Medium-size cyclophanes, 74[1] Synthesis of novel helically twisted *anti*-1,2-areno[2.*n*]metacyclophanes

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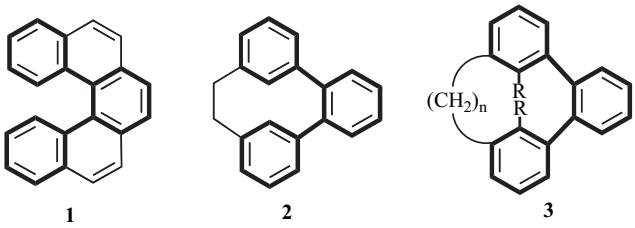
An *anti*-8,17-dimethoxy[2.3]metacyclophan-1,2-dione was converted to the corresponding helically twisted 1,2-naphtho[2.3]metacyclophane by the condensation with 1,2-phenylenediacetonitrile.

Keywords: cyclophanes, [2.*n*]metacyclophan-1,2-dione, condensation, chirality, resolutions

Understanding of the structure–chiroptics relationships of helical molecules is of theoretical and synthetic importance. Distortion of aromatic systems by disturbance of the conjugated π-electron array of conformationally rigid helicenes such as **1**[2,3] provided a useful way to gain knowledge about chiroptics of organic molecules. Recently, J. P. Gao *et al.* reported the chiroptical properties of benzo[2.2]MCP **2** (MCP = metacyclophane), which contains the structurally less rigid helically twisted *o*-terphenyl.[4] Considering the similarity in π-conjugation, it occurred to us that, if resolvable and stable, optically pure bridged *o*-terphenyl derivatives would have a high optical activity as [5]helicene **1** does. They succeeded to resolve racemic benzo[2.2]MCP **2** to the each enantiomers in high optical purity by chemical and chromatographic resolutions and studied the thermal racemisation. Although the high optical rotation ([α] = –3210 at 365 nm, 20°C), the slow racemisation (racemisation half-life time, $t_{1/2}$ = 243.4 min. at 100°C) due to the cyclophane ring inversion.[5]

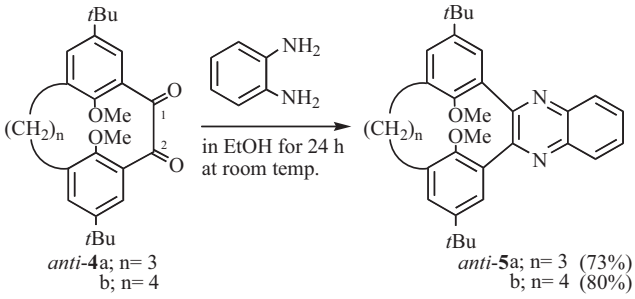
Thus, there is substantial interest to synthesise the internally substituted benzo[2.*n*]MCPs **3** having the rigid helically twisted *o*-terphenyl skeleton, in which the racemisation barriers arising from the ring inversion supposed to be very high and completely restriction can be possible.

On the other hand, we have reported the preparation of *anti*-[2.*n*]MCP-1,2-diones[6] by using the reductive coupling of carbonyl compounds by low-valent titanium, the McMurry reaction[7,8] as a key step. These compounds afforded convenient starting materials for the attempted preparation of *anti*-areno[2.*n*]MCPs. We report here on a first synthesis of chiral *anti*-areno[2.*n*]MCPs and structural properties in solution.

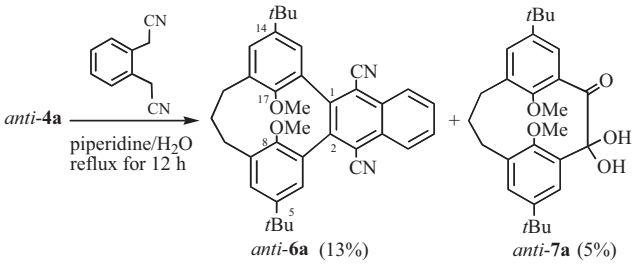


1 2 3

Fig. 1



Scheme 1



Scheme 2

Results and discussion

Preparations of *anti*-5,14-di-*tert*-butyl-8,17-dimethoxy[2.3]MCP-1,2-dione (*anti*-**4a**) and *anti*-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-1,2-dione (*anti*-**4b**) were carried out according to our previous paper[6] by using the *tert*-butyl group as a positional protective group on the aromatic ring. Reaction of diketones *anti*-**4a** and *anti*-**4b** with *o*-phenylenediamine in ethanol at room temperature for 24 h afforded in 73 and 80% the desired [2.3]- (*anti*-**5a**) and [2.4]MCP (*anti*-**5b**) having a quinoxaline skeleton.

