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

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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. DFT calculations were carried out to estimate the energy-minimized structures of the synthesized metacyclophanes.

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.

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 Fig. 1), both in solution and the solid state are also described.

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-

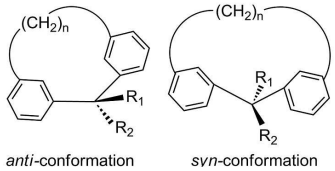

Fig. 1 Possible configurations of [*n*.1]MCPs.

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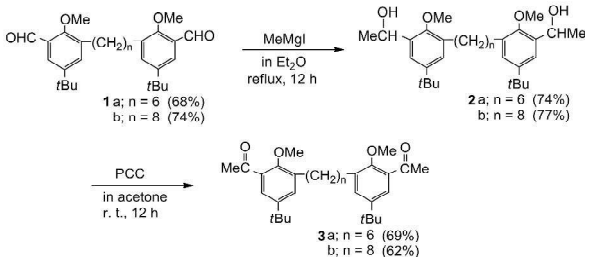
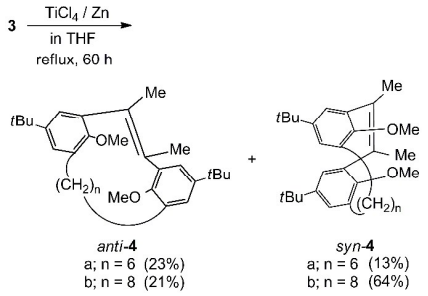


Scheme 1 Synthesis of 1,6-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl) hexane **3a** and 1,8-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)octane **3b**.



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**. 1,2-dimethyl[2.8]MCP-1-ene **4b**.

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 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-methoxy phenyl)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] 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 and *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 = 2.7Hz) 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 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 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 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 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 Fig. 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

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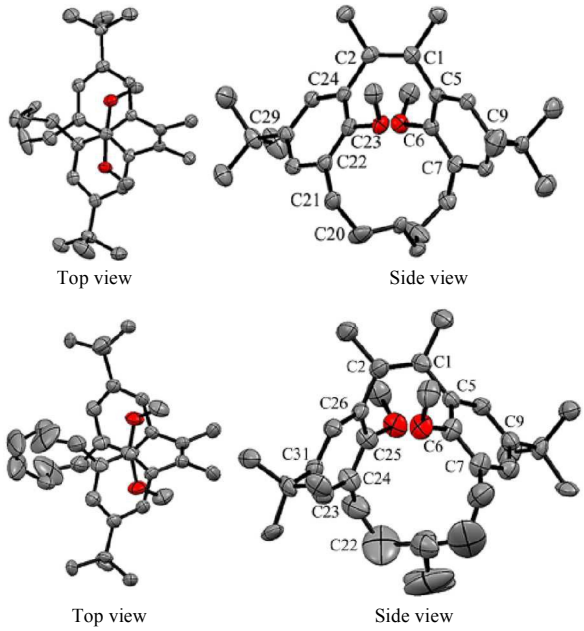
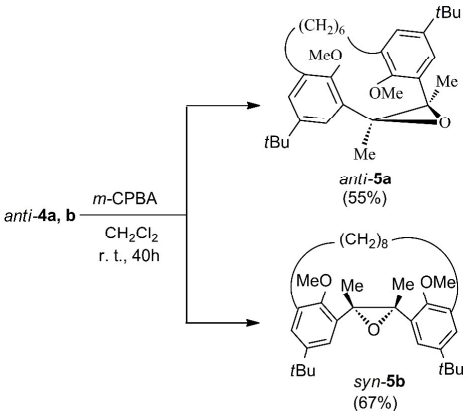


Fig. 2 ORTEP drawings of Top: *anti*-5,17-di-*tert*-butyl-8,20-dimethoxy-1,2-dimethyl[2.6]MCP-1-ene **4a**; and Bottom: *anti*-5,19-di-*tert*-butyl8,22-dimethoxy-1,2-dimethyl[2.8]MCP-1-ene **4b**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

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.

