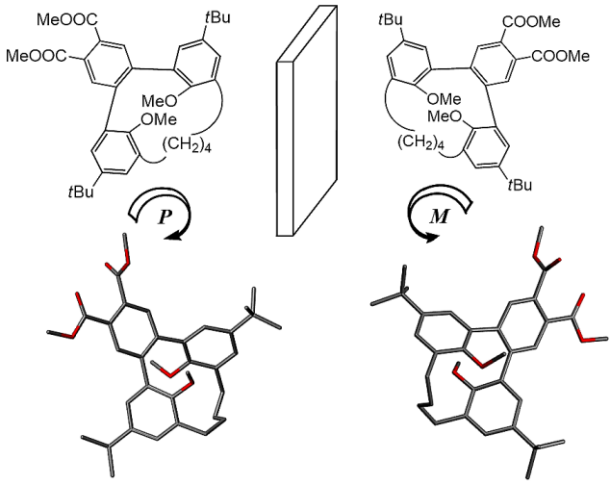


Fig. 4. Schematic diagram of *M*-**9** (left side) and *P*-**9** (right side).

Therefore, the compound is chiral and the *M*- and *P*-isomers are packed alternatively in the crystal as depicted schematically in Figure 5 (CCDC 908369).

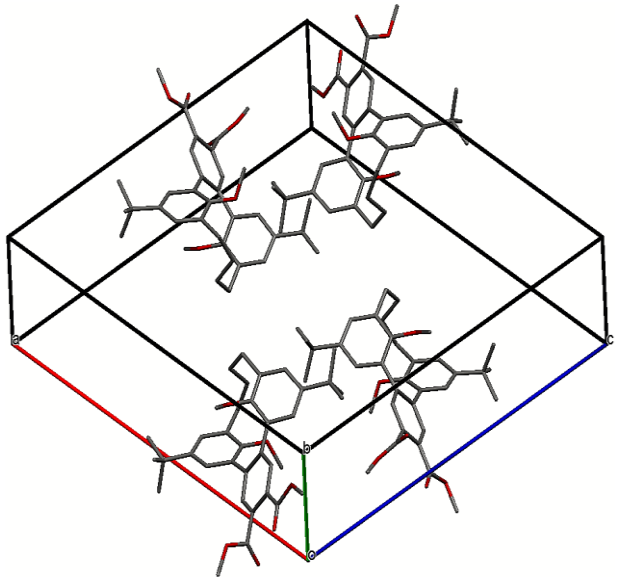


Fig. 5. Packing drawing of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**9**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The chiral properties of the compound *anti*-**9** in solution were investigated by chromatographic resolution using a chiral column. Interestingly, *anti*-**9** 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*-**9** could be accomplished by chromatographic separation using a chiral column. In fact, we have succeeded in resolving each *P*- and *M*-enantiomer. The circular dichroism (CD) spectra of the separated enantiomer with precise mirror images are shown in Figure 6.

From Figure 6, 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.

