Synthesis and intramolecular hydrogen bonding of *syn*-9-hydroxy-18-substituted [3.3]metacyclophanes

Kazuya Tazoe, Xing Feng, Bigyan Sharma, Shinpei Miyamoto, and Takehiko Yamato

Abstract: Various *anti*-9-methoxy[3.3]metacyclophane-2,11-diones are exclusively obtained by the coupling reaction of the corresponding 1,3-bis(bromomethyl)benzenes and 2,6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butylanisole in dimethylformamide (DMF) with an excess of sodium hydride, from which the corresponding *syn*-[3.3]metacyclophanes (MCPs) are synthesized via anti/syn-isomerization during the Wolff–Kishner reduction. Demethylation of *syn*-9-methoxy[3.3]MCPs with BBr_3 afforded the corresponding *syn*-9-hydroxy[3.3]MCPs in good yields. The existence of the strong intramolecular hydrogen bonding between the 9-hydroxy group and the 18-substituents, such as F, OH, and OMe groups at the opposing aromatic rings, are observed in solution and in the solid state. A distinct low-field shift of the phenolic OH proton was observed in the ^{1}H NMR spectrum compared with that of the 18-unsubstituted analog. Furthermore, O–H···F through-space coupling was observed.

Key words: metacyclophanes, conformation, anti/syn-isomerization, intramolecular hydrogen bonding, through-space coupling.

Résumé : Diverses *anti*-9-méthoxy[3,3]métacyclophane-2,11-diones peuvent être préparées à l'état pur par une réaction de couplage des 1,3-bis(bromométhyl)benzènes et du 2,6-bis[2-isocyano-2-(tolylsulfonyl)éthyl]-4-*tert*-butylanisole, dans le diméthylformamide (DMF), en présence d'un excès d'hydrure de sodium; ces dicétones, soumises à une réaction de Wolff–Kishner, conduisent aux *syn*[3,3]métacyclophanes (MCPs), par le biais d'une isomérisation anti/syn au cours de cette réduction. La déméthylation des *syn*-9-méthoxy[3,3]MCPs, à l'aide de BBr_3, conduit à la formation de *syn*-9-hydroxy[3,3]MCPs, avec de bons rendements. Il a été possible d'observer, tant en solution qu'à l'état solide, l'existence de fortes liaisons hydrogènes intramoléculaires entre le groupe hydroxyle en position 9 et les substituants en position 18, tels le F ou les groupes OH et OMe attachés aux noyaux aromatiques opposés. En RMN du ^{1}H, par comparaison avec l'analogue non substitué en position 18, on a observé un déplacement caractéristique à bas champ pour le proton du OH phénolique. De plus, on a observé un couplage O–H···F à travers l'espace.

Mots-clés : métacyclophanes, conformation, isomérisation anti/syn, liaison hydrogène intramoléculaire, couplage à travers l'espace.

[Traduit par la Rédaction]

Introduction

The synthesis and stereochemical aspects of conformationally mobile [3.3]MCPs (MCP = metacyclophane) have been of interest until now with particular attention[1–4] paid to dithia[3.3]MCPs, which possess an anti-stepped conformation. The pioneering work of the conformational investigation of 2,11-dithia[3.3]MCPs was reported by Vögtle and Schunder.[5] Shinmyozu et al.[6] reported the first preparation and conformational behavior in the carbocyclic [3.3]MCPs and their analogues (Fig. 1). [3.3]MCP exists in the syn geometry with a chair–chair arrangement of the trimethylene chains in the crystal state.[7–9] The preferred geometry of [3.3]MCP in solution is also a syn on the basis of the ^{1}H NMR spectrum, in which [3.3]MCP shows a strong temperature-dependent phenomenon at low temperature.[10–14]

Shinmyozu et al.[6] prepared [3.3]MCP using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) as the cyclization reagent, followed by Wolff–Kishner reduction. They made studies of syn/anti conversions in other [3.3]MCPs, especially in relation to the size of substituents such as halogens.[15] Like the parent compound, 9-halo[3.3]MCPs prefer the syn conformation, but the corresponding 2,11-diones favour the anti arrangement. Even one internal halogen substituent is sufficient to allow the isolation of a discrete syn- or anti-isomer. Although the effect on the ratio of syn- and anti-conformers of [3.3]MCPs was reported, it is still not clear what the effects are, not only properties of the internal substituents, but also having unsymmetrically substituted benzene rings arising from charge-transfer-type interactions between two benzene rings, as well as steric effects of substituents at the 6- and 15-positions.

Interestingly, all of the previously synthesized [3.3]MCPs are internally unsubstituted [3.3]MCP-2,11-diones and it is surprising that there are very few reports[16,17] on the preparation

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Fig. 1. syn- and anti-Conformers of [3.3]metacyclophane (MCP).

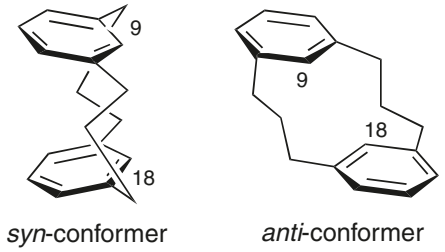
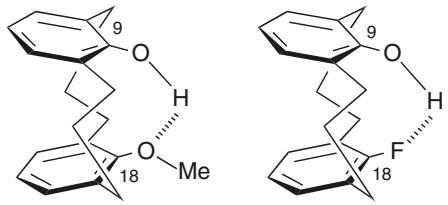


Fig. 2. Proposed intramolecular hydrogen bonding of *syn*-9-hydroxy-18-methoxy[3.3]MCP and *syn*-9-hydroxy-18-fluoro[3.3]MCP (MCP = metacyclophane).



of 9-methyl- or 9-methoxy analogues despite the fact that the chemical shift of the internal substituents, such as methyl and methoxy groups, provides a convenient probe for ^{1}H NMR studies of any possible conformational changes.