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 ppm (J = 2.4 Hz) 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.



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 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 centered 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 a *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* interconversion 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-

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.

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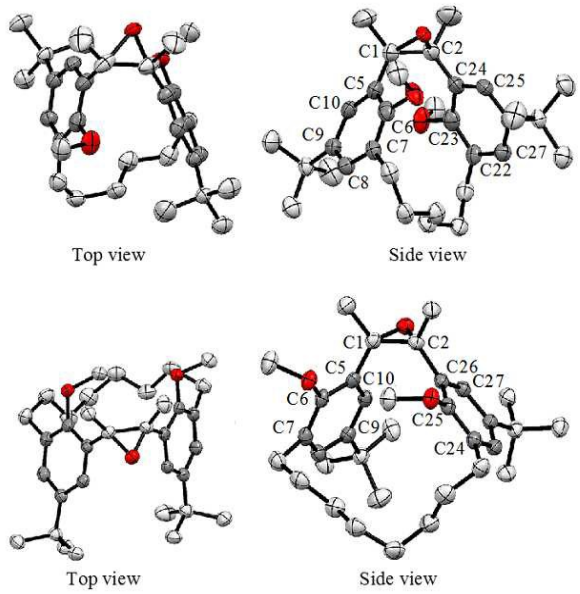
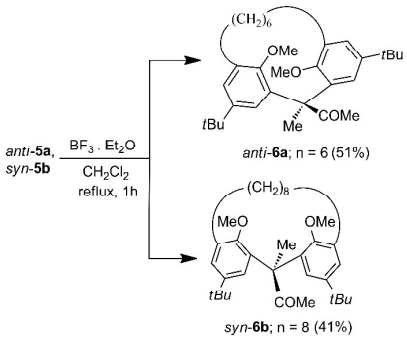


Fig. 3 ORTEP drawings of Top: *anti*-5,17-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,20-dimethoxy[2.6]MCP **5a**; and Bottom: *syn*-5,19-di-*tert*-butyl-1,2-epoxy-1,2-dimethyl-8,22-dimethoxy[2.8]MCP **5b**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

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 (Fig. 3). 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.



Scheme 4 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**.

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 (Fig. 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. 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 catalyzed 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.

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.

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.

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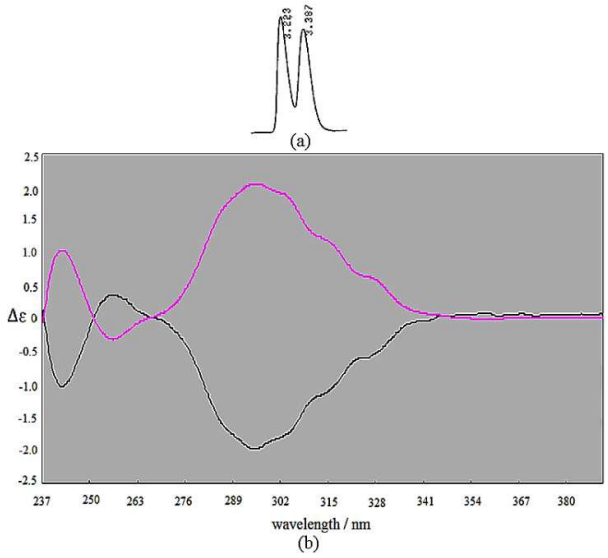

Fig. 4 (a) Chromatogram of *anti*-13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl[6.1]MCP **6a** (HPLC on chiral column). Daicel chiralpak ADeH. Eluent: hexanes. (b) CD spectra of *P*- and *M*-enantiomers of inherently chiral MCP *anti*-13-acetyl-9,16-di-*tert*-butyl-12,19-dimethoxy-13-methyl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