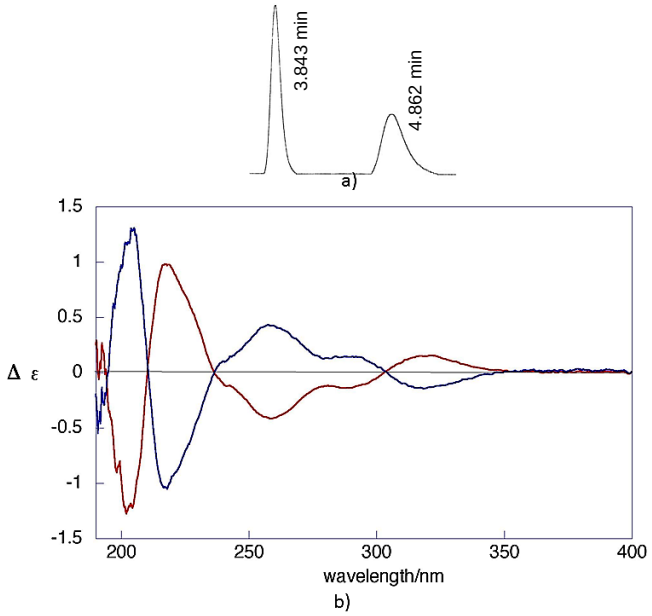


Fig. 6. (a) Chromatogram of *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**9** (HPLC on chiral column). Daicel chiralpak ADeH. Eluent: hexanes. (b) CD spectra of *P*- and *M*-enantiomers of inherently chiral *anti*-1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-4',5'-dimethylcarboxylate *anti*-**9**.

First, one enantiomer which was optically resolved with a chiral column was left in solution (ambient temperature) for 3 weeks, and during this period, no peak for the after-distillate was observed. 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. It was left for 1 day to investigate whether racemization occurred (SI Figure 21). 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*-**9** was dissolved in CH_2Cl_2 and the specific rotation measurement was carried out. The specific rotation of compound *anti*-**9** was $[\alpha]_D$ = + 72 (faster-moving enantiomer on Daicel Chiralpac AD-H with 1 v/v % ethanol in hexane as the eluent) at 240 nm. The specific expected rotation was small because compound *anti*-**9** had a carbon crosslinking chain length of 4, and so it was a flexible compound.

3. Conclusions

In summary, a straightforward and effective method for the synthesis of areno-bridged [2.4]MCP *anti*-**9** by successive Diels–Alder reactions from 1,2-dimethylene[2.4]MCP **7**, together with its chiral conformation is described herein. The conformational behaviour and chirality of [2.4]MCPs were studied both in solution and in the solid state. The racemate of each areno-bridged [2.4]MCP can be readily separated by chiral HPLC to give the enantiomeric pure structure of which absolute configurations have been confirmed by CD spectroscopy. Further mechanistic details of the shorter chain containing [2.*n*]MCP derivatives are currently being investigated and will be reported on in due course.

4. Experimental section

MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. 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 Yanaco MT-5. UV-vis spectra were recorded on a Perkin Elmer Lambda 19 UV/VIS/NIR spectrometer. 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}.

Materials

Unless otherwise stated, all other reagents used were purchased from commercial sources and were used without further purification. The preparation of 1,4-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)butane **1** was described previously.[17–19]

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

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 **1** (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 (3 × 100 mL). The extract was washed with water (2 × 100 mL), 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 **2** (9.35 g, 95%) as colourless prisms. m.p. 110–112 °C. IR: ν_{max} (KBr) 3328, 2965, 2857, 2827, 2359, 2344, 1481, 1463, 1363 and 1294 cm^{-1}. δ_H ($CDCl_3$) 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, m), 7.13 (2H, d, *J* = 2.6 Hz) and 7.28 (2H, d, *J* = 2.6 Hz). δ_C ($CDCl_3$) 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. MS (EI): *m/z*: 471 [M^+]. $C_{30}H_{46}O_4$ (470.68): Anal. Calcd for C 76.55, H 9.85; Found C 76.23, H 9.90.

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

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 **2** (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 **3** (8.06 g, 74%) as colourless prisms (MeOH). m.p. 112–113 °C. IR: ν_{max} (KBr) 2966, 1671, 1572, 1469, 1458, 1222, 1004 and 890 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. FABMS: *m/z*: 467.6131 [M^+]. $C_{30}H_{42}O_4$ (467.6690): Anal. Calcd for C 77.21, H 9.07; Found C 76.95, H 9.16.

