Synthesis and conformational studies of 9-substituted [3.3]metacyclophane-2,11-diones and conversion to the corresponding [3.3]metacyclophanes

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Various *anti*-9-substituted [3.3]MCP-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*-butylbenzenes in dimethylformamide (DMF) with an excess of sodium hydride, from which the corresponding *syn*-[3.3]MCP are synthesised *via anti-syn*-isomerisation during the Wolff–Kishner reduction.

Keywords: metacyclophanes, cyclisation, conformation, CH–π–interaction, Wolff–Kishner reduction, *anti-syn*-isomerisation

The synthesis and stereochemical aspects of conformationally mobile [3.3]MCPs (MCP = metacyclophane) have been of interest for the past decade, with particular attention[1-3] 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 *et al.*[4] Shinmyozu and his co-workers[5] have reported the first preparation and conformational behaviour in the carbocyclic [3.3]MCPs and their analogues. [3.3]MCP exists in the *syn* geometry with a chair–chair arrangement of the trimethylene chains in the crystal state. The preferred geometry of [3.3]MCP in solutionis also a *syn* on the basis of ^{1}H NMR spectrum, in which [3.3]MCP shows strong temperature-dependent phenomenon at low temperature.[6–10]

Shinmyozu and co-workers[5] prepared [3.3]MCP using (*p*-tolylsulfonyl)methylisocyanide (TosMIC) as the cyclisation reagent, followed by Wolff–Kishner reduction. They have studied *syn-anti* conversions in other [3.3]MCPs, especially in relation to the size of the substituents such as halogens.[11] 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.

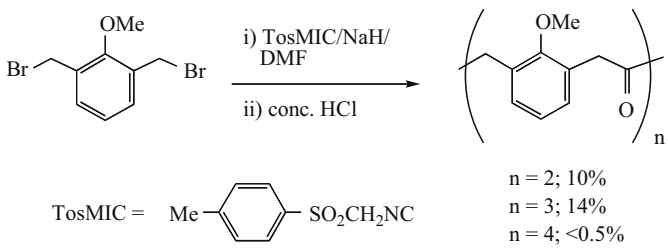
All of the previous compounds are internally unsubstituted [3.3]MCP-2,11-diones and it is surprising that there are very few reports[12,13] on the preparation of 9-methyl- or 9-methoxy-analogues despite the fact that the chemical shift of the internal substituents, such as methyl and methoxy group provides a convenient probe for ^{1}H NMR studies of any possible conformational changes. We report here the synthesis and stereochemical assignments of 9-substituted [3.3]MCP-2,11-diones and conversion to the corresponding [3.3]MCPs by Wolff–Kishner reduction. The substituent effects on the formation of the *syn*- and *anti*-conformations are discussed.

Results and discussion

Vögtle reported[14–17] the preparation of carbocyclic [3$_n$]MCPs using TosMIC[18,19] as the cyclisation reagent, which was applied in a new cyclisation procedure without phase-transfer conditions.[20-24]

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 the product separation from the other macrocyclic oligoketones, *i.e.* trimer and tetramer. Therefore, it has been very difficult to obtain sufficient amounts of the above compounds to investigate their chemical behaviour.

Therefore, we have selected the stepwise cyclisation of TosMIC adduct **2** with 1,3-bis(bromomethyl)-5-substituted benzenes **3** to prepare the desired cyclic dimer **4**. The starting compounds, 2,6-bis(bromomethyl)-4-*tert*-butyl-1-substituted benzenes **1**, are easily prepared by bromomethylation of 4-*tert*-butyltoluene and 4-*tert*-butylanisole[25] using the *tert*-butyl group as a positional protecting group on the aromatic ring.[26–32] Although TosMIC adduct **2a** and **2b** were obtained in 77 and 78% yields by the reaction of **1a** and **1b** with TosMIC as a mixture of two isomers, *i.e. meso* and *dl*, the attempted separation of these isomers of **2** pure failed. The preparation of 1,3-bis(bromomethyl)-5-substituted benzenes **3** are carried out by the treatment of 1,3-dimethyl-5-substituted benzenes with *N*-bromosuccinimide as following the reported procedure.[28,30] The cyclic diketones **4** were synthesised by coupling the 1,3-bis(bromomethyl)-5-substituted benzenes **3** with TosMIC adduct **2** under highly diluted conditions in DMF with an excess of sodium hydride as shown in Scheme 2. We have improved the addition procedure in Vögtle's



