Medium-size cyclophanes, 77.[1] Synthesis and addition of bromine to *syn*-[2.*n*]meta-cyclophan-1-enes

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McMurry cyclisation of 1,*n*-bis(3-formyl-2-methoxyphenyl)alkanes afforded *syn*-dimethoxy[2.*n*]metacyclophan-1-enes, in which *cis*-addition of bromine to the bridged double bond in CH_2Cl_2 was observed.

Keywords: cyclophanes, [2.*n*]metacyclophan-1-ene, McMurry reaction, conformation, bromination, *cis*-addition

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 not realised until 85 years later. Mitchell *et al.*[3] have successfully prepared *syn*-[2.2]MCP at low temperature by using (arene)chromiumcarbonyl complexation to control the stereochemistry. Later, Itô *et al.*[4] have also isolated and characterised *syn*-[2.2]MCP without complexation. However, *syn*-[2.2]MCP isomerises readily to the *anti*-isomer above 0°C. On the other hand, Boekelheide[5] and Staab[6] succeeded in synthesising intra-annularly substituted *syn*-[2.2]MCP-1-enes, respectively. However, reports on synthesis and reactions of *syn*-[2.*n*]MCP-1-enes have not been published so far.

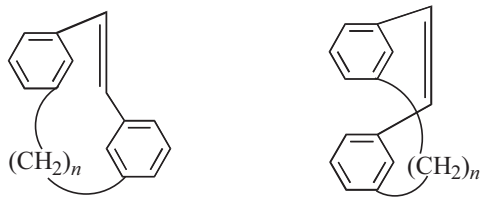
Cram *et al*. reported[7] the addition of bromine across the bridging double bond of [2.2]paracyclophan-1-ene which afforded the corresponding *cis* adduct. Similarly, we previously found[8] that addition of bromine to *anti*-dimethyl[2.3]MCP-1-ene afforded the *cis* adduct resulting from addition to the bridging double bond. A similar reaction with *anti*-dimethyl[2.4]MCP-1-ene, however, gave a mixture of the *cis* adduct formed by the addition to the bridging double bond and the *trans* adduct containing a brominated internal methyl group. Therefore, the orientation of the addition of bromine to *anti*-dimethyl[2.4]MCP-1-ene is ambiguous since the internal bromomethyl group might affect the orientation of the bromine addition. We have reported that the bromination of *anti*-dimethoxy[2.4]MCP-1-ene affords exclusively *cis*-adduct to the bridged double bond since formation of a brominated internal methyl group is not possible.[9] Thus, there is substantial interest in the bromination of longer methylene bridged dimethoxy[2.*n*]MCP-1-enes with bromine.

Recently, we have reported the preparation of 1,2-dimethyl[2.*n*]MCP-1-enes[10] using the reductive coupling of carbonyl compounds by low-valent titanium (the McMurry reaction[11,12]) as a key step. We now report on the synthesis of *syn*- and *anti*-[2.5]- and -[2.6]MCP-1-ene using the low-valent titanium induced McMurry reaction and the addition of bromine to the bridged double bond.

Results and discussion

1,5-Bis(5-*tert*-butyl-2-methoxyphenyl)pentane **1a** and 1,6-bis(5-*tert*-butyl-2-methoxyphenyl)hexane **1b** have been prepared according to our previous paper.[13] The $TiCl_4$ formylation of compounds **1a** and **1b** with dichloromethyl methyl ether at 20°C gave the desired 1,*n*-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)alkanes **2a** and **2b** in 42 and 67% yields, respectively.

1,*n*-Bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)alkanes (**2**) was subjected to reductive coupling by the McMurry reaction following the improved Grützmacher's procedure[14] (Scheme 1). Thus, the reductive coupling reaction of 1,5-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)pentane **2a** carried out using $TiCl_4$–Zn in refluxing THF under the high dilution conditions afforded the desired compound *syn*-5,16-di-*tert*-butyl-8,19-dimethoxy[2.5]MCP-1-ene (*syn*-**3a**) in 27% along with *anti*-12-*endo*-hydroxy-13-*endo*-hydroxy-8,16-di-*tert*-butyl-11,19-dimethoxy[5.2]MCP (*meso*-*anti*-**4a**) in 32% yield. However, the formation of the another possible conformational isomer *anti*-**3a** was not observed. Similarly, the reductive coupling reaction of 1,6-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)hexane **2b** carried out under the same conditions described above afforded 5,17-di-*tert*-butyl-8,20-dimethoxy[2.6]MCP-1-ene (**3b**) in 15% along with *anti*-13-*endo*-hydroxy-14-*endo*-hydroxy-9,17-di-*tert*-butyl-12,20-dimethoxy[6.2]MCP (*meso*-*anti*-**4b**). However, several attempted isolations of pure *meso*-*anti*-**4b** failed. We have converted crude *meso*-*anti*-**4b** to the corresponding diacetate *meso*-*anti*-**5b** by treatment with acetic anhydride and pyridine at room temperature in 16% yield from the above McMurry coupling reaction. Interestingly, the ^{1}H NMR spectrum of **3b** shows two kinds of methoxy protons, each as a singlet. By careful column chromatography (silica gel, Wako C-300), two isomers, *anti*-**3b** and *syn*-**3b**, are separated in 5 and 10% yield, respectively. They are thermally stable and do not interconvert at 180°C in DMSO solution and at 400°C in the solid state.



anti-conformation *syn*-conformation

Fig. 1 Possible conformations of [2.*n*]metacyclophan-1-enes.