The structures of products *anti*-**5a** and *anti*-**5b** were determined on the basis of their elemental analyses and spectral data. For example, the ^{1}H NMR spectrum of *anti*-**5a** shows internal methoxy protons as a singlet at δ 2.99 ppm and two aromatic protons as a set of doublets at δ 7.20 and 7.35 ppm (J = 2.4 Hz). The higher field shift for the methoxy protons at δ 2.99 ppm than that for *anti*-5,14-di-*tert*-butyl-8,17-dimethoxy-[2.3]MCP-1-ene (δ 3.16 ppm)[6,9] suggests the strong additional shielding effect by the quinoxaline ring introduced. Similar higher field shift was observed in *anti*-**5b** at δ 3.07 ppm in comparison with that of *anti*-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-1-ene (δ 3.24 ppm).[10] The conformations of *anti*-**5a** and *anti*-**5b** in solution are rigid and the signals of the benzylic methylene protons do not coalesce below 150°C as expected (in $CDBr_3$). The energy barriers to flipping being above 25 kcal mol^{-1}.

To resolve these 1,2-quinoxalino[2.*n*]MCP derivatives, chromatographic resolutions were attempted. Several attempted chromatographic separations for compounds *anti*-**5a** and *anti*-**5b** using a chiral column (Dicel chiralpak AD-H) failed. Only a single peak was obtained using compounds *anti*-**5** with various solvent systems and the chiral column. Therefore, we have planned to convert an *anti*-[2.3]MCP-1,2-dione *anti*-**4a** to the helically twisted *anti*-1,2-naphtho[2.3]MCP *anti*-**6a** by the condensation with 1,2-phenylenediacetonitrile.[11]

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Reaction of *anti*-**4a** with 1,2-phenylenediacetonitrile in the presence of piperidine in water under reflux for 12 h afforded the desired *anti*-1,2-naphtho[2.3]MCP *anti*-**6a** in 13% yield along with the corresponding [2.3]MCP-1-one *anti*-**7a** in 5% yield. Similar result was obtained in the presence of NaOEt under EtOH reflux for 24 h to afford *anti*-**6a** and *anti*-**7a** in 11 and 6% yields, respectively. On the other hand, when lithium diisopropylamide (LDA) in THF or 10% Bu_4NOH in EtOH at room temperature was employed, the desired product *anti*-**6a** was not obtained. Only a mixture of intractable products was obtained.

Although the detailed mechanism of formation of *anti*-5,14-di-*tert*-butyl-2,2′-dihydroxy-8,17-dimethoxy[2.3]MCP-1-one *anti*-**7a** is not clear in the present stage, one might assume the hydration of one of the carbonyl group in the 1,2-diketone occurred to release the strain of the MCP-1,2-dione structure by conversion from sp^2 carbon to sp^3 carbon at C_1 position like the hydration of [2.2]MCP-1,10-dione, which permitted the isolation of a stable dihydrate. For [2.2]MCP-1,10-dione it had been shown that the enhanced reactivity towards nucleophiles can be attributed to a relief of steric strain on rehybridisation.[12]

The structures of the products obtained in the present work were determined from their elemental analyses and spectral data. Especially, the mass spectral data for *anti*-**6a** ($M^+ = 542$) strongly supports the condensation product structure. The conformation of *anti*-**6a** was readily apparent. From its ^1H NMR spectrum the internal methoxy protons show an upfield shift due to the ring current of the opposite benzene ring.[5,13] The ^1H NMR spectrum of conformer *anti*-**6a** shows the methoxy protons at δ 3.04 ppm. The aromatic protons of conformer *anti*-**6a** are observed at δ 7.19 and 7.21 ppm. The above data show that the structure of *anti*-**6a** is the *anti*-conformer. Similar to *anti*-**5a**, the conformation of *anti*-**6a** in solution is also rigid and the signals of the benzylic methylene protons do not coalesce below 150°C in $CDBr_3$.