On the other hand, the cyclophane skeleton is suitable for realizing the ideal C–X (X = O, F)···H–O distance, angles, and evaluating the intramolecular hydrogen bond (Fig. 2). Especially, the C–F···H–O hydrogen bond is a new type of hydrogen bond, which was first proposed by Glusker and co-workers[18] in 1983. Following their work, research studies and discussions have been continued by many researchers who are still making efforts to confirm the hydrogen bonds using a variety of methods. Based on this speculation, we employed the cyclophane skeleton for investigating the C–F···H–O hydrogen bond. Phenol and fluorobenzene units in *syn*-9-hydroxy-18-fluoro[3.3]MCP could be fixed and close to each other. Here, we report the synthesis and stereochemical assignments of 9-methoxy-18-substituted [3.3]MCP-2,11-diones and their conversion to the corresponding 9-hydroxy-18-substituted [3.3]MCPs by Wolff–Kishner reduction followed by demethylation with BBr_3. The intramolecular hydrogen bonding between the 9-hydroxyl group and 18-substituents is also discussed.

Results and discussion

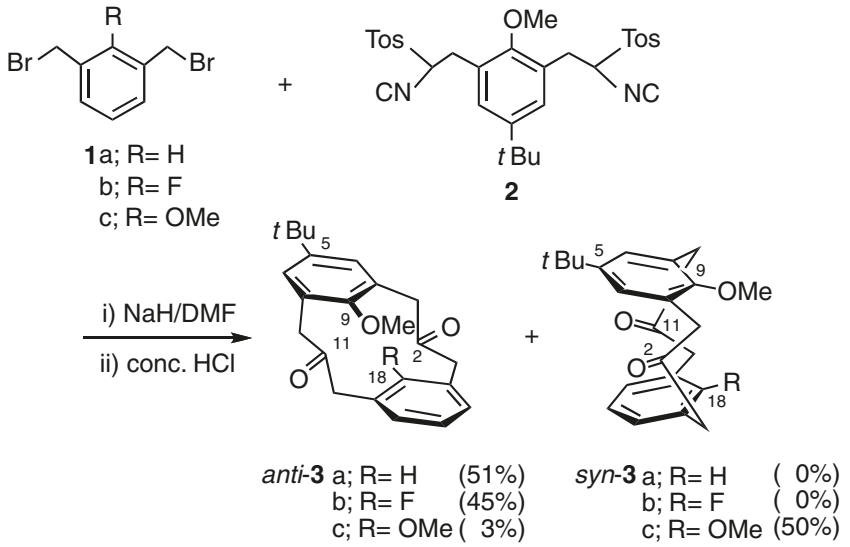
Vögtle and co-workers[19–21] reported the preparation of carbocyclic [3$_n$]MCPs using TosMIC[22,23] as the cyclization reagent, which was applied in a new cyclization procedure without phase-transfer conditions.[24–28] This strategy can be employed for the preparation of [3.3]MCP containing two benzene rings. However, the preparation of [3.3]MCPs using the TosMIC method is difficult because of its low yield as well as the difficulty of product separation from the other macrocyclic oligoketones, i.e., trimers and tetramers. Therefore, it has been very difficult to obtain sufficient amounts of the above compounds to investigate their chemical behavior.

Therefore, we selected the stepwise synthetic route, i.e., the preparation of the TosMIC adduct **2** first and then the cyclization of **2** with 1,3-bis(bromomethyl)-1-substituted benzenes **1** to prepare the desired cyclic dimer **3**. The preparation of 1,3-bis(bromomethyl)-1-substituted benzenes **1** are carried out by the treatment of 1,3-dimethyl-1-substituted benzenes with *N*-bromosuccinimide by the reported procedure.[29–31] The starting compound (2,6-bis(bromomethyl)-4-*tert*-butylanisole) was easily prepared by bromomethylation of 4-*tert*-butylanisole[32,33] using the *tert*-butyl group as a positional protecting group on the aromatic ring.[29–35] Although TosMIC adduct **2** was obtained in 78% yield by the reaction of 2,6-bis(bromomethyl)-4-*tert*-butylanisole with TosMIC as a mixture of two isomers, i.e., meso and dl, the attempted pure separation of these isomers of **2** failed. The cyclic diketones **3** were synthesized by coupling the 1,3-bis(bromomethyl)-1-substituted benzenes **1** with TosMIC adduct **2** under highly diluted conditions in DMF with an excess of sodium hydride as shown in Scheme 1. We have improved the addition procedure in Vögtle and co-workers' method.[19–21] Thus, to a suspension of NaH in DMF was dropped a solution of **1** and TosMIC adducts **2** in DMF at room temperature. This not only improves the yield of the desired ketones but also makes the handling of the base (solid NaH) easier. The ^{1}H NMR spectrum of **3** shows methoxy protons as a singlet except for diketone **3c**, which shows two kinds of methoxy protons, each as a singlet. By careful column chromatography (silica gel, Wako C-300), two conformers, *anti*-**3c** and *syn*-**3c**, were separated. They are thermally stable and do not interconvert at 150 °C in DMSO solution nor at 400 °C in the solid state.

