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

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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 chirality of the two conformers was characterized by circular dichroism (CD) spectra of the separated enantiomer which are perfect mirror images of each other.



## 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 75 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 compound 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]

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 yet to be published. Helical chirality is one type of chiral system that does not contain any stereogenic centers.[14–17]

Very recently, we reported the synthesis and a conformational study of the areno-bridged [2.10]MCP together with its chiral 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*-

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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 its inherent chirality.

## 2. Results and discussion

The starting compound 1,4-bis(5-*tert*-butyl-3-formyl-2-methoxy- phenyl)butane **1** was easily prepared from 1,4-bis(5-*tert*-butyl-2-methoxyphenyl)butane according to the reported 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.

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.[23,24] Elemental analysis and spectral data were used to resolve the structures of compounds **2** and **3**. Furthermore, the $^1H$ NMR spectroscopic signals of **2** and **3** were also unambiguously assigned.

Compound **3** was further subjected to reductive coupling by following the McMurry reaction through the upgraded Grützmacher's procedure (Scheme 2).[12] 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.[25]

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 $^1H$ NMR spectrum. The $^1H$ NMR spectrum of *anti*-**4** in $CDCl_3$ exhibits a singlet at $\delta$ 3.24 ppm for the methoxy protons, a singlet at $\delta$ 1.32 ppm for the *tert*-butyl protons and a pair of doublets at $\delta$ 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 easily evaluated from the chemical shift of the methoxy protons at $\delta$ 3.68 ppm. Here, the *tert*-butyl proton of *syn*-**4** is observed at higher field, *viz* $\delta$ 1.11 ppm, due to the shielding effect of the aromatic ring. The aromatic protons of *syn*-**4** are reported at much higher field ($\delta$ 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**.

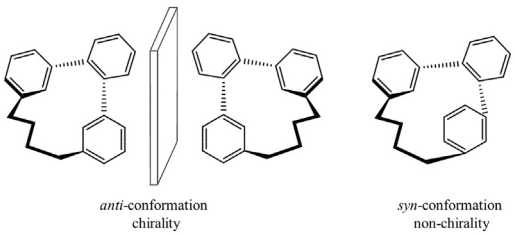
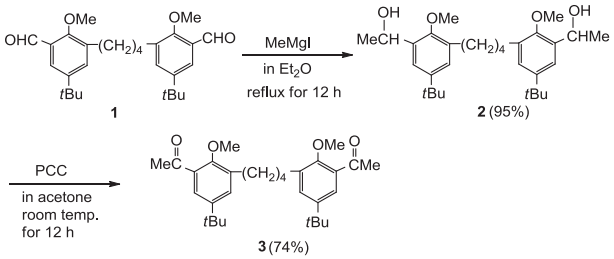
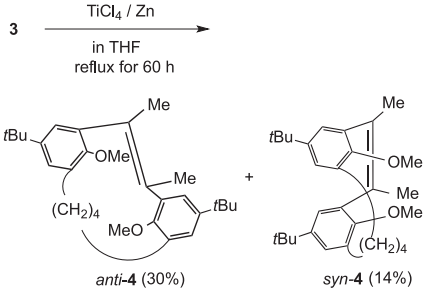



**Fig. 1.** Possible conformations of areno-bridged [2.4]MCPs.




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




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

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 C30–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–C18, C2–C17, C7–C22, C4–C21, C1–C16, 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** (Fig. 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.

Bromination of **4** with 4.4 equiv. of benzyltrimethyl-ammonium tribromide (BTMA-$Br_3$)[26] in $CH_2Cl_2$ solution at room temperature for 24 h afforded the corresponding 1,2-bis(bromomethyl)-5,15-di-