The ^1H NMR spectrum of *anti*-**7a** shows two internal methoxy resonances as singlets at δ 3.09, 3.18 ppm. One of the two methoxy protons is in a deshielding region of oxygen atom of *exo*-OH on the ethylene bridge. In contrast, the aromatic protons were observed as four doublets at δ 6.89, 7.08, 7.18 and 7.30 ppm, which are almost same as that for the *exo*-Br arrangement of 1-*exo*-bromo-5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP (δ 7.3 ppm).[14] Furthermore, two kinds of OH protons were observed at δ 4.15 and 5.38 ppm. The IR spectrum of *anti*-**7a** also shows two absorption peaks of the hydroxyl stretching vibration at 3476, 3402 cm^{-1} and carbonyl stretching vibration at 1715 cm^{-1}. These observations strongly suggest the structure of *anti*-**7a** as a vicinal dihydroxy ketone.

1,2-Naphtho[2.3]MCP *anti*-**6a** does adopt a helically twisted structure as shown in Fig. 2.

Chromatographic resolution using a chiral column was attempted for the present 1,2-naphthol[2,3]MCP *anti*-**6a**. As mentioned previously, compounds *anti*-**5a** and *anti*-**5b** came out as a single peak under the same chromatographic conditions using different solvent systems. Interestingly, *anti*-**6a** gave two-well-resolved peaks in the ratio of 50 : 50 as shown in Fig. 3. This finding strongly suggests the resolution of racemic *anti*-**6a** could be achieved by chromatographic separation using a chiral column.

Conclusions

In conclusion, we have succeeded for the first time to prepare a novel helically twisted *anti*-1,2-naphtho[2.3]MCP *anti*-**6a** and chromatographic resolution using a chiral column. Since the presently prepared *anti*-1,2-naphtho[2.3]MCP *anti*-**6a** was internally substituted by the methoxy groups, the racemisation barriers arising from the ring inversion supposed to be very high to lead the completely restriction. Therefore, resolved *anti*-1,2-naphtho[2.*n*]MCPs would be valuable building blocks for making optically active compounds and polymers. Further studies on the photochemical properties of 1,2-naphtho[2.*n*]MCPs are now in progress.

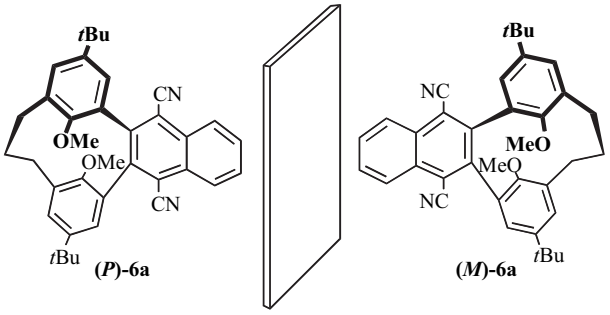

Fig. 2

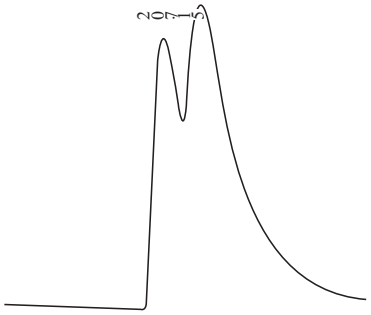

Fig. 3 Chromatogram of *anti*-**6a** (HPLC on chiral column). Daicel chiralpak AD-H. Eluent: hexane.

Experiment

^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 *anti*-5,14-di-*tert*-butyl-8,17-dimethoxy[2.3]MCP-1,2-dione (*anti*-**4a**) and *anti*-5,15-di-*tert*-butyl-8,18-dimethoxy[2.4]MCP-1,2-dione (*anti*-**4b**) were previously described.[6]

Reaction of anti-**4a** *with o-phenylenediamine*: To a solution of *anti*-**4a** (40 mg, 0.095 mmol) in ethanol (10 cm^3) was added *o*-phenylenediamine (11.3 mg, 0.104 mmol) at room temperature. After the reaction mixture had been stirred at room temp for 24 h, the solvent was evaporated *in vacuo* to leave a residue. The residue was washed successively with 10% aqueous hydrochloric acid, water, and ethanol to afford *anti*-**5a** (54 mg) as a brown solid. Recrystallisation from methanol afforded *anti*-**5a** (33 mg, 71%) as pale brown prisms, >300°C; 1.35 (18H, s, *t*Bu), 1.95 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.42–2.61(4H, m, $ArCH_2CH_2CH_2Ar$), 2.99 (6H, s, O*Me*), 7.20 (2H, d, *J* = 2.4, Ar–*H*), 7.35 (2H, d, *J* = 2.4, Ar–*H*), 7.77–7.80 (2H, m, Ar-*H*), 8.22–8.26 (2H, m, Ar–*H*); *m*/*z* 494 (M^+) (Found C, 80.19; H, 7.76; N, 5.65. $C_{33}H_{38}N_2O_2$ (494.68) requires C, 80.13; H, 7.74; N, 5.66%).

