Medium-size cyclophanes, 75[1] Synthesis of *anti*-[2.3]metacyclophan-1-ene and conversion to *syn*-1,2-epoxy[2.3]metacyclophane

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McMurry cyclisation of 1,3-bis(5-formyl-2-methoxyphenyl)propane afforded *anti*-6,13-dimethoxy[2.3]metacyclophan-1-ene, which was converted to the corresponding *syn*-1,2-epoxyl[2.3]metacyclophane by treatment of *m*-chloroperbenzoic acid.

Keywords: cyclophanes, [2.3]metacyclophan-1-ene, McMurry reaction, conformation, strained molecules, epoxidation

Although the parent [2.2]metacyclophane (MCP = metacyclophane) was first reported as early as in 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] 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]MCPs, respectively. However, reports on synthesis and reactions of *syn*-[2.*n*]MCP have not been published.

On the other hand, A. Merz *et al.* reported the stereospecific epoxidation of (*E*)- and (*Z*)-stilbene crown ethers with *m*-chloroperbenzoic acid to afford the epoxy crown ethers.[7] Oda *et al.* also reported the epoxidation of *trans*-diethylstilbestrol with *m*-chloroperbenzoic acid to afford the racemic *trans*-diethylstilbestrol oxide.[8] Thus there is substantial interest to synthesise the [2.*n*]MCP-1-enes and conversion to 1,2-epoxy[2.*n*]MCP, which can adopt the *syn*-conformation and the flexibility arising from the ring inversion can be completely restricted.

Recently, we have reported the preparation of 1,2-dimethyl[2.*n*]MCP-1-enes[9] by using the reductive coupling of carbonyl compounds by low-valent titanium, the McMurry reaction[10,11] as a key step. We now report on the synthesis of *anti*-[2.3]MCP-ene using the low-valent titanium induced McMurry reaction and conversion to *syn*-1,2-epoxy[2.3]MCP. The conformational studies of these MCPs in solution are also described.

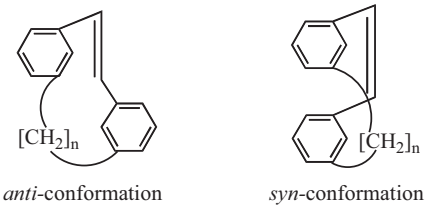
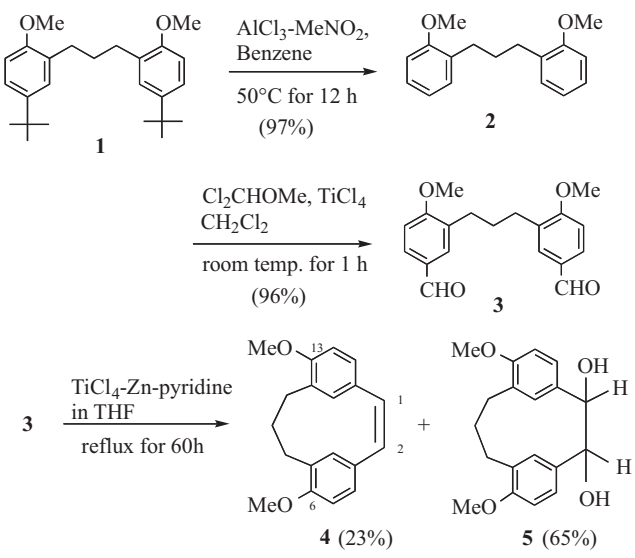


Fig. 1



Scheme 1

Results and discussion

1,3-Bis(5-*tert*-butyl-2-methoxyphenyl)propane **1** has been prepared according our previous papers.[9] The $AlCl_3$–$MeNO_2$-catalysed *trans*-*tert*-butylation of **1** in benzene at 50°C for 12 h afforded 1,3-bis(2-methoxyphenyl)propane **2** in good yield. The $TiCl_4$ formylation of compound **2** with dichloromethyl methyl ether at 20°C gave the desired 1,3-bis(5-formyl-2-methoxyphenyl)propane **3** in good yield. 1,3-Bis(2-formyl-5-*tert*-butyl-3-methoxyl)phenyl)propane (**3**) was subjected to reductive coupling by the McMurry reaction following the improved Grützmacher's procedure[12] (Scheme 1). Thus, the reductive coupling reaction of **3** carried out using $TiCl_4$–Zn in the presence of pyridine in refluxing THF under the high dilution conditions afforded the desired compound 6,13-dimethoxy[2.3]MCP-1-ene (**4**) in 23% along with 1,2-dihydroxy-6,13-dimethoxy-[2.3]MCP (**5**) in 65% yield. Surprisingly, when the present cyclisation reaction was carried out in the absence of pyridine, the yield of **4** increased to 69%. This result was quite different from that of the similar McMurry cyclisation of 1,3-bis(5-acetyl-2-methoxyphenyl)propane, which afforded the corresponding [3.1]MCP by the $TiCl_4$ or acids induced pinacol rearrangements.[9b]