The structures of **3** were elucidated by elemental analyses and spectral data. For instance, the mass spectral data for *anti*-**3a** (M^+ = 350) strongly supports a cyclic structure. The IR spectrum of *anti*-**3a** shows the absorption of the carbonyl stretching vibration around 1697 cm^{-1}. The ^{1}H NMR spectrum (in $CDCl_3$) of *anti*-**3a** exhibits two sets of doublets at δ 3.32 and 3.74 ppm (J = 14.2 Hz) and δ 3.33 and 3.48 ppm (J = 12.2 Hz) for the Ar*CH*$_2$CO*CH*$_2$Ar methylene protons and a singlet for the internal methoxy group at an upfield shift δ 3.33 ppm from anisole (δ 3.75 ppm) owing to the ring current of the opposing aromatic ring.[1,2,29,30,36–40] Similarly, the internal aromatic proton at the 18-position was observed at higher field, δ 5.39 ppm compared with that of the **1a** at δ 7.28 ppm. These observations strongly suggest that *anti*-**3a** adopts the anti-conformation. Similarly, the assignments of structures for other anti-conformers in *anti*-**3b** and *anti*-**3c** were readily apparent from their ^{1}H NMR spectra. Thus, upfield shifts of methoxy protons were observed at δ 3.13 ppm for *anti*-**3b** and δ 3.16 ppm for *anti*-**3c**. In contrast, the methoxy protons of *syn*-**3c** were observed at δ 3.55 and 3.56 ppm. Further, the aryl hydrogens at the 5,7-positions can clearly be seen to be shielded at δ 6.66 ppm by the adjacent ring, a common consequence of a face-to-face benzene ring.[36–45] Also the *tert*-butyl protons were observed at higher field, δ 1.12 ppm, compared with that of the *anti*-**3c** at δ 1.32 ppm owing to the strong shielding effect of the benzene ring. These observations strongly suggest that compound *syn*-**3c** adopts a syn-conformation.

Thus, the 9-methoxy analogue is exclusively formed as the anti-conformer independent of substituents R of 1,3-bis(bromomethyl)-1-substituted benzenes **1**, but the 9,18-dimethoxy

Scheme 1. Synthesis of *anti*-6-*tert*-butyl-9-methoxy-18-substituted [3.3]metacyclophane-2,11-diones **3**.



analogue **3c** is formed as a mixture of syn- and anti-conformers. Although the detailed reaction pathway of the formation of *syn*-**3c** is still not clear from the present results, one might propose the through-space interaction between the nonbonding electron pairs of the oxygen atom of both methoxy groups at the 9- and 18-positions and the opposite aromatic π-electrons, which may disfavour the formation of the anti-conformer.

The Wolff–Kishner reduction of *syn*- and *anti*-diketone **3c** afforded the desired *syn*- and *anti*-6-*tert*-butyl-9,18-dimethoxy[3.3]MCPs (**4c**) in 80% and 85% yields, respectively. No syn/anti-isomerization was observed under the reaction conditions used (Scheme 2).

In contrast, the attempted Wolff–Kishner reduction of *anti*-diketone *syn*-**3a**, carried out under the same reaction conditions as **3c**, led to *syn*-6-*tert*-butyl-9-methoxy[3.3]MCP (*syn*-**4a**) in 80% yield. No formation of the corresponding anti-conformer was observed under the reaction conditions used.

The structure of *syn*-**4a** has been elucidated by elemental analyses and spectral data. The ^{1}H NMR spectrum (in $CDCl_3$) of *syn*-**4a** exhibits a singlet at δ 3.67 ppm for the methoxy protons. Further, a singlet of the intra-annular proton H_{18} was observed at δ 7.18 ppm in addition to the resonances at δ 6.55 ppm for the 5,7-protons and at δ 6.54 and 6.73 ppm for the other three protons of the opposing aromatic rings, which clearly can be seen to be shielded by the adjacent ring, a common consequence of a face-to-face benzene ring.[36–45] Also, the *tert*-butyl protons were observed at higher field (δ 1.09 ppm) compared with that of the *anti*-**3a** at δ 1.35 ppm owing to the strong shielding effect of the benzene ring. These observations strongly suggest that compound *syn*-**4a** adopts a syn-conformation.

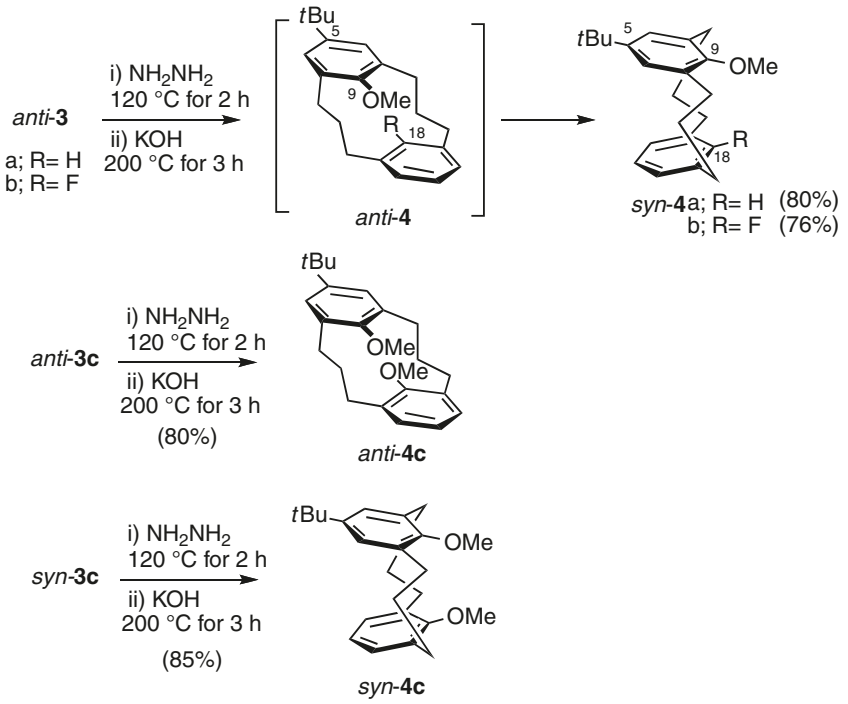
Interestingly, a similar result was obtained for the reduction of *anti*-**3b** to afford *syn*-6-*tert*-butyl-18-fluoro-9-methoxy[3.3]MCP (*syn*-**4b**) carried out under the same reaction conditions. anti/syn-Isomerization was observed under the reaction conditions used (Scheme 2). These findings strongly suggest that the ring inversion to the thermodynamically more stable syn-conformation is possible in the 9-methoxy[3.3]MCPs **4a** and **4b**.