*4.3. McMurry coupling reaction of (**3**)*

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 **3** (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 (3 × 200 mL). 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*-**4** and *syn*-**4** as a colourless solid. Each eluents were recrystallized from hexane to afford *anti*-**4** (1.07 g, 30%) and *syn*-**4** (0.82 g, 21%), respectively.

anti-5,15-Di-*tert*-butyl-8,18-dimethoxy-1,2-dimethyl[2.4] metacyclophan-1-ene (*anti*-**4**) was obtained in 45% yield as colourless prisms (MeOH). m.p. 174–175 °C. IR: ν_{max} (KBr) 2966, 1476, 1450, 1229, 1019 and 875 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. FABMS: *m/z*: 434.6185 [M^+]. $C_{30}H_{42}O_2$ (434.6533): Anal. Calcd for 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*-**4**) was obtained in 21% yield as colourless prisms (hexane). m.p. 174–175 °C. IR: ν_{max} (KBr) 2952, 1454, 1472, 1362, 1218, 1015 and 868 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. FABMS: *m/z*: 434.32 [M^+]. $C_{30}H_{42}O_2$ (434.65): Anal. Calcd for C 82.90, H 9.74; Found C 82.68, H 9.70.

*4.4. Bromination of anti-**4** with BTMA–Br_3 in CH_2Cl_2*

To a solution of *anti*-**4** (185 mg, 0.44 mmol) in CH_2Cl_2 (24 mL) was added BTMA-Br_3 (750 mg, 2.0 mmol, 4.4 equiv.) 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 (3 × 10 mL). 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*-**6** (227 mg, 87%) as colourless prisms (hexane). m.p. 148–149 °C. IR: ν_{max} (KBr) 2966, 2900, 2856, 1649, 1553, 1476, 1454, 1354, 1262, 1203, 1170, 1107, 1019, 923, 879, 857, 805, 639, 573 and 529 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. MS (EI): *m/z* found 590, 592, 594 [M^+]. $C_{30}H_{40}Br_2O_2$ (592.45): Anal. Calcd for C 60.82, H 6.81; Found C 60.91, H 6.73.

*4.5. Debromination of **6** with zinc powder*

To a solution of *anti*-**6** (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 (3 × 10 mL). 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*-**7**) (57 mg, 89%) as colourless prisms (hexane). m.p. 148–149 °C. IR: ν_{max} (KBr) 2966, 2900, 2856, 1649, 1553, 1476, 1454, 1354, 1262, 1203, 1170, 1107, 1019, 923, 879, 857, 805, 639, 573 and 529 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. FABMS: *m/z*: 432.6028 [M^+]. $C_{30}H_{40}O_2$ (432.6374): Anal. Calcd for C 83.21, H 9.15; Found C 83.36, H 9.21.

*4.6. Deals-Alder Reaction of **7** with dimethyl acetylenedicarboxylate*

A solution of compound *anti*-**7** (70 mg, 0.17 mmol) and dimethyl acetylenedicarboxylate (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 5,15-di-*tert*-butyl-1,2-(3',6'-dihydrobenzo)-8,18-dimethoxy[2.4]metacyclophane-4',5'-dimethylcarboxylate *anti*-**8** (95 mg, 97%) as a pale yellow oil. δ_H ($CDCl_3$) 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). MS (EI): *m/z* 574 [M^+]. $C_{36}H_{46}O_6$ (574.75): Anal. Calcd for C 83.21, H 9.15; Found C 83.36, H 9.21.

*4.7. Oxidation of **8** with DDQ*

A solution of *anti*-**8** (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 colourless solid. Recrystallization from methanol afforded 1,2-dibenzo-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]metacyclophane-4',5'-dimethylcarboxylate *anti*-**9** (37.4 mg, 71%) as colourless prisms (MeOH). m.p. 205–207 °C. IR: ν_{max} (KBr) 2856, 1730 (C=O), 1477, 1219 and 1019 cm^{-1}. δ_H ($CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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. EI (MS): *m/z* 572 [M^+]. $C_{36}H_{44}O_6$ (572.73): Anal. Calcd for C 75.50, H 7.74; Found C 75.71, H 7.69.

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Supplementary data

Electronic Supplementary Information (ESI) available: Details of single-crystal X-ray crystallographic data for compounds *anti*-**4**, *syn*-**4** and **9**; ^{1}H, ^{13}C NMR for compounds **2**–**9**. For ESI and other electronic format see DOI: 10.1039/x0xx00000x

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