Scheme 1

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method.[14–17] Thus, to a suspension of NaH in DMF a solution of **3** and TosMIC adducts **2** was added dropwise 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 **4** shows methoxy protons as a singlet except diketone **4d**, which shows two kinds of methoxy protons, each as a singlet. By careful column chromatography (silica gel, Wako C-300), two isomers, *anti*-**4d** and *syn*-**4d**, are separated. They are thermally stable and do not interconvert at 150 °C in DMSO solution and at 400 °C in the solid state.

The structures of **4** have been elucidated by elemental analyses and spectral data. For instance, the mass spectral data for *anti*-**4d** (M^+ = 364) strongly supports a cyclic dimeric structure. The IR spectrum of *anti*-**4d** shows the absorption of the carbonyl stretching vibration around 1697 cm^{-1}. The ^{1}H NMR spectrum (in $CDCl_3$) of *anti*-**4d** exhibits two sets of doublets at δ = 3.28, 3.76 ppm (J = 15.0 Hz) and δ = 3.40, 3.45 ppm (J = 13.2 Hz) for the ArCH_2COCH_2Ar methylene protons and a singlet for the internal methoxy group at an upfield shift δ = 3.36 ppm from anisole (δ = 3.75 ppm) due to the ring current of the opposing aromatic ring.[26-28,33-38] Similarly, the internal aromatic proton at 18-position was observed at a higher field, δ 5.39 ppm compared to that of the **3b** at δ 7.28 ppm. These observations strongly suggest that compound *anti*-**4d** adopts the *anti*-conformation.

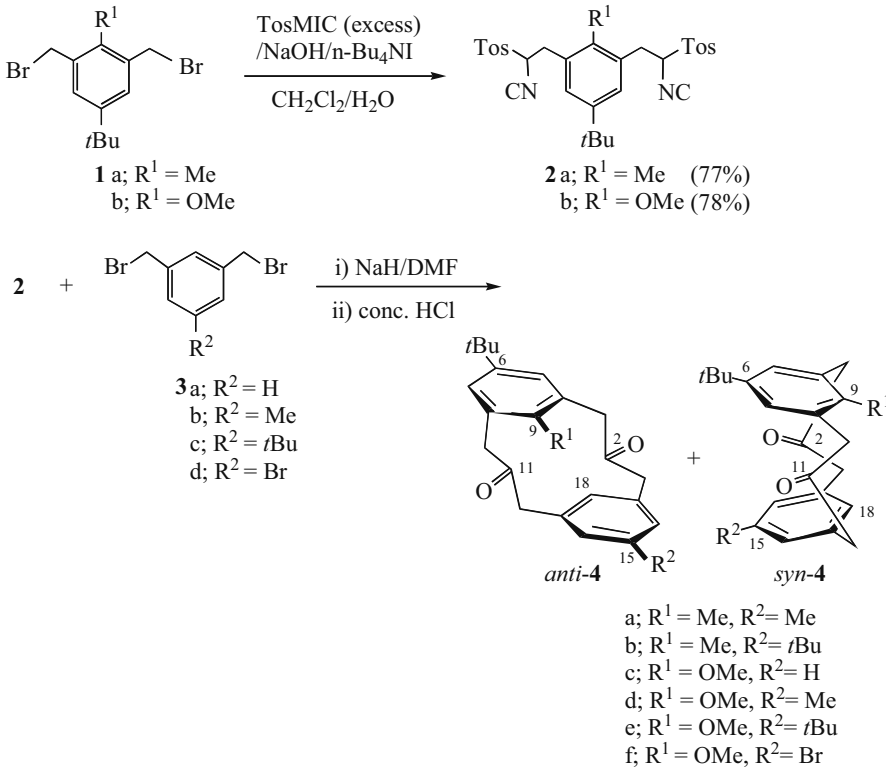
In contrast, the methoxy proton of *syn*-**4d** is observed at δ 3.63 ppm. Furthermore, the aryl hydrogens at 5,7-positions can clearly be seen to be shielded at δ 6.61 ppm by the adjacent ring, a common consequence of a face-to-face benzene ring.[33–43] Also the *tert*-butyl protons was observed at higher field, δ 0.89 ppm compared to that of the *anti*-**4d** at δ 1.34 ppm due to the strong shielding effect of the benzene ring. These observations strongly suggest that compound *syn*-**4d** adopts *syn*-conformation. Similarly, the assignments of structures for other *anti* conformers were readily apparent from their ^{1}H NMR spectra. The chemical shifts (δ) of the internal methoxy protons, the internal protons at the 18-position, the protons of substituent at 15 position, aromatic protons and the *tert*-butyl protons of *anti*-9-substituted [3.3]MCP-2,11-diones *anti*-**4a–f** and *syn*-6-*tert*-butyl-9-methoxy-15-methyl[3.3]MCP-2,11-dione *syn*-**4d** are compiled in Table 2.