On the other hand, as mentioned previously, we reported that *syn*-**3c** and *anti*-**3c** are thermally stable and do not interconvert at 150 °C in DMSO solution nor at 400 °C in the solid state. Although the detailed mechanistic conclusion to rationalize the present observation of anti-to-syn conversion is not clear, one might assume the similar behaviour that the [3.3]MCP exists in the syn geometry with a chair–chair arrangement of the trimethylene chains.[10]

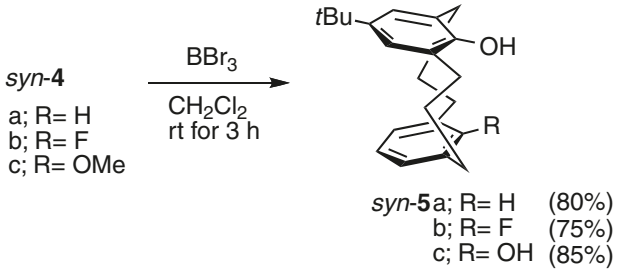
Demethylation of *syn*-9-methoxy[3.3]MCPs *syn*-**4a** and *syn*-**4b** with BBr_3 in dichloromethane affords the corresponding *syn*-9-hydroxy[3.3]MCPs *syn*-**5a** and *syn*-**5b** in 80% and 75% yields, respectively (Scheme 3). No formation of the corresponding anti-conformer was observed under the reaction conditions used. This finding suggests that the ring inversion to the thermodynamically stable anti-conformation is not possible in the 9-hydroxy[3.3]MCPs, which seem to have sufficient space for the conformational flipping as demonstrated by the molecular models. The same treatment of *syn*-9,18-dimethoxy[3.3]MCP *syn*-**4c** gives the corresponding *syn*-9,18-dihydroxy[3.3]MCP *syn*-**5c** in 85% yield.

The conformations of hydroxy[3.3]MCPs *syn*-**5** in solution, which have been prepared in the present work, are rigid and the signals of the methylene bridge do not coalesce below 130 °C in $CDBr_3$, the energy barriers to flipping being above 25 kcal mol^{-1} (1 cal = 4.184 J). The ^{1}H NMR spectrum (in $CDCl_3$) exhibits the signals for hydroxyl groups at around δ 4.61 ppm for *syn*-**5a** and at δ 4.81 ppm for *syn*-**5b**. The latter appeared as a doublet ($J_{H–F}$ = 6.6 Hz) that is coupled with the fluorine atom at the 18-position. These data show the existence of the intramolecular hydrogen bonding between two hydroxy groups among the opposing aromatic rings. The chemical shifts of the phenolic OH proton of *syn*-**5b** in $CDCl_3$ at concentrations of 1.0×10^{-1}, 1.0×10^{-2}, and 1.0×10^{-3} mol/L were the same within experimental error (δ_{OH} (*syn*-**5b**) = 4.81 ppm). Therefore, the C–F···H–O hydrogen bond is obvious in the ^{1}H NMR spectra. Moreover, specific phenomena were seen in the spectrum of *syn*-**5b**, viz., the OH signal appeared as a doublet ($J_{H–F}$ = 6.6 Hz), which shows the through-space coupling with the fluorine atom. By irradiation of the F atom, the coupling

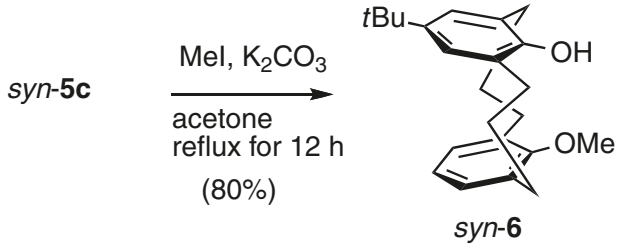
Scheme 2. Synthesis of *syn*- and *anti*-6-*tert*-butyl-9-methoxy-18-substituted [3.3]metacyclophanes **4**.



Scheme 3. Demethylation of *syn*-9-methoxy[3.3]metacyclophanes (*syn*-**4**) with BBr_3.



Scheme 4. O-Methylation of *syn*-6-*tert*-butyl-9,18-dihydroxy[3.3] metacyclophane (*syn*-**5c**).



disappeared and the doublet became a singlet. Furthermore, in a donating solvent such as [D_6]DMSO, the signal appeared as a singlet. This is further evidence of an O–H···F interaction.

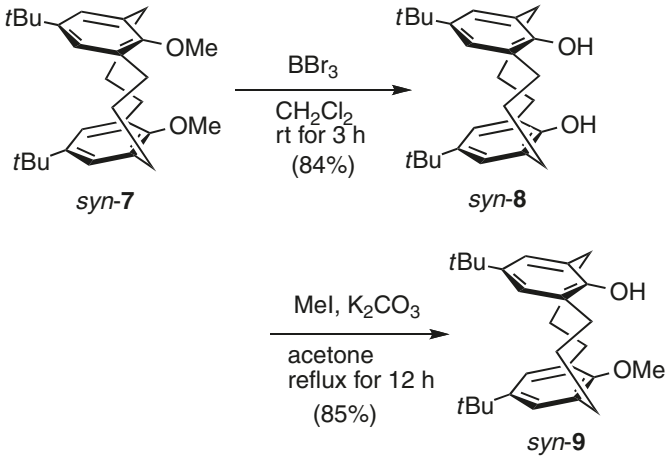
On the other hand for *syn*-9,18-dihydroxy[3.3]MCP (*syn*-**5c**), the signals of the OH protons were not observed clearly in $CDCl_3$ nor in benzene-d_6, different from those of *syn*-**5a** and *syn*-**5b**. This phenomena seems to be due to the faster exchange of intramolecular hydrogen bonding between unsymmetrical hydroxyl groups than NMR time scale. To studythe intramolecular hydrogen bonding of *syn*-**5c** in more detail, we attempted introduction of a methyl group to the one of the hydroxyl groups of *syn*-**5c**. Thus, reaction of *syn*-**5c** with methyl iodide was carried out in the presence of potassium carbonate in acetone reflux for 12 h. We succeeded in the preparation of the mono-O-methylation product *syn*-**6** in 80% yield (Scheme 4). The chemical shift of the phenolic OH proton of *syn*-**6** in $CDCl_3$ was observed at a lower magnetic field at δ 6.81 ppm owing to the intramolecular hydrogen bonding between 18-methoxy groups.