The structures of products **3a** and **3b** were determined on the basis of their elemental analyses and spectral data. Especially, the mass spectral data for **3a** and **3b** (M^+ = 420 for **3a** and both M^+ = 434 for *syn*-**3b** and *anti*-**3b**) strongly support the cyclic structure. The conformations of **3a** and **3b** were readily apparent from their ^{1}H NMR spectrum. For example, ^{1}H NMR spectrum of *anti*-**3b** in $CDCl_3$ shows a singlet at δ 3.13 ppm for methoxy protons, a singlet at δ 6.56 ppm for olefinic protons, and a pair of doublets (J = 2.4 Hz) at δ 7.02, 7.03 ppm for aromatic protons. Thus the methoxy protons should show an upfield shift at δ 3.13 ppm due to the ring current of the opposite aromatic ring.[15,16] The structure of the *syn*-confomer is also readily assigned from the chemical shift of the methoxy protons at δ 3.67 ppm. Also the *tert*-butyl proton of *syn*-**3b** was observed at a higher field, δ 1.11 ppm, due to the shielding effect of the benzene ring. The aromatic protons of *syn*-conformer *syn*-**3b** are observed much higher field (δ 6.51, 6.81 ppm) than those of *anti*-conformer *anti*-**3b** at δ 7.02 and 7.03 ppm. The above data show that the structure of *anti*-**3b** is the *anti*-conformer, whereas the structure of *syn*-**3b**

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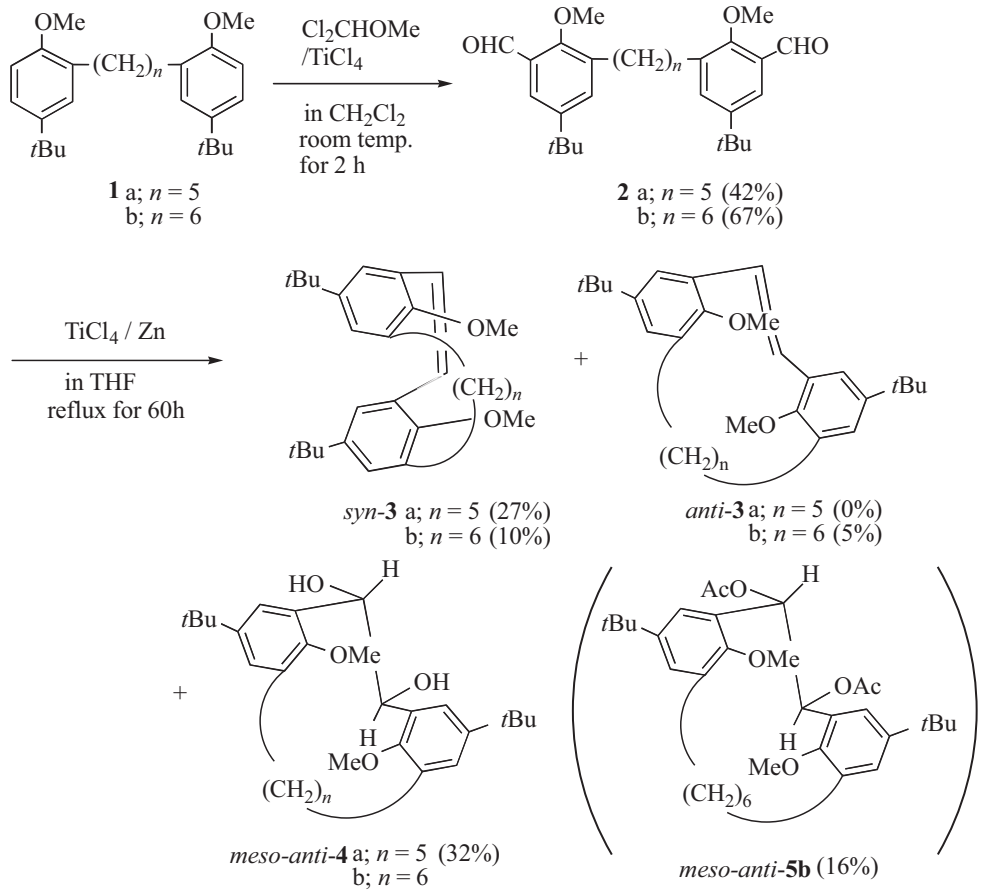