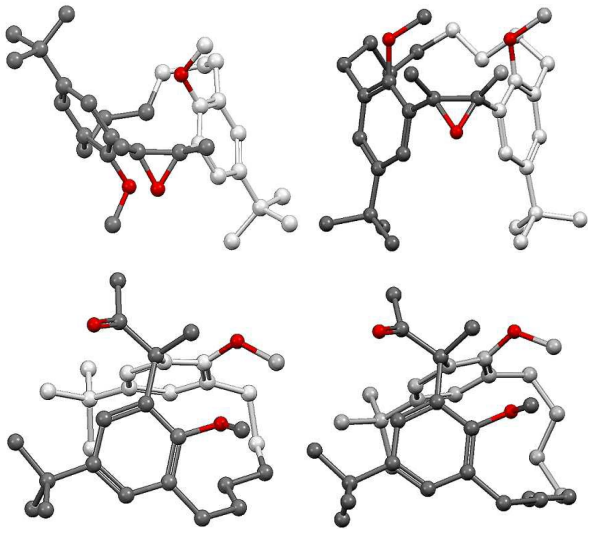

Fig. 5 DFT geometry-optimized structures of *anti*-**5a** (top left), *syn*-**5b** (top right), *anti*-**6a** (bottom left) and *syn*-**6b** (bottom right). Colour code: carbon = dark and light grey, and oxygen = red. Hydrogen atoms omitted for clarity.

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 Fig. 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**.

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 Fig.5.

The trend for the stabilities of **6** and **5** could tentatively be rationalized on the basis of 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 (Fig. 3 and 5).

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.

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.

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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.

Experimental

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 Me4Si. 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}.

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]

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 (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 1,6-bis(5-*tert*-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl)hexane **2a** (7.71 g, 74%) as colourless 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}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s, *t*Bu), 1.51–1.70 (6H, m, C*H*$_2$), 1.52 (6H, d, *J* = 6.6 Hz, C*H*$_3$), 2.26–2.36 (4H, m, C*H*$_2$), 2.58–2.68 (4H, m, C*H*$_2$), 3.77 (6H, s, OC*H*$_3$), 5.16–5.25 (2H, bs, O*H*), 7.11 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 7.27 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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 colourless prisms. M.p. 107–108 °C. IR (KBr): υ_{max} = 3313, 2915, 1469, 1295, 1174, 1115, 1000 and 879 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (18H, s, *t*Bu), 1.36–1.45 (4H, m, C*H*$_2$), 1.52 (6H, d, *J* = 6.6 Hz, C*H*$_2$), 1.58–1.69 (6H, m, C*H*$_3$), 2.33 (4H, s, C*H*$_2$), 2.59–2.63 (4H, m, C*H*$_2$), 3.77 (6H, s, OC*H*$_3$), 5.20 (2H, bs, O*H*), 7.12 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 7.27 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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 colourless 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, *t*Bu), 1.42–1.50 (4H, m, C*H*$_2$), 1.45 (4H, s, C*H*$_2$), 1.61–1.72 (4H, m, C*H*$_2$), 2.63 (6H, s, C*H*$_3$), 3.73 (6H, s, OC*H*$_3$), 7.33 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 7.41 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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

Compound **3b** was synthesized in the same manner as described above for **3a** and obtained (6.91 g, 62%) as colourless 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, *t*Bu) ,1.37–1.46 (12H, m, C*H*$_2$), 1.55–1.68 (4H, m, C*H*$_2$), 2.63 (6H, s, C*H*$_3$), 3.73 (6H, s, OC*H*$_3$), 7.34 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 7.41 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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,

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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.