We have also carried out a similar partial O-methylation of the corresponding *syn*-6,15-di-*tert*-butyl-9,18-dihydroxy[3.3]MCP (*syn*-**8**; Scheme 5), which was prepared by demethylation of *syn*-6,15-di-*tert*-butyl-9,18-dimethoxy[3.3]MCP (*syn*-**7**)[46] with BBr_3, to afford the compound *syn*-**9** in 85% yield. Similarly, a distinct low-field shift of the phenolic OH proton was observed in the ^{1}H NMR spectrum of *syn*-**9** (δ 7.04 ppm) compared to that of the OMe-free analog *syn*-**5a** (δ 4.61 ppm).

Conclusions

Various anti-9-substituted [3.3]MCP-2,11-diones were exclusively obtained by the coupling reaction of the corresponding 1,3-bis(bromomethyl)-1-substituted benzenes **1** and 2,6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butylanisole **2** in DMF with an excess of sodium hydride. In the case of the coupling reaction of 1,3-bis(bromomethyl)anisole **1c** with **2**, a mixture of *anti*-**3c** and *syn*-**3c** was obtained owing to the repulsive interaction between the unshared electrons of the methoxy groups at the 9- and 18-positions and the opposite aromatic π-electrons, which may disfavour the formation of *anti*-**3c**. The corresponding *syn*-[3.3]MCPs *syn*-**4** were synthesized via anti/syn-isomerization by the Wolff–Kishner reduction. Demethylation of *syn*-9-methoxy[3.3] MCPs *syn*-**4** with BBr_3 afforded the corresponding *syn*-hydroxy[3.3]MCPs *syn*-**5** in good yields. The existence of

Scheme 5. O-Methylation of *syn*-6,15-di-*tert*-butyl-9,18-dihydroxy [3.3]metacyclophane (*syn*-**8**).



the strong intramolecular hydrogen bonding between the 9-hydroxy group and the 18-substituents at the opposing aromatic rings, such as the F atom and the OMe group, were observed in solution and in the solid state. Actually, evidence for the C–F···H–O hydrogen bond was obtained from the results of the crystallographic analysis. In the ^{1}H NMR spectrum, the O–H bond signal of *syn*-**5b** appears at a lower field than that of the fluorine-free analog *syn*-**5a**. Furthermore, through-space coupling between the F atom and the OH proton is observed. Similarly, a distinct lowfield shift of the phenolic OH proton was observed in the ^{1}H NMR spectrum of *syn*-**9** compared with that of the OMe-free analog *syn*-**5a**. Further studies on the chemical properties of *syn*-9-hydroxy-18-substituted [3.3]MCPs *syn*-**5**, *syn*-**6**, and *syn*-**9** are now in progress.

Experimental

All melting points are uncorrected. ^{1}H NMR spectra were recorded on a Nippon Denshi JEOL FT-300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Nippon Denshi JIR-AQ2OM mass spectrometer at an ionization energy of 70 eV using a direct-inlet system through GLC; the *m*/*z* values reported include the parent ion peak. IR spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Elemental analyses were performed by Yanaco MT-5. GLC analyses were performed on a Shimadzu GC (GC-14A); silicone OV-1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}.

Materials

2,6-Bis(bromomethyl)-4-*tert*-butylanisole was prepared using the reported procedure.[32,33] The preparations of 1,3-bis(bromomethyl)-1-substituted benzenes (**1a**–**1c**) have been previously described.[47,48] *syn*-6,15-Di-*tert*-butyl-9,18-dimethoxy[3.3]metacyclophane (*syn*-**7**) was prepared using the reported procedure.[46]

Preparation of the TosMIC adduct 2 — Typical procedure

To a mixture of 20% aqueous NaOH (40 mL) and CH_2Cl_2 (50 mL) was added *n*-Bu_4NI (700 mg, 1.9 mmol) followed by a solution of TosMIC (8 g, 41 mmol) in CH_2Cl_2 (50 mL). After the reaction, the mixture was stirred at room temperature for 30 min and then a solution of 2,6-bis(bromomethyl)-4-*tert*-butylanisole (4.0 g, 11 mmol) in CH_2Cl_2 (50 mL) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with water (100 mL), and was extracted with CH_2Cl_2 (3 × 100 mL). It was washed with water (100 mL), dried with Na_2SO_4, and concentrated in vacuo to leave a residue. To this residue methanol (100 mL) was added and the mixture was left overnight in the refrigerator to give 4.97 g (78%) of 2,6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butylanisole (**2**) as pale brown prisms (hexane), mp 150–151 °C. ν_{max} (KBr, cm^{-1}): 2134 (CN). δ_H ($CDCl_3$): 1.26, 1.27 (9H, each s, *t*-Bu), 2.49, 2.50 (6H, each s, *Me*), 2.87, 2.99 (2H, each dd, J = 11.7, 13.7 Hz, *CH*$_2$), 3.66, 3.77 (2H, each dd, J = 2.9, 13.7 Hz, *CH*$_2$), 3.76, 3.80 (3H, each s, *OMe*), 4.73, 4.83 (2H, each dd, J = 2.9, 11.7 Hz, *CH*), 7.19, 7.20 (2H, each s, Ar-*H*), 7.44, 7.46 (4H, d, J = 8.3 Hz, Ar-*H*), 7.87, 7.93 (4H, d, J = 8.3 Hz, Ar-*H*). *m*/*z*: 578 (M^+). Anal. calcd for $C_{31}H_{34}N_2O_5S_2$ (578.75): C 64.34, H, 5.92, N 4.84); found: C 64.56, H 5.87, N 4.73.