Scheme 1

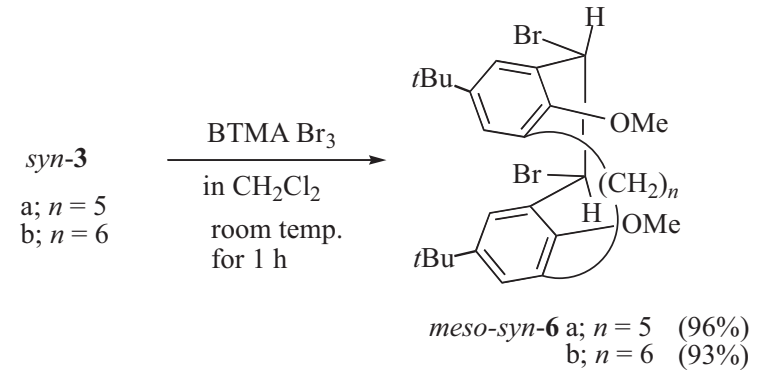
is the *syn*-conformer. We have assigned the structure of *syn*-**3a** in a similar fashion. Thus, the structure of the *syn*-confomer is also readily assigned from the chemical shift of the internal methoxy protons as a singlet at δ 3.70 ppm. Interestingly, the bridged methylene protons for $CH_2CH_2CH_2CH_2CH_2$ in the compound *syn*-**3a** are located in different spaces with one of them folded into the π-cavity formed by two benzene rings. Thus, a higher field signal at δ –0.90–0.10 ppm was observed. The individual peaks of the methylene protons for middle CH_2 in the pentane bridge do not coalesce below 140°C in [D_6]DMSO and the energy barrier to conformational wobbling is above 25 kcal mol^{-1}.

We previously assigned[17] the ^{1}H NMR signals of 1-*exo*-5,13-trichloro-8,16-dimethyl[2.2]MCP, and we have assigned the ^{1}H NMR signals of *meso-anti*-**4a** in a similar fashion. Thus, the structure of the *anti*-confomer is also readily assigned from the chemical shift of the internal methoxy protons and the bridged methine protons both as a singlet at δ 3.32 and 4.85 ppm, respectively. The other two aromatic protons was observed at δ 6.93 and 7.47 ppm; the latter protons are in a strongly deshielding region of oxygen atom of *endo*-OH on ethylene bridge. These observations are strongly supported that the two OH groups are *endo, endo*-arrangement and therefore, **4a** is found to be *trans*-diol. Similarly, the structures of *meso-anti*-**4b** and *meso-anti*-**5b** were assigned to be *trans*-diol and *trans*-diacetate with *endo, endo*-arrangement.

Attempted bromination of *syn*-5,16-di-*tert*-butyl-8,19-dimethoxy [2.5]MCP-1-ene (*syn*-**3a**) with 1.1 equiv. of bromine carried out in a dichloromethane solution at room temperature for 1 h led to the stereoselective *cis*-addition to the bridged double bond to afford *meso-syn*-**6a** (*endo-endo*-Br) in 60% yield along with the starting compound in 40%. Bromination of *syn*-**3a** carried out with an equimolar amount of benzyltrimethylammonium tribromide (BTMA Br_3) in dichloromethane for 1 h, which was recently found to be a convenient solid brominating agent,[18] resulted to afford same bromine adduct *meso-syn*-**6a** in 96% yield along with the recovery of the starting compound *syn*-**3a** in 4%. (Scheme 2). Similarly, treatment of *syn*-5,17-di-*tert*-butyl-8,20-dimethoxy[2.6]MCP-1-ene (*syn*-**3b**) with an equimolar amount of BTMA Br_3 under the reaction conditions above led to the stereoselective *cis*-addition to the bridged double bond to afford *meso-syn*-**6b** in 93% yield.

The structures of the products obtained in the bromine addition of *syn*-**3** were determined from their elemental analyses and spectral data. On the basis of the spectral data, *meso-syn*-**6a** and *meso-syn*-**6b** are assigned the structures, *syn*-12-*endo*-bromo-13-*endo*-bromo-8,16-di-*tert*-butyl-11,19-dimethoxy[5.2]MCP and *syn*-13-*endo*-bromo-14-*endo*-bromo-9,17-di-*tert*-butyl-12,20-dimethoxy[6.2]MCP, respectively. ^{1}H NMR spectrum of *meso-syn*-**6a** in $CDCl_3$ shows a singlet at δ 6.55 ppm for methine protons and a doublet (J = 2.4 Hz) at δ 7.56 ppm for two aromatic protons which are in a strongly deshielding region of *endo*-Br atom on ethylene bridge. These data are strongly supported that the two Br atoms are *endo*- and *endo*-arrangement and therefore, *meso-syn*-**6a** is found to be *cis*-adduct to the bridged double bond. Similarly, ^{1}H NMR spectrum of *meso-syn*-**6b** in $CDCl_3$ shows a singlet at δ 6.33 ppm for methine protons, a doublet (J = 2.4 Hz) at δ 7.55 ppm for two aromatic protons which are in a strongly deshielding region of *endo*-Br atom on ethylene bridge. Thus, the two Br atoms are both *endo*-arrangement and therefore, *meso-syn*-**6b** is found to be *cis*-adduct to the bridged double bond.

Cram *et al*. reported[7] that [2.2]paracyclophan-1-ene underwent solely *cis*-addition of bromine to give *cis*-1,2-dibromo[2.2]paracyclophane and the stereospecificity and stereochemical direction of this reaction was explained



Scheme 2

by the formation of highly strained phenonium ions as intermediates.