Thus 9-substituted analogue is exclusively formed in the *anti*-conformer independent on R^1 of 2,6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butyl-1-substituted benzenes **2** and R^2 of 1,3-bis(bromomethyl)-5-substituted benzenes **3**, but only 9-methoxy-15-methyl analogue **4d** is formed in a mixture of *syn*- and *anti*-conformers. These findings suggest that in the case of 9-methyl analogue the aromatic π–π interaction of two opposite benzene rings and the steric crowdness by the bulky *tert*-butyl group at the external positions 6 and 15 may inhibit the formation of the *syn*-conformer in the [3.3]MCP-2,11-diones system, Furthermore, the CH–π interaction[44-51] between 9-methyl group and the opposite aromatic π-electrons

Table 1 *Anti*-to-*syn* ratios in TosMIC cyclisation of **2** with **3**

Substrate		Product yield/%[a]	Isomer distribution/%[b]	
2(R^1)	**3**(R^2)		*anti*	*syn*
Me	Me	**4a** (48)	100	0
Me	*t*Bu	**4b** (53)	100	0
OMe	H	**4c** (72)	100	0
OMe	Me	**4d** (71)	60	40
OMe	*t*Bu	**4e** (72)	100	0
OMe	Br	**4f** (50)	100	0

[a]Isolated yields. [b]*anti*-to-*syn* ratios determined by ^{1}H NMR spectroscopy at 20 °C



Scheme 2

Table 2 ^{1}H NMR spectral data of 6-*tert*-butyl-9-substituted [3.3]MCP-2,11-diones 4[a]

Compound	R^1 protons		H_{18}	R^2 protons		Benzene protons	*tert*-Butyl protons
anti-**4a**	Me	0.94	4.80	Me	2.14	6.86, 7.29	1.37
anti-**4b**	Me	0.97	4.94	*t*Bu	1.24	7.15, 7..5	1.24
anti-**4c**	OMe	3.34	5.54	H	7.06[b]	7.10, 7.20	1.35
anti-**4d**	OMe	3.36	5.39	Me	2.22	6.84, 7.36	1.34
anti-**4e**	OMe	3.26	5.29	*t*Bu	2.27	7.08, 7.19	1.36
anti-**4f**	OMe	3.40	5.58	Br	–	7.18, 7.19	1.34
syn-**4d**	OMe	3.63	7.22	Me	1.91	6.61, 6.97	0.89

[a]Determined in $CDCl_3$ by using $SiMe_4$ as a reference and expressed in ppm given.
[b]Midpoint value of multiplet.

may also favour the formation of *anti*-conformer in the process of the cyclisation reaction. The CH–π interaction involving aliphatic CH moieties is well documented[44] as either a conformation-controlling intramolecular process or a crystal-structure controlling intermolecular force, especially for inclusion complexes of calixarene derivatives.[45-51]

Although in the case of 9-methoxy analogue the detailed reaction pathway of the formation of *syn*-**4d** is still not clear from the present results, one might propose the CH–π interaction between the methyl group at 15 position and the opposite aromatic π-electrons, which may increase the formation of the *syn*-conformer during the present coupling reaction in spite of being the through-space interaction between the non-bonding electron pairs of the oxygen atom of the methoxy group and the opposite aromatic π-electrons of the *anti*-conformer, which may disfavour the formation of the latter.