Stepwise cyclization of TosMIC adduct 2 and dibromide 1a

To a suspension of NaH (2.1 g, 51 mmol) in DMF (150 mL) a solution of **2** (4.7 g, 8.5 mmol) and **1a** (5.0 g, 8.5 mmol) in DMF (35 mL) was added dropwise over a period of 6 h. After the suspension was stirred for an additional 5 h at room temperature, it was quenched with ice water (300 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water (200 mL), dried with Na_2SO_4, and concentrated in vacuo to 15 mL. Concentrated HCl (15 mL) was added and the solution was stirred for 15 min. The organic layer was again extracted with CH_2Cl_2 (3 × 100 mL), washed with water (2 × 100 mL), dried with Na_2SO_4, and concentrated and condensed under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give crude *anti*-**3a** as a pale yellow solid. Recrystallization from methanol afforded *anti*-6-*tert*-butyl-9-methoxy[3.3]metacyclophane-2,11-dione (*anti*-**3a**, 1.52 g, 51%) as colourless prisms (MeOH), mp 110–111 °C. ν_{max} (KBr, cm^{-1}): 1698 (C=O). δ_H ($CDCl_3$): 1.35 (9H, s, *t*-Bu), 3.32 (2H, d, J = 14.2 Hz, *CH*$_2$), 3.33 (3H, s, O*Me*), 3.33 (2H, d, J = 12.2 Hz, *CH*$_2$), 3.48 (2H, d, J = 12.2 Hz, *CH*$_2$), 3.74 (2H, d, J = 14.2 Hz, *CH*$_2$), 5.55 (1H, s, Ar-*H*), 7.05–7.10 (3H, m, Ar-*H*), 7.25 (2H, s, Ar-*H*). *m*/*z*: 350 (M^+). Anal. calcd for $C_{23}H_{26}O_3$ (350.46): C 78.83, H 7.48; found: C 78.71, H 7.48.

Similarly, compound *anti*-**3b** was obtained in 45% yield.

anti-6-*tert*-Butyl-9-furuoro-18-methoxy[3.3]metacyclophane-2,11-dione (*anti*-**3b**) was obtained as colourless prisms (MeOH), mp 109–111 °C. ν_{max} (KBr, cm^{-1}): 1697 (C=O). δ_H ($CDCl_3$): 1.25 (9H, s, *t*-Bu), 3.13 (3H, s, OMe), 3.20 (4H, d, J = 14.9 Hz, *CH*$_2$), 3.67 (4H, d, J = 14.9 Hz, *CH*$_2$), 6.89 (1H, t, J = 6.0 Hz, Ar-*H*), 7.06 (2H, t, J = 7.2 Hz, Ar-*H*), 7.12 (2H, s, Ar-*H*). *m*/*z*: 368 (M^+). Anal. calcd. for $C_{23}H_{25}FO_3$ (368.44): C 74.98, H 6.84; found: C 74.64, H 7.00.

Stepwise cyclization of TosMIC adduct 2 and dibromide 1c

To a suspension of NaH (2.1 g, 51 mmol) in DMF (150 mL) a solution of **2** (4.7 g, 8.5 mmol) and **1c** (5.0 g, 8.5 mmol) in DMF (35 mL) was added dropwise over a

period of 6 h. After the suspension was stirred for an additional 5 h at room temperature, it was quenched with ice water (300 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water (200 mL), dried with Na_2SO_4, and concentrated in vacuo to 15 mL. Concentrated HCl (15 mL) was added, and the solution was stirred for 15 min. The organic layer was extracted again with CH_2Cl_2 (3 × 100 mL), washed with water (2 × 100 mL), dried with Na_2SO_4, and concentrated and condensed under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as the eluent to give crude *anti*-**3c** as a pale yellow solid. The anti:syn ratio was determined as 5:95 by the ^{1}H NMR spectrum. The residue was chromatographed on silica gel using $CHCl_3$ as the eluent to give crude *anti*-**3c** and *syn*-**3c** as a pale yellow solid and a pale yellow oil, respectively. Recrystallization from hexane afforded *anti*-**3c** (96 mg, 3%). Crude *syn*-**3c** was again chromatographed on silica gel using $CHCl_3$ as the eluent to afford 1.62 g (50%) of *syn*-**3c** as a pale yellow oil.

anti-6-*tert*-Butyl-9,18-dimethoxy[3.3]metacyclophane-2,11-dione (*anti*-**3c**) was obtained as colourless prisms (hexane), mp 198–199 °C. ν_{max} (KBr, cm^{-1}): 1685 (C=O). δ_H ($CDCl_3$): 1.32 (9H, s, *t*-Bu), 3.16 (6H, s, O*Me*), 3.23 (4H, d, J = 14.6 Hz, CH_2), 3.60 (2H, d, J = 14.6 Hz, CH_2), 3.63 (2H, d, J = 14.6 Hz, CH_2), 6.93–6.99 (1H, m, Ar-*H*), 7.17 (2H, s, Ar-*H*) and 7.16–7.18 (2H, m, Ar-*H*). *m*/*z*: 380 (M$^+$). Anal. calcd for $C_{24}H_{28}O_4$ (380.49): C 75.75, H 7.42; found: C 75.56, H 7.54.

syn-6-*tert*-Butyl-9,18-dimethoxy[3.3]metacyclophane-2,11-dione (*syn*-**3c**) was obtained as a pale yellow oil. ν_{max} (NaCl, cm^{-1}): 1688 (C=O). δ_H ($CDCl_3$): 1.12 (9H, s, *t*-Bu), 3.32 (4H, d, J = 12.7 Hz, CH_2), 3.55 (3H, s, O*Me*), 3.56 (3H, s, O*Me*), 4.30 (4H, d, J = 12.7 Hz, CH_2), 6.48–6.54 (1H, m, Ar-*H*), 6.66 (2H, s, Ar-*H*), 6.65–6.68 (2H, m, Ar-*H*). *m*/*z*: 380 (M$^+$). Anal. calcd for $C_{24}H_{28}O_4$ (380.49): C 75.76, H 7.42; found: C 75.62, H 7.35.