Similarly, reaction of *anti*-**4b** with *o*-phenylenediamine was carried out under the same reaction conditions described above to afford *anti*-**5b** in 80% yield as pale brown prisms, 236–237°C; 1.25–1.31 (4H, m), 1.36 (18H, s, *t*Bu), 2.08–2.13 (2H, m, $ArCH_2CH_2CH_2CH_2Ar$), 2.84–2.93 (2H, m, $ArCH_2CH_2CH_2CH_2Ar$), 3.07 (6H, s, O*Me*), 7.03 (2H, d, *J* = 2.4, Ar–*H*), 7.42 (2H, d, *J* = 2.4, Ar–*H*), 7.78–7.82 (2H, m, Ar–*H*), 8.23–8.27 (2H, m, Ar–*H*); *m*/*z* 508 (M^+) (Found C, 80.39; H, 7.85; N, 5.56. $C_{34}H_{40}N_2O_2$ (508.71) requires C, 80.28; H, 7.93; N, 5.51%).

*Reaction of anti-***4** *with 1,2-phenylenediacetonitrile***:** A solution of crude *anti*-**4a** (50 mg, 0.118 mmol), 1,2-phenylenediacetonitrile (20 mg, 0.13 mmol), piperidine (1.5 cm^3), and water (0.25 cm^3) was refluxed for 12 h. After the reaction mixture was cooled to room temperature, the solvent was evaporated *in vacuo* to leave a residue. The residue was column chromatographed over silica gel with CH_2Cl_2 as eluent to give *anti*-**6a** (8 mg, 13%) and *anti*-**7a** (3 mg, 5%) as colourless solid. Recrystallisation of from methanol gave *anti*-**6a** as light yellow prisms; m.p. 256–257°C; δ_H ($CDCl_3$) 1.35 (18H, s, *t*Bu), 1.95 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.42–2.61(4H, m, $ArCH_2CH_2CH_2Ar$), 3.04 (6H, s, O*Me*), 7.19 (2H, d, *J* = 2.4, Ar–*H*), 7.21 (2H, d, *J* = 2.4, Ar–*H*), 7.85–7.88 (2H, m, Ar–*H*), 8.45–8.49 (2H, m, Ar–*H*); *m*/*z* 542 (M^+) (Found C, 81.87; H, 7.09; N, 5.12. $C_{37}H_{38}N_2O_2$ (542.73) requires C, 81.89; H, 7.06; N, 5.16%).

*Anti-5,14-Di-tert-butyl-2,2'-dihydroxy-8,17-dimethoxy[2.3]-metacyclophane-1-one (anti-***7a***)*: Obtained as colourless prisms, m.p. 274–276°C; ν_{max} (KBr)/cm^{-1} 3476, 3402 (OH), 1715 (C=O); δ_H($CDCl_3$) 1.28 (9H, s, *t*Bu), 1.29 (9H, s, *t*Bu), 1.94–2.06 (2H, m, $ArCH_2CH_2CH_2Ar$), 2.35–2.70 (4H, m, $ArCH_2CH_2CH_2Ar$), 3.09 (3H, s, O*Me*), 3.18 (3H, s, O*Me*), 4.15 (1H, s, O*H*), 5.38 (1H, s, O*H*), 6.89 (1H, d, *J* = 2.4, Ar–*H*), 7.08 (1H, d, *J* = 2.4, Ar–*H*), 7.18 (1H, d, *J* = 2.4, Ar–*H*), 7.30 (1H, d, *J* = 2.4, Ar–*H*); *m*/*z* 422 (M^+–H_20) (Found C,73.68; H, 8.50. $C_{27}H_{36}O_5$ (440.58) requires C, 73.61; H, 8.24%).

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