In the present system, the fact that *cis*-adduct *meso-syn*-**6a** (*endo-endo*-Br) is exclusively obtained is explained on the basis of phenonium ions such as **A** as an intermediate in the sequences rather than the nonclassical bromonium ion intermediate **B**[19,20] in the bromine addition process. The steric effect of the internal methoxy groups for the *exo*-Br addition to the carbocation intermediate **A** or the presence of the four membered transition state rather than the nonclassic bromonium ion intermediate **B** in the process of bromination might be also considered. The absence of **B** might be attributed to the strain of this intermediate. It was also found in spite of being the number of methylene units within the polymethylene bridge increased from five to six, bromine addition to the bridging double-bond proceeds exclusively via *cis*-addition, different from *trans*-addition as has been reported for bromine addition in normal alkene systems.[19]

In contrast, bromination of *anti*-5,17-di-*tert*-butyl-8,20-dimethoxy[2.6]MCP-1-ene (*anti*-**3b**) with 1.1 equiv. of BTMA Br_3 in dichloromethane at room temperature for 1 h afforded a mixture of *cis*-adduct *rac-anti*-**6b** (*endo-exo*-Br) and *trans*-adduct *meso-anti*- **6b** (*exo-exo*-Br) in the ratio of 80 : 20 in 71% yield (Scheme 3).

The structures of *rac-anti*-**6b** and *meso-anti*-**6b** were determined from their elemental analyses and spectral data. The ^{1}H NMR spectrum of *rac-anti*-**6b** in $CDCl_3$ shows two sets of doublets (J = 3.9 Hz) at δ 5.51 and 5.78 ppm for bridged methine protons and a doublet (J = 2.2 Hz) at δ 8.04 ppm for one aromatic proton which is in a region strongly deshielded by the *endo*-Br atom on the ethylene bridge. These data strongly support the fact that the two Br atoms are in an *endo*- and *exo*-arrangement and therefore, *rac-anti*-**6b** is found to be *cis*-adduct to the bridging double bond. In contrast, ^{1}H NMR spectrum of *meso-anti*-**6b** in $CDCl_3$ shows a singlet at δ 5.98 ppm for methine protons and no

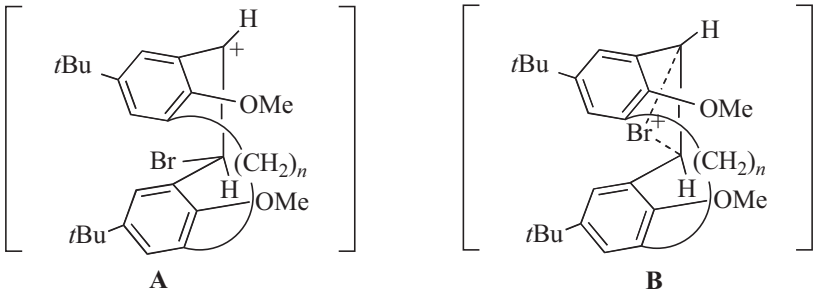
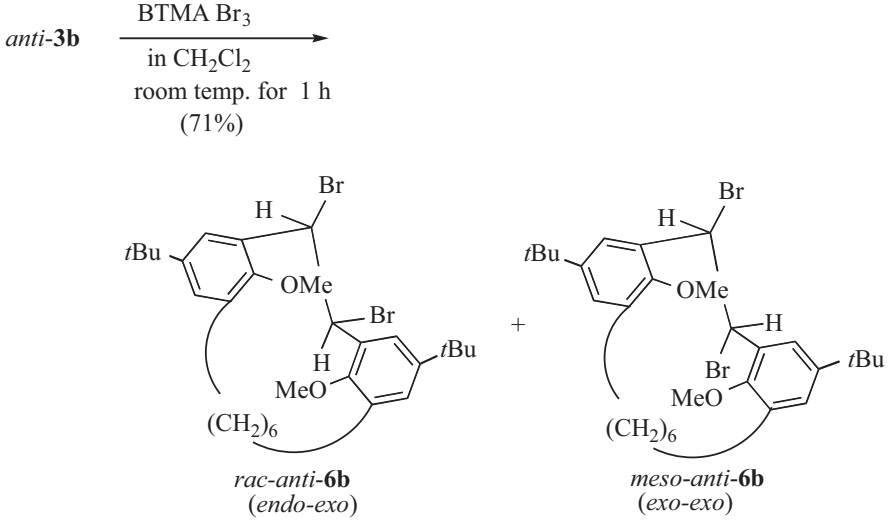


Fig. 2



Scheme 3

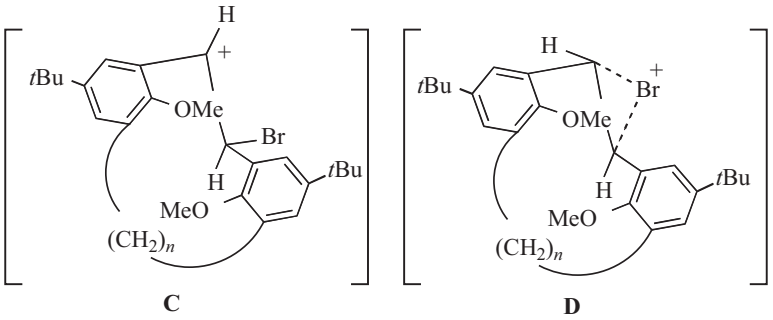


Fig. 3

deshielded aromatic protons were observed at δ 6.95 and 7.43 ppm, but the methoxy protons were observed at δ 3.65 ppm, which is in a region strongly deshielded by the *exo*-Br atom on the ethylene bridge. These data are strongly supported that the two Br atoms are both *exo*-arrangement and therefore, *meso-anti*-**6b** is found to be *trans*-adduct to the bridged double bond.