Wolff–Kishner reduction of anti-*3a*

A mixture of *anti*-**3a** (1.20 g, 3.42 mmol), KOH (1.28 g, 23.0 mmol), 100% hydrazine hydrate (0.35 mL, 6.2 mmol), and triethylene glycol (3 × 50 mL) was heated at 120 °C for 2 h and then at 220 °C for 3 h. The cooled mixture was poured into water (50 mL), acidified with diluted HCl, extracted with CH_2Cl_2 (3 × 50 mL), washed with water (2 × 20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane/benzene (1:1) as the eluent to give crude *syn*-**4a** as a colourless solid. Recrystallization from MeOH afforded *syn*-6-*tert*-butyl-9-methoxy[3.3]metacyclophane (*syn*-**4a**), which was obtained as colourless prisms (882 mg, 80%), mp 112–114 °C. δ_H ($CDCl_3$): 1.09 (9H, s, *t*-Bu), 1.70–1.82 (2H, m, CH_2), 2.30–2.37 (2H, m, CH_2), 2.47–2.76 (6H, m, CH_2), 3.00–3.09 (2H, m, CH_2), 3.67 (3H, s, O*Me*), 6.54 (2H, d, J = 7.0 Hz, Ar-*H*), 6.55 (2H, s, Ar-*H*), 6.73 (1H, t, J = 7.0 Hz, Ar-*H*), 7.18 (1H, s, Ar-*H*). *m*/*z*: 322 (M$^+$). Anal. calcd for $C_{23}H_{30}O$ (322.49): C 85.66, H 9.38; found: C 85.65, H 9.39.

Compounds *syn*-**4b** and *syn*-**4c** were similarly prepared in 76% and 85% yield, respectively.

syn-6-*tert*-Butyl-9-furuoro-18-methoxy[3.3]metacyclophane (*syn*-**4b**) was obtained as colourless prisms (MeOH), mp 146–148 °C. δ_H ($CDCl_3$): 1.06 (9H, s, *t*-Bu), 1.69–1.82 (2H, m, CH_2), 2.25–2.53 (6H, m, CH_2), 2.88–3.12 (4H, m, CH_2), 3.47 (6H, s, O*Me*), 6.41–6.50 (5H, m, Ar-*H*). *m*/*z*: 340 (M$^+$). Anal. calcd for $C_{23}H_{29}FO$ (340.49): C 81.14, H 8.59; found: C 81.21, H 8.70.

syn-6-*tert*-Butyl-9,18-dimethoxy[3.3]metacyclophane (*syn*-**4c**) was obtained as colourless prisms (hexane), mp 82–84 °C. δ_H ($CDCl_3$): 1.15 (9H, s, *t*-Bu), 1.81–1.89 (2H, m, CH_2), 2.45–2.52 (6H, m, CH_2), 3.03–3.13 (4H, m, CH_2), 3.48 (3H, s, O*Me*), 3.49 (3H, s, O*Me*), 6.48–6.56 (5H, m, Ar-*H*). *m*/*z*: 352 (M$^+$). Anal. calcd for $C_{24}H_{32}O_2$ (352.52): C 81.77, H 9.15; found: C 81.58, H 9.11.

Wolff–Kishner reduction of anti-*3c*

A mixture of *anti*-**3c** (1.20 g, 3.3 mmol), KOH (1.28 g, 23.0 mmol), 100% hydrazine hydrate (0.35 mL, 6.2 mmol), and triethylene glycol (3 × 50 mL) was heated at 120 °C for 2 h and then at 220 °C for 3 h. The cooled mixture was poured into water (50 mL), acidified with diluted HCl, extracted with CH_2Cl_2 (3 × 50 mL), washed with water (2 × 20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane/benzene (1:1) as the eluent to give crude *anti*-**4c** as a colourless solid. Recrystallization from hexane afforded *anti*-6-*tert*-butyl-9,18-dimethoxy[3.3]metacyclophane (*anti*-**4c**) was obtained as colourless prisms (930 mg, 80%), mp 220–222 °C. δ_H ($CDCl_3$): 1.34 (9H, s, *t*-Bu), 2.05–2.15 (4H, m, CH_2), 2.31–2.42 (4H, m, CH_2), 2.57–2.69 (4H, m, CH_2), 3.10 (3H, s, O*Me*), 3.15 (3H, s, O*Me*), 6.85–6.88 (1H, m, Ar-*H*), 6.95–6.87 (4H, m, Ar-*H*). *m*/*z*: 352 (M$^+$). Anal. calcd for $C_{24}H_{32}O_2$ (352.52): C 81.77, H 9.15; found: C 81.69, H 9.04.

Reaction of syn-*4a with* BBr_3

To a solution of *syn*-**4a** (60 mg, 0.186 mmol) in CH_2Cl_2 (6 mL) at 0 °C was gradually added a solution of BBr_3 (0.087 mL, 0.922 mmol) in CH_2Cl_2 (0.1 mL). After the reaction mixture had been stirred at room temperature for 3 h, it was poured into ice water (10 mL) and then extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo to leave a residue. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane/$CHCl_3$ (4:1) as the eluent to give crude *syn*-**5a** as a colourless solid. Recrystallization from MeOH afforded *syn*-6-*tert*-butyl-9-hydroxy[3.3]metacyclophane (*syn*-**5a**) was obtained as a brown oil (46 mg, 80%). ν_{max} (NaCl, cm^{-1}): 3424 (OH). δ_H ($CDCl_3$): 1.03 (9H, s, *t*-Bu), 1.72–1.81 (2H, m, CH_2), 2.25–2.32 (2H, m, CH_2), 2.42–2.52 (2H, m, CH_2), 2.54–2.56 (2H, m, CH_2), 2.59–2.68 (2H, m, CH_2), 2.81–2.90 (2H, m, CH_2), 4.61 (1H, s, *OH*), 6.46 (2H, s, Ar-*H*), 6.48 (2H, d, J = 6.0 Hz, Ar-*H*), 6.72 (1H, t, J = 6.0 Hz, Ar-*H*). *m*/*z*: 308 (M$^+$). Anal. calcd for $C_{22}H_{28}O$ (308.46): C 85.66, H 9.15; found: C 85.56, H 9.31.