The structures of **4** and **5** were elucidated based on their elemental analyses and spectral data. Especially, the mass spectral data for **4** and **5** (M^+ = 280 for **4** and 314 for **5**) strongly support the cyclic structure. The conformation of **4** was readily apparent from its ^1H NMR spectrum. Thus, the internal aromatic proton shows an upfield shift (δ 5.95 ppm) due to the ring current of the opposite benzene ring.[13] The ^1H NMR spectrum of the [2.3]MCP-1-ene **4** prepared in the present paper shows that its structure corresponds exclusively to the *anti*-conformer. In addition, the protons of the trimethylene bridge give rise to two multiplets centred at δ = 2.35 and 1.95 ppm, respectively, providing a fast interconversion of the two anti conformations of **4** by ring flipping. However, as the temperature of the solution in $CDCl_3/CS_2$ (1 : 3) is decreased, a single peak of the benzyl protons splits into two multiplets at δ 1.98 and 2.95 ppm below 10°C. The energy barrier to the conformational ring flipping estimated from the coalescence temperature (*Tc*) is 12.8 kcal mol^{-1}. We have assigned the structure of **5** in a similar fashion. Thus, the structure of the

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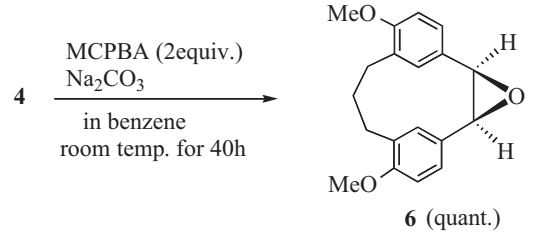
anti-confomer is also readily assigned from the chemical shift of the internal aromatic protons as a doublet at δ 4.99 (J = 2.4 Hz). The other two aromatic protons were observed at δ 6.80 and 7.21 ppm; the latter protons are in a strongly deshielding region of oxygen atom of *endo*-OH on the ethylene bridge. These observations strongly support that the two OH groups are *endo, endo*-arrangement and therefore, **5** is found to be *trans*-diol.

The epoxidation of **4** with *m*-chloroperbenzoic acid afforded the desired 1,2-epoxy[2.3]MCP **6** as a colourless oil in quantitative yield. Compound **6** was labile in solution and slowly decomposed at room temperature.

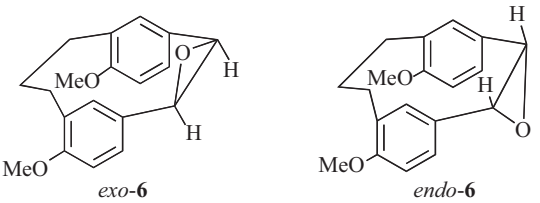
The 300 MHz ^{1}H NMR spectrum of **6** showed a doublet of the intra-annular proton H_i at δ 7.01 ppm (J = 2.0 Hz) in addition to the resonances at δ 6.28 and 6.65 ppm for the other two protons of the aromatic rings. These observations strongly suggest that its structure corresponds exclusively to the *syn*-conformation. The intra-annular proton H_i was observed at the slightly lower field (δ 7.01 ppm) than that of the corresponding *syn*-6,13-dimethoxy-1,2-dimethyl[2.3]MCP-1-ene (δ 6.95 ppm)) due to being in a deshielding region of oxygen atom of oxirane. In addition, the oxirane protons of the ethanobridge were shifted downfield about 0.8 ppm at δ 4.68 ppm in comparison with the *cis*-stilbene oxide (δ 3.88 ppm).[14] The oxirane protons might get closer into the deshielding ring current zone of the benzene rings. These findings strongly suggest the *exo*-epoxide structure of **6** and *syn*-epoxidation from *exo*-attack to the double bond of *syn*-**4** formed during the ring inversion of *anti*-**4** might be sterically favourable.