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 (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*-**4a** and *syn*-**4a** as a colourless solid. Each eluents were 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 colourless 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, CH_2), 0.83 (2H, m, CH_2), 1.26 (4H, m, CH_2), 1.31 (18H, s, *t*Bu), 2.10 (2H, m, CH_2), 2.22 (6H, s, CH_3), 2.52 (2H, m, CH_2), 3.34 (6H, s, OCH_3) 6.89 (2H, d, *J* = 2.7 Hz, Ar-*H*) and 7.04 (2H, d, *J* = 2.7 Hz, Ar-*H*) 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 colourless 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, CH_2), 0.85 (2H, m, CH_2), 1.11 (18H, s, *t*Bu), 1.30 (4H, m, CH_2), 2.18 (6H, s, CH_3), 2.28 (2H, m, CH_2), 2.80 (2H, m, CH_2), 3.67 (6H, s, OCH_3), 6.64 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 6.77 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.95 (6H, m, CH_2), 1.12–1.33 (6H, m, CH_2), 1.28 (18H, s, *t*Bu), 2.01–2.11 (2H, m, CH_2), 2.15 (6H, s, CH_2), 2.59–2.70 (2H, m, CH_2), 3.52 (6H, s, OCH_3), 6.86 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 7.01 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94–1.12 (6H, m, CH_2), 1.12 (18H, s, *t*Bu), 1.27–1.36 (6H, m, CH_2), 2.13–2.23 (2H, m, CH_2), 2.20 (6H, s, CH_3), 2.73–2.85 (2H, m, CH_2), 3.69 (6H, s, OCH_3), 6.74 (2H, d, *J* = 2.4 Hz, Ar-*H*) and 6.82 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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 (2 × 10 mL). The combined extracts were washed with water (2 × 10 mL), 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 colourless prisms (MeOH). M.p. 192–193 °C. IR (KBr): υ_{max} = 2944, 2856, 1472, 1450, 1352, 1229, 1085, 1019, 875 and 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.25–0.35 (4H, m, CH_2), 0.70–0.81 (4H, m, CH_2), 1.30 (9H, s, *t*Bu), 1.31 (9H, s, *t*Bu), 1.73 (3H, s, CH_3), 1.95 (3H, s, CH_3), 2.21–2.35 (2H, m, CH_2), 2.44–2.53 (2H, m, CH_2), 3.39 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 6.94 (1H, d, *J* = 2.4 Hz, Ar-*H*), 6.95 (1H, d, *J* = 2.4 Hz, Ar-*H*), 7.29 (1H, d, *J* = 2.4 Hz, Ar-*H*) and 7.38 (1H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.71–0.97 (4H, m, CH_2), 1.16 (18H, s, *t*Bu), 1.31–1.42 (4H, m, CH_2), 1.48–1.59 (4H, m, CH_2), 1.88 (6H, s, CH_3), 2.16–2.26 (2H, m, CH_2), 2.87–2.94 (2H, m, CH_2), 3.80 (6H, s, OCH_3), 6.84 (2H, d, *J* =

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2.4 Hz, Ar-*H*) and 7.11 (2H, d, *J* = 2.4 Hz, Ar-*H*) 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.

General procedure for the acid catalyzed rearrangement of epoxymetacyclophane *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 (2 × 10 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (10 mL), water (2 × 10 mL), 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 colourless 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, CH_2), 0.80–0.95 (2H, m, CH_2), 1.30 (9H, s, *t*Bu), 1.32 (9H, s, *t*Bu), 1.26–1.37 (4H, m, CH_2), 1.71 (3H, s, CH_3), 1.76 (3H, s, CH_3), 2.20–2.30 (2H, m, CH_2), 2.34–2.47 (2H, m, CH_2), 3.29 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 7.05 (1H, d, *J* = 2.4 Hz, Ar-*H*), 7.12 (1H, d, *J* = 2.4 Hz, Ar-*H*), 7.25 (1H, d, *J* = 2.4 Hz, Ar-*H*) and 7.28 (1H, d, *J* = 2.4 Hz, Ar-*H*) 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.

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 colourless 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, CH_2), 1.16 (18H, s, *t*Bu), 1.24–1.34 (4H, s, CH_2), 1.54–1.64 (4H, m, CH_2), 2.25–2.35 (2H, m, CH_2), 2.37 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.82–2.95 (2H, m, CH_2), 3.71 (6H, s, OCH_3) and 6.87 (4H, dd, *J* = 2.4 Hz, Ar-*H*) 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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Notes and references

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† **Electronic Supplementary Information (ESI) available:** Details of the single-crystal X-ray crystallographic data and DFT computational data and xyz files. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x/

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