Compounds *syn*-**5b** and *syn*-**5c** were similarly prepared in 75% and 85% yield, respectively.

syn-6-*tert*-Butyl-18-furuoro-9-hydroxy[3.3]metacyclophane (*syn*-**5b**) was obtained as a pale yellow oil. ν_{max} (NaCl, cm^{-1}): 3354 (OH). δ_H ($CDCl_3$): 1.13 (9H, s, *t*-Bu), 1.80–1.92 (2H, m, CH_2), 2.33–2.43 (2H, m, CH_2), 2.52–2.65 (2H, m, CH_2), 2.52–2.65 (2H, m, CH_2), 2.95–3.01 (4H, m, CH_2), 4.81 (1H,

d, J = 6.6 Hz, *OH*), 6.49–6.98 (5H, m, Ar-*H*). *m/z*: 326 (M^+). Anal. calcd for $C_{22}H_{27}FO$ (326.46): C 80.94, H 8.34; found: C 80.76, H 8.35.

syn-6-*tert*-Butyl-9,18-dihydroxy[3.3]metacyclophane (*syn*-**5c**) was obtained as colourless prisms (hexane), mp 80–82 °C. ν_{max} (KBr, cm^{-1}): 3210 (OH). δ_H ($CDCl_3$): 1.15 (9H, s, *t*-Bu), 1.81–1.89 (2H, m, CH_2), 2.45–2.52 (6H, m, CH_2), 3.03–3.13 (4H, m, CH_2), 6.48–6.56 (5H, m, Ar-*H*). *m/z*: 324 (M^+). Anal. calcd $C_{22}H_{28}O_2$ (324.47): C 81.44, H 8.7; found: C 81.58, H 8.9.

O-Methylation of syn-*6-*tert-*butyl-9,18-dihydroxy[3.3] metacyclophane (*syn-*5c) in the presence of potassium carbonate*

A mixture of *syn*-**5c** (81 mg, 0.25 mmol) and potassium carbonate (86.4 mg, 1.25 mmol) in dry acetone (16 mL) was heated at reflux for 1.5 h under nitrogen. Then methyl iodide (0.16 mL, 2.5 mmol) was added and the mixture was heated at reflux for 6 h. After cooling of the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a colourless oil, which was then chromatographed over silica gel (Wako, C-300; 100 g) with hexane/benzene (1:1) as the eluent to give a colourless solid, which was recrystallized from MeOH to afford *syn*-6-*tert*-butyl-9-hydroxy-18-methoxy[3.3]metacyclophane (*syn*-**6**) as colourless prisms (76 mg, 80%), mp 44–46 °C. ν_{max} (KBr, cm^{-1}): 3354 (OH). δ_H ($CDCl_3$): 1.11 (9H, s, *t*-Bu), 2.21–2.28 (4H, m, CH_2), 2.58–2.65 (4H, m, CH_2), 2.86–2.97 (4H, m, CH_2), 6.40–6.53 (3H, m, Ar-*H*), 6.60 (2H, s, Ar-*H*), 6.81 (1H, s, *OH*). *m/z*: 338 (M^+). Anal. calcd for $C_{23}H_{30}O_2$ (338.49): C 81.61 H 8.93; found: C 81.43, H 8.81.

Demethylation of syn-*6,15-di-*tert-*butyl-9,18-dimethoxy[3.3] metacyclophane (*syn-*7) with BBr_3*

To a solution of *anti*-**7**[46] (200 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) at 0 °C was gradually added a solution of BBr_3 (1.0 mL, 10.6 mmol) in CH_2Cl_2 (1 mL). After the reaction mixture had been stirred at room temperature for 3 h, it was poured into ice water (20 mL), extracted with CH_2Cl_2 (2 × 10 mL), washed with water (2 × 10 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude *syn*-**8** as a colourless solid. Recrystallization from methanol afforded 156 mg (84%) of *syn*-6,15-di-*tert*-butyl-9,18-dihydroxy[3.3] metacyclophane (*syn*-**8**). *syn*-**8** was obtained as colourless prisms (MeOH), mp 166–167 °C. ν_{max} (KBr, cm^{-1}): 3439 (OH). δ_H ($CDCl_3$): 1.11 (18H, s), 2.21–2.28 (4H, m), 2.58–2.65 (4H, m), 2.86–2.97 (4H, m), 5.30 (2H, s, OH), 6.62 (4H, s). *m/z*: 380 (M^+). Anal calcd for $C_{26}H_{36}O_2$ (380.58): C 82.06, H 9.53; found: C 82.33, H 9.51.

Compounds *syn*-**9** was similarly prepared in 85% yield by O-methylation of *syn*-**8** in the presence of potassium carbonate under the same conditions as *syn*-**5c**.

syn-6,15-Di-*tert*-butyl-9-hydroxy-18-methoxy[3.3]metacyclophane (*syn*-**9**) was obtained as colourless prisms (MeOH/$CHCl_3$, 1:1), mp 170–171 °C. ν_{max} (KBr, cm^{-1}): 3345 (OH). δ_H ($CDCl_3$): 1.11 (18H, s, *t*-Bu), 2.23–2.31 (4H, m, CH_2), 2.50–2.64 (4H, m, CH_2), 2.98–3.28 (4H, m, CH_2), 3.65 (3H, s, O*Me*), 6.54 (2H, s, Ar-*H*), 6.63 (2H, s, Ar-*H*), 7.04 (1H, s, *OH*). *m/z*: 394 (M^+). Anal calcd for $C_{27}H_{38}O_2$ (394.6): C 82.18, H 9.71; found: C 82.45, H 9.50.

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