As mentioned previously, we have reported the bromination of *anti*-dimethoxy[2.4]MCP-1-ene to afford exclusively *cis*-adduct to the bridged double bond to the bridging double bond.[7] The fact that *cis*-adduct *rac-anti*-**6b** is mainly obtained indicates the preferential existence of the carbocation intermediate **C** rather than the nonclassic bromonium ion intermediate **D** in the process of bromination.[19,20] The less formation of **D** might be attributed to the strain of this intermediate. When the number of methylene bridge are increased by two, the *cis*-addition of *anti*-[2.6]MCP-1-ene (*anti*-**3b**) with bromine competed with *trans*-addition due to the decrease of strain of the intermediate **D** (Fig. 3). Thus, the ratio of *cis*-adduct to *trans*-adduct decreased by increasing the number of the methylene group of the present *anti*-[2.*n*]MCP-1-enes *anti*-**3**.

This result is quite different from that obtained with the addition of bromine to the corresponding *syn*-dimethoxy[2.6]MCP-1-ene (*syn*-**3b**), which afforded exclusively *cis*-adduct to the bridged double bond.

Conclusions

We have demonstrated a convenient preparation of *syn*- and *anti*-dimethoxy[2.5]- and [2.6]MCP-1-ene **3** by McMurry reaction of the corresponding 1,*n*-bis(3-formyl-2-methoxyphenyl)alkanes **2**. The bromination of *syn*-dimethoxy[2.5]- and [2.6]- MCP-1-ene **3** with $BTMABr_3$ afforded exclusively *cis*-adduct to the bridged double bond. In contrast, *anti*-dimethoxy[2.6]MCP-1-ene resulted to afford a mixture of *cis*- and *trans*-adducts to the bridged double bond. The different stereoselectivity for the bromine addition in *syn*- and *anti*-dimethoxy[2.5]- and [2.6]MCP-1-enes **3** was observed. Further studies on the chemical properties of *syn*- and *anti*-dibromodimethoxy[*n*.2]MCPs **6** are now in progress.

Experimental

^1H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system.

Materials

Preparations of 1,*n*-bis(5-*tert*-butyl-2-methoxyphenyl)alkanes **1** has been previously described.[13]

Preparation of 1,n-bis(5-tert-butyl-3-formyl-2-methoxyphenyl) alkanes (**2**)*–typical procedure*

To a solution of 1,5-bis(5-*tert*-butyl-2-methoxyphenyl)pentane (**1a**) (3.42 g, 9 mmol) and Cl_2CHOCH_3 (2.28 cm^3, 25.2 mmol) in CH_2Cl_2 (20 cm^3) was added a solution of $TiCl_4$ (6.0 cm^3, 54.5 mmol) in CH_2Cl_2 (20 cm^3) at 0°C. After the reaction mixture was stirred at room temp. for 2 h, it was poured into a large amount of ice/water (200 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (Wako C-300, 200 g) with $CHCl_3$ as eluent to give crude **2a** (4.0 g, 95%). Recrystallisation from hexane gave 1.76 g (42%) of *1,5-bis (5-tert-butyl-3-formyl-2-methoxyphenyl)pentane* (**2a**): Colourless prisms (hexane), m.p. 89–90°C; ν_{max}(KBr)/cm^{-1}: 1692 (C=O); $\delta_H(CDCl_3)$: 1.31 (18H, s, *t*Bu), 1.42–1.53 (2H, m, *CH*$_2$), 1.64–1.70 (4H, m, *CH*$_2$), 2.65–2.71 (4H, m, *CH*$_2$), 3.87 (6H, s, O*Me*), 7.47 (2H, d, *J* = 2.4 Hz, Ar*H*), 7.71 (2H, d, *J* = 2.4 Hz, Ar*H*), 10.36 (2H, s, *CHO*); *m/z*: 452 (M^+) (Found C, 77.01; H, 8.74. $C_{29}H_{40}O_4$ (452.64) requires C, 76.95; H, 8.91%).

Compound **2b** was similarly prepared in 67% yield.

1,6-Bis(5-tert-butyl-3-formyl-2-methoxyphenyl)hexane (**2b**): Colourless prisms (hexane), m.p. 108–109°C; ν_{max}(KBr)/cm^{-1}: 1692 (C=O); $\delta_H(CDCl_3)$: 1.32 (18H, s, *t*Bu), 1.42–1.53 (4H, m, *CH*$_2$), 1.59–1.70 (4H, m, *CH*$_2$), 2.65–2.71 (4H, m, *CH*$_2$), 3.87 (6H, s, O*Me*), 7.47 (2H, d, *J* = 2.4 Hz, Ar*H*), 7.70 (2H, d, *J* = 2.4 Hz, Ar*H*), 10.36 (2H, s, *CHO*); *m/z*: 466 (M^+) (Found C, 77.37; H, 9.18. $C_{30}H_{42}O_4$ (466.67) requires C, 77.21; H, 9.07%).