The protons of the trimethylene bridge gave rise to a complicated signal pattern as expected for a rigid *syn*-[2.3]MCP. The protons of the benzylic CH_2 group were observed as two multiplets centred at δ 2.58 and 2.90 ppm which were further split by coupling with the protons of the central CH_2 group. This central CH_2 group was also observed as two multiplets centred at δ 1.28 and 2.21 ppm. The peak pattern ascribed to six chemically distinct protons of the propano bridge proved the absence of a *syn–syn* interconversion which would exchange H_A and H_B of each CH_2 group. These findings suggest the rigid structure of 1,2-epoxy[2.3]MCP **6** at this temperature. In fact, the signals of the benzyl protons of **6** do not coalesce below 150°C in $CDBr_3$, and the energy barrier of flipping is above 25 kcal mol^{-1}. This result suggests that the introduction of oxirane ring into the ethano bridge can strongly reduce the flexibility arising from the ring inversion.



6 (quant.)

Scheme 2



exo-**6** *endo*-**6**

Fig. 2

Conclusions

We have demonstrated a convenient preparation of *anti*-6,13-dimethoxy[2.3]MCP-1-ene **4** by McMurry reaction of 1,3-bis(5-formyl-2-methoxyphenyl)propane **3**. The epoxidation of **4** with *m*-chloroperbenzoic acid afforded the desired 1,2-epoxy[2.3]MCP **6**, which adopts rigid *syn*-conformation. Further studies on the chemical properties of *syn*-1,2-epoxy-6,13-dimethoxy[2.3]MCP **6** are now in progress.

Experimental

^{1}H 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

Preparation of 1,3-bis(5-*tert*-butyl-2-methoxylphenyl)propane (**1**) was previously described.[9a]

Trans-tert-butylation of **1** *to give* **2**: To a solution of **1** (2.21 g, 6.0 mmol) in benzene (16 cm^3) was added a solution of anhydrous aluminum chloride (1.60 g, 12.0 mmol) in nitromethane (3.2 cm^3). After the reaction mixture was stirred for 12 h at 50°C, the reaction was quenched by the addition of 10% hydrochloric acid, and the solution was washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (Wako C-300, 300 g) with hexane–benzene (1:1) as eluent to give crude **2** as a colourless solid. Recrystallisation from petroleum ether gave 1,3-bis(2-methoxyphenyl)propane (**2**) (1.5 g, 97%) as colourless prisms, m.p. 63–65°C; δ_H ($CDCl_3$) 1.83–1.95 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.67 (4H, t, J = 7.8 Hz, $ArCH_2CH_2CH_2Ar$), 3.77 (6 H, s, Me), 6.79–6.88 (4H, m, Ar–*H*), 7.12–7.17 (4H, m, Ar–*H*); *m/z* 256 (M^+) (Found: C, 79.45; H, 7.58. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.86%).

Preparation of 1,3-bis(5-formyl-2-methoxyphenyl)propane (**3**): To a solution of **2** (1.15 g, 4.5 mmol) and Cl_2CHOCH_3 (1.14 cm^3, 12.6 mmol) in CH_2Cl_2 (10 cm^3) was added a solution of $TiCl_4$ (3.0 cm^3, 27.3 mmol) in CH_2Cl_2 (10 cm^3) at 0°C. After the reaction mixture was stirred at room temp. for 1 h, it was poured into a large amount of ice/water (50 cm^3) and extracted with CH_2Cl_2 (20 cm^3 × 2). 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 benzene as eluent to give **3** (1.35 g, 96%) as a colourless solid. Recrystallisation from hexane gave **3** as colourless prisms, m.p. 82–84°C; ν_{max} (KBr)/cm^{-1} 1679 (C=O); δ_H($CDCl_3$) 1.90–1.96 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.71 (4H, t, J = 7.8 Hz, $ArCH_2CH_2CH_2Ar$), 3.91 (6 H, s, O*Me*), 6.91 (2H, d, J = 7.8 Hz, Ar–*H*), 7.70 (2H, d, J = 2.0 Hz, Ar–*H*), 7.72 (2 H, dd, J = 2.0, 7.8 Hz, Ar–*H*), 9.86 (2H, s, *CHO*); *m/z* 312 (M^+) (Found C, 72.85; H, 6.55. $C_{19}H_{20}O_4$ (312.37) requires C, 73.06; H, 6.45%).