General procedure for the McMurry coupling reaction of **2**

The McMurry reagent was prepared from $TiCl_4$ (23.8 g, 125 mmol) of and 18 g (275 mmol) of Zn powder in 500 cm^3 of dry THF, under nitrogen. A solution of 1,6-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)hexane **2b** (1.40 g, 3 mmol) in dry THF (100 cm^3) 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 an additional 8 h, cooled to room temperature, and hydrated with aqueous 10% K_2CO_3 (200 cm^3) at 0°C. The reaction mixture was extracted with CH_2Cl_2 (3 × 200 cm^3). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane/benzene (1:1) and benzene as eluents to give *anti*-**3b** (65 mg, 5%) and *syn*-**3b** (130 mg, 10%), respectively. The $CHCl_3$ eluent afforded crude *meso-anti*-**4b** (614 mg) as a pale brown oil. Since several attempted pure isolations failed, crude *meso-anti*-**4b** was converted to diacetate. Thus a solution of crude *meso-anti*-**4b** in acetic anhydride (3.5 cm^3) and pyridine 7.5 cm^3) was stirred at room temperature for 24 h. The reaction mixture was poured into a large amount of ice/water (40 cm^3) and extracted with CH_2Cl_2 (2 × 30 cm^3). The combined extracts were washed with 3% HCl aq. (2 × 10 cm^3) and water, dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (Wako C-300, 200 g) with hexane: benzene 1:1 as eluent to give crude *meso-anti*-**5b** as a colourless solid. Recrystallisation from hexane gave 273 mg (16% from McMurry coupling reaction) of *meso-anti*-**5b** as colourless prisms.

anti-5,17-Di-tert-butyl-8,20-dimethoxy[2.6]metacyclophan-1-ene (*anti*-**3b**): Colourless prisms (MeOH), m.p. 114–115°C; ν_{max}(KBr)/cm^{-1}: 2918, 1480, 1215, 1114, 1020, 881, 807, 735; $\delta_H(CDCl_3)$: 0.73–0.95 (4H, m, *CH*$_2$), 1.14–1.43 (4H, m, *CH*$_2$), 1.32 (18H, s, *t*Bu), 2.18–2.32 (2H, m, *CH*$_2$), 2.58–2.82 (2H, m, *CH*$_2$), 3.13 (6H, s, O*Me*), 6.56 (2H, s, *CH*), 7.02 (2H, d, *J* = 2.4 Hz, Ar*H*), 7.03 (2H, d,

J = 2.4 Hz, Ar*H*); *m/z*: 434 (M^+) (Found C, 82.98; H, 9.71. $C_{30}H_{42}O_2$ (434.67) requires C, 82.90; H, 9.74%).

syn-5,17-Di-tert-butyl-8,20-dimethoxy[2.6]metacyclophan-1-ene (*syn*-**3b**): Colourless prisms (MeOH), m.p. 62–64°C; ν_{max}(KBr)/cm^{-1}: 2962, 1479, 1327, 1215, 1019, 883, 810; δ_H($CDCl_3$): 0.51–0.58 (2H, m, CH_2), 0.77–0.93 (2H, m, CH_2), 1.01–1.35 (4H, m, CH_2), 1.11 (18H, s, *t*Bu), 2.25–2.28 (2H, m, CH_2), 2.75–2.89 (2H, m, CH_2), 3.67 (6H, s, O*Me*), 6.51 (2H, d, J = 2.4 Hz, Ar*H*), 6.81 (2H, d, J = 2.4 Hz, Ar*H*) 6.88 (2H, s, *CH*); *m/z*: 434 (M^+) (Found C, 82.89; H, 9.79. $C_{30}H_{42}O_2$ (434.67) requires C, 82.90; H, 9.74%).

anti-13-endo-Acetoxy-14-endo-acetoxy-9,17-di-tert-butyl-12,20-dimethoxy[6.2]metacyclophane (*meso-anti*-**5b**): Colourless prisms (hexane), m.p. 214–216°C; ν_{max}(KBr)/cm^{-1}: 1744 (C=O); δ_H($CDCl_3$): 0.51–0.93 (2H, m, CH_2), 1.32 (18H, s, *t*Bu), 1.25–1.36 (2H, m, CH_2), 1.42–1.58 (4H, m, CH_2), 2.14 (6H, s, CO*Me*), 2.20–2.30 (2H, m, CH_2), 2.41–2.53 (2H, m, CH_2), 3.46 (6H, s, O*Me*), 6.25 (2H, s, *CH*), 7.04 (2H, d, J = 2.4 Hz, Ar*H*), 7.36 (2H, d, J = 2.4 Hz, Ar*H*); *m/z*: 552 (M^+) (Found C, 73.96; H, 9.05. $C_{34}H_{48}O_6$ (552.76) requires C, 73.88; H, 8.75%).

Compounds *syn*-**3a** and *meso-anti*-**4a** were similarly prepared in 27 and 32% yields, respectively.

syn-5,16-Di-tert-butyl-8,19-dimethoxy[2.5]metacyclophan-1-ene (*syn*-**3a**): Colourless prisms (MeOH), m.p. 125–127°C; δ_H($CDCl_3$): –0.90–0.10 (1H, m, CH_2), 0.79–0.96 (1H, m, CH_2), 1.12 (18H, s, *t*Bu), 1.10–1.22 (2H, m, CH_2), 1.53–1.69 (2H, m, CH_2), 2.07–2.18 (2H, m, CH_2), 2.91–3.02 (2H, m, CH_2), 3.70 (6H, s, O*Me*), 6.58 (2H, d, J = 2.7 Hz, Ar*H*), 6.68 (2H, d, J = 2.7 Hz, Ar*H*), 6.96 (2H, s, *CH*); *m/z*: 420 (M^+) (Found C, 82.55; H, 9.61. $C_{29}H_{40}O_2$ (420.64) requires C, 82.81; H, 9.59%).

anti-12-endo-Hydroxy-13-endo-hydroxy-8,16-di-tert-butyl-11,19-dimethoxy[5.2]metacyclophane (*meso-anti*-**4a**): Colourless prisms [hexane/benzene (5:1)], m.p. 224–226°C; ν_{max}(KBr)/cm^{-1}: 3386 (OH); δ_H($CDCl_3$): 1.32 (18H, s, *t*Bu), 1.15–1.35 (6H, m, CH_2), 1.98–2.11 (2H, m, CH_2), 2.48–2.59 (2H, m, CH_2), 2.81 (2H, s, *OH*, replaced by D_2O), 3.32 (6H, s, O*Me*), 4.85 (2H, s, *CH*), 6.93 (2H, d, J = 2.4 Hz, Ar*H*), 7.47 (2H, d, J = 2.4 Hz, Ar*H*); *m/z*: 454 (M^+) (Found C, 76.44; H, 9.33. $C_{29}H_{42}O_4$ (454.66) requires C, 76.61; H, 9.31%).

Reaction of syn-[2.n]metacyclophan-1-enes (**3**) *with BTMA Br_3–typical procedure*

To a solution of *syn*-**3a** (42 mg, 0.10 mmol) in CH_2Cl_2 (4 cm^3) was added BTMA Br_3 (43 mg, 0.11 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 1 h, it was poured into a large amount of ice/water (50 cm^3) and extracted with CH_2Cl_2 (50 cm^3 × 2). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue recrystallised from hexane gave 56 mg (96%) of *syn*-12-*endo-bromo*-13-*endo-bromo*-8,16-*di-tert-butyl*-11,19-*dimethoxy[5.2]metacyclophane* (*meso-syn*-**6a**): Colourless prisms (hexane), m.p. 195–198°C; ν_{max}(KBr)/cm^{-1}: 2962, 1480, 1461, 1295, 1205, 1005, 885, 581; δ_H($CDCl_3$): –0.18–0.02 (2H, m, CH_2), 0.58–0.79 (2H, m, CH_2), 1.16 (18H, s, *t*Bu), 1.52–1.78 (2H, m, CH_2), 2.05–2.27 (2H, m, CH_2), 2.72–2.93 (2H, m, CH_2), 3.66 (6H, s, O*Me*), 6.55 (2H, s), 6.76 (2H, d, J = 2.4 Hz, Ar*H*), 7.56 (2H, d, J = 2.4 Hz, Ar*H*); *m/z*: 578, 580, 582 (M^+) (Found C, 59.81; H, 6.76. $C_{29}H_{40}Br_2O_2$ (580.45) requires C, 60.01; H, 6.95%).

Compound *meso-syn*-**6b** was similarly prepared in 93% yield.

syn-13-*endo-Bromo*-14-*endo-bromo*-9,17-*di-tert-butyl*-12,20-*dimethoxy*[6.2]*metacyclophane* (*meso-syn*-**6b**): Colourless prisms (hexane), m.p. 181–182°C; ν_{max}(KBr)/cm^{-1}: 2962, 1480, 1461, 1295, 1205, 1005, 885, 581; δ_H($CDCl_3$): 0.44–0.58 (2H, m, CH_2), 0.84–0.97 (2H, m, CH_2), 1.09–1.48 (4H, m, CH_2), 1.16 (18H, s, *t*Bu), 2.25–2.39 (2H, m, CH_2), 2.70–2.84 (2H, m, CH_2), 3.65 (6H, s, O*Me*), 6.33 (2H, s, *CH*), 6.89 (2H, d, J = 2.4 Hz, Ar*H*), 7.55 (2H, d, J = 2.4 Hz, Ar*H*); *m/z*: 592, 594, 596 (M^+) (Found C, 60.91; H, 7.12. $C_{30}H_{42}Br_2O_2$ (594.47) requires C, 60.61; H, 7.12%).

*Bromination of anti-**3b** with BTMA Br_3:* To a solution of *anti*-**3b** (22 mg, 0.05 mmol) in CH_2Cl_2 (2 cm^3) was added BTMA Br_3 (21.4 mg, 0.055 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 1 h, it was poured into a large amount of ice/water (50 cm^3) and extracted with CH_2Cl_2 (50 cm^3 × 2). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated to give 21 mg (71%) of a mixture of *anti*-13-*endo-bromo*-14-*exo-bromo*- (*rac-anti*-**6b**) and *anti*-13-*exo-bromo*-14-*exo-bromo*-9,17-*di-tert-butyl*-12,20-*dimethoxy*[6.2]*metacyclophane* (*meso-anti*-**6b**) in the ratio of 80 : 20 (determined by ^{1}H NMR spectrum) as colourless solid; δ_H($CDCl_3$): *rac-anti*-**6b**; 0.70–1.02 (4H, m, CH_2), 1.29 (9H, s, *t*Bu), 1.20–1.45 (4H, m, CH_2), 1.36 (9H, s, *t*Bu), 2.03–2.20 (2H, m, CH_2), 2.75–2.90 (2H, m, CH_2), 3.20 (3H, s, O*Me*), 3.36 (3H, s, O*Me*), 5.51 (1H, d, J = 3.9 Hz, *CH*), 5.78 (1H, d, J = 3.9 Hz, *CH*), 6.92 (1H, d, J = 2.9 Hz, Ar*H*), 7.10 (1H, d, J = 2.9 Hz, Ar*H*), 7.13 (1H, d, J = 2.2 Hz, Ar*H*), 8.04 (1H, d, J = 2.2 Hz, Ar*H*); *meso-anti*-**6b**; 0.70–1.02 (4H, m, CH_2), 1.07–1.43 (4H, m, CH_2), 1.27 (18H, s, *t*Bu), 2.16–2.38 (2H, m, CH_2), 2.58–2.72 (2H, m, CH_2), 3.65 (6H, s, O*Me*), 5.98 (2H, s, *CH*), 6.95 (2H, d, J = 2.4 Hz, Ar*H*), 7.43 (2H, d, J = 2.4 Hz, Ar*H*); *m/z*: 592, 594, 596 (M^+) (Found C, 60.45; H, 7.26. $C_{30}H_{42}Br_2O_2$ (594.47) requires C, 60.61; H, 7.12%).