McMurry coupling reaction of **3**: The McMurry reagent was prepared from $TiCl_4$ [23.8 g (13.8 cm^3), 125 mmol] and Zn powder (18 g, 275 mmol) in dry THF (500 cm^3) under nitrogen. A solution of 1,3-bis(5-formyl-2-methoxyphenyl)propane **3** (2.81 g, 9.0 mmol) and pyridine (22.8 cm^3, 200 mmol) in dry THF (250 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 additional 8 h, cooled to room temperature, and treated with aqueous 10% K_2CO_3 (200 cm^3) at 0°C. The reaction mixture was extracted with CH_2Cl_2 (200 cm^3 × 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, 300 g) with hexane–benzene (2:1) and $CHCl_3$–EtOAc (1 : 1) as eluents to give **4** (590 mg, 23%) and **5** (1.83 g, 65%) as colourless solids.

6,13-Dimethoxy[2.3]metacyclophan-1-ene **4** was obtained as prisms (from methanol), m.p. 133–135°C; ν_{max} (KBr)/cm^{-1} 2936, 1496, 1288; δ_H($CDCl_3$) 1.93–1.98 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.35 (4H, broad s, $ArCH_2CH_2CH_2Ar$), 3.82 (6H, s, O*Me*), 5.95 (2H, d, J = 2.4 Hz, Ar–*H*), 6.58 (2H, s), 6.68 (2H, d, J = 8.2 Hz, Ar–*H*), 6.93 (2H, dd, J = 2.4, 8.2 Hz, Ar–*H*); *m/z* 280 (M^+) (Found C, 81.32; H, 7.15. $C_{19}H_{20}O_2$ (280.37) requires C, 81.40; H, 7.19%).

1,2-Dihydroxy-6,13-dimethoxy[2.3]metacyclophane **5** was obtained as prisms (from petroleum ether), m.p. 218–219°C; ν_{max} (KBr)/cm^{-1} 3563, 3327 (OH); δ_H($CDCl_3$) 1.80–1.95 (2H, m, $ArCH_2CH_2CH_2Ar$), 1.98–2.12 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.75 (2H, s, *OH*), 2.94–3.05 (2H, m, $ArCH_2CH_2CH_2Ar$), 3.86 (6H, s,

O*Me*), 4.34 (2H, s, *CH*), 4.99 (2H, d, *J* = 2.4 Hz, Ar–*H*), 6.80 (2 H, d, *J* = 7.8 Hz, Ar–*H*), 7.21 (2H, dd, *J* = 7.8, 2.1 Hz, Ar–*H*); *m/z* 314 (M^+) (Found C, 72.53; H, 7.06. $C_{19}H_{22}O_4$ (314.38) requires C, 72.59; H, 7.05%).

Epoxidation of **4** *with m-CPBA*: To a suspension of **4** (226 mg, 0.70 mmol) and $NaHCO_3$ (116 mg, 1.4 mmol) in benzene (35 cm^3) was added *m*-CPBA (350 mg, 1.4 mmol) and the mixture was stirred for 40 h. The reaction mixture was diluted with water (20 cm^3), and extracted with CH_2Cl_2 (10 $cm^3 \times 2$). The combined extracts were washed with 10% Na_2CO_3 (10 $cm^3 \times 2$) and water (10 $cm^3 \times 2$), dried with Na_2SO_4 and concentrated to give 207 mg (100%) of *syn*-1,2-epoxy-6,13-dimethoxy[2.3]metacyclophane (**6**) as colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.28 (1H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 2.21 (1H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 2.58 (2H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 2.90 (2H, m, Ar*CH*$_2$CH$_2$*CH*$_2$Ar), 3.61 (6 H, s, O*Me*), 4.68 (2H, s, *CH*), 6.28 (2H, d, *J* = 8.3 Hz, Ar–*H*), 6.65 (2H, dd *J* = 8.3, 2.0 Hz, Ar–*H*), 7.01 (2H, d, *J* = 2.0 Hz, Ar–*H*. MS *m/z*: M^+ 296. Anal. calcd. for $C_{19}H_{20}O_3$ (296.37): C 77.00, H 6.80; found: C 77.08, H 6.78.

Estimation of activation energy of ring flipping: The rate constant (k_c) of the observed conformational interconversion at the coalescence (T_c) can be calculated by using eqn (1). The free energy of activation ($\Delta G_c^{\neq}$) at coalescence can then be estimated by using Eyring equation (eqn (2)).[15]

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

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

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