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References

1 Medium-sized cyclophanes. part 76: J. Hu, R. Ueno, M. Miyazaki and T. Yamato, *J. Chem. Res.*, 2007, 408.
2 M. Pelligrin, *Recl. Trav. Chim. Pays-Bas Belg*., 1899, **18**, 458.
3 R.H. Mitchell, T.K. Vinod and G.W. Bushnell, *J. Am. Chem. Soc.,* 1985, **107**, 3340.
4 Y. Fujise, Y. Nakasato and S. Itô, *Tetrahedron Lett*., 1986, **27**, 2907.
5 (a) R.H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.,* 1974, **96**, 1547; (b) Y.-H. Lai and H.-L. Eu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 233.
6 H.A. Staab, W.R.K. Riebel and C. Krieger, *Chem. Ber.,* 1985, **118**, 1230.
7 (a) R.E. Singler and D.J. Cram, *J. Am. Chem. Soc.,* 1972, **94**, 3512; (b) D.J. Cram, R.B. Hornby, E.A. Truesdale, H.J. Reich, M.H. Delton and J.M. Cram, *Tetrahedron*, 1974, **30**, 1757.
8 T. Yamato, A. Miyazawa, K. Kobayashi, and M. Tashiro, *J. Chem. Res. (S)*, 1991, 182.
9 (a) T. Yamato, J. Matsumoto, S. Ide, K. Suehiro, and M. Tashiro, *Chem. Ber.*, 1993, **126**, 447; (b) T. Yamato, M. Sato, K. Noda, J. Matsumoto and M. Tashiro, *J. Chem. Res. (S)* 1993, 394. *(M)* 2601.
10 (a) T. Yamato, K. Fujita, K. Futatsuki and H. Tsuzuki, *Can. J. Chem.,* 2000, **78**, 1089; (b) T. Yamato, K. Fujita and H. Tsuzuki, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2089; (c) T. Yamato, S. Miyamoto, T. Hironaka and Y. Miura, *Org. Lett.,* 2005, **7**, 3.
11 (a) J.E. McMurry, M.P. Fleming, K.L. Kees and L.R. Krepski, *J. Org. Chem.*, 1978, **43**, 3255; (b) J.E. McMurry, *Acc. Chem. Res.*, 1983, **16**, 405; (c) J.E. McMurry, G.J. Haley, J.R. Matz, J.C. Clardy and G.V. Duyne, *J. Am. Chem. Soc.*, 1984, **106**, 5018; (d) J.E. McMurry, *Chem. Rev.*, 1989, **89**, 1513.
12 (a) T. Yamato, K. Fujita, K. Okuyama and H. Tsuzuki, *New. J. Chem.,* 2000, 221; (b) T. Yamato, K. Fujita, T. Abe and H. Tsuzuki, *New J. Chem*., 2001, **25**, 728.
13 T. Yamato, J. Matsumoto, M. Sato, K. Noda and M. Tashiro, *J. Chem. Soc. Perkin Trans. 1*, 1995, 1299.
14 H. -F. Grützmacher and E. Neumann, *Chem. Ber.,* 1993, **126**, 1495.
15 (a) *Cyclophanes* (P.M. Keehn and S.M. Rosenfield (eds)), Academic Press: New York, 1983, vols 1&2; (b) F. Vögtle, *Cyclophane-Chemistry*, Wiley: Chichester, 1993.
16 (a) M. Tashiro and T. Yamato, *J. Org. Chem.,* 1981, **46**, 4556; (b) M. Tashiro and T. Yamato, *J. Org. Chem*., 1983, **48**, 1461.
17 (a) M. Tashiro, T. Yamato and K. Kobayashi, *J. Org. Chem.*, 1984, **49**, 3380; (b) T. Yamato, J. Matsumoto, T. Ando, K. Tokuhisa and M. Tashiro, *J. Chem. Res. (S)*, 1991, 276.
18 S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa and T. Okamoto, *Chem. Lett*., 1987, 627.
19 T.G. Traylor, *Acc. Chem. Res.*, 1969, **2**, 152.
20 (a) M.J.S. Dewar and R.C. Fahey, *J. Am. Chem. Soc.*, 1963, **85**, 2245; (b) M.J.S. Dewar and R.C. Fahey, *J. Am. Chem. Soc.*, 1963, **85**, 2248; (c) J. Meinwald, Y.C. Meinwald and T.N. Baker, *J. Am. Chem. Soc.*, 1963, **85**, 2613.