The Wolff–Kishner reduction of *syn*-diketone *syn*-**4d** afforded the desired *syn*-6,15-di-*tert*-butyl-9,18-dimethoxy[3.3]MCP (*syn*-**5d**) in 85% yield. No formation of the corresponding *anti*-conformer has been observed under the reaction conditions used.

The structure of *syn*-**5d** has been elucidated by elemental analyses and spectral data. The ^{1}H NMR spectrum (in $CDCl_3$) of *syn*-**5d** exhibits a singlet at δ 3.63 ppm for the methoxy protons. Furthermore, a singlet of the intra-annular proton H_{18} at δ 6.94 ppm in addition to the resonances at δ 6.26 and 6.48 ppm for the other two protons of the aromatic rings which can clearly be seen to be shielded by the adjacent ring, a common consequence of a face-to-face benzene ring.[33-38] Also the *tert*-butyl protons and methyl protons were observed at higher field, δ 1.03 and 1.96 ppm compared to those of the *anti*-**4d** at δ 1.34 and 2.22 ppm due to the strong shielding effect of the benzene ring. These observations strongly suggest that compound *syn*-**5d** adopts *syn*-conformation.

Interestingly, similar results were obtained in the case of reduction of *anti*-**4c**–**e** to afford *syn*-**5c**–**e** carried out under the same reaction conditions. *anti*-*syn*-Isomerisation was observed under the reaction conditions used (Scheme 3). These findings strongly suggest that the ring inversion to the thermodynamically more stable *syn*-conformation is possible in the 9-methoxy[3.3]MCPs **5c**–**e**.

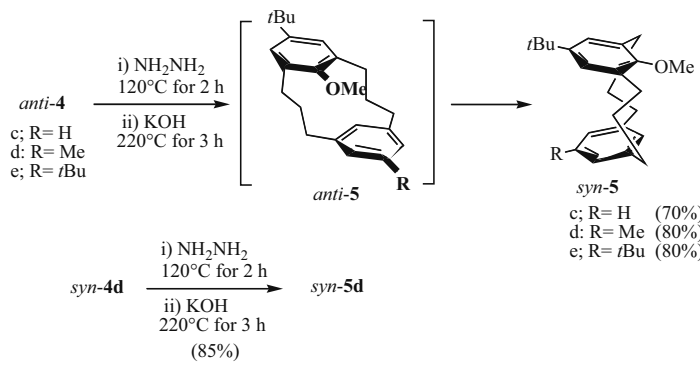
On the other hand, as mentioned previously we have reported that *syn*-**4d** and *anti*-**4d** are thermally stable and do not interconvert at 150 °C in DMSO solution and at 400 °C in the solid state. Although the detailed mechanistic conclusion to rationalise the present observation of *anti*-to-*syn*-conversion 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.[5]

Conclusions

Various *anti*-9-substituted [3.3]MCP-2,11-diones are exclusively obtained by the coupling reaction of the corresponding 2,6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butylbenzenes **2** and 1,3-bis(bromomethyl)-5-substituted benzenes **3** in dimethylformamide (DMF) with an excess of sodium hydride. In the case of the coupling reaction of *2,*6-bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butylanisole **2b** with 1,3-bis(bromomethyl)-5-methylbenzene **3b** a mixture of *anti*-**4d** and *syn*-**4d** was obtained due to the CH–π interaction between the methyl group at 15-position and the opposite aromatic π-electrons, which may favour the formation of *syn*-**4d**. Further studies on the chemical properties of the two conformers *syn*- and *anti*-**4** and **5** are now in progress.

Experimental

All melting points are uncorrected. ^{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-HX110A ultrahigh performance mass spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5.



Scheme 3

Materials

2,6-Bis(bromomethyl)-4-*tert*-butyltoluene (**1a**) and 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**1b**) were prepared by the reported procedure.[25,52] The preparations of 1,3-bis(bromomethyl)-5-substituted benzenes (**3a**–**d**) were previously described.[28,30]

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 mixture was stirred at room temperature for 30 min, a solution of dibromide **1a** (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 left overnight in the refrigerator to give 2,6-bis [2-isocyano-2-(tolylsulfonyl)ethyl]-4-*tert*-butyltoluene (**2a**) (4.90 g, 77%) as pale brown prisms, m.p. 176 °C (dec.); ν_{max} (KBr)/cm^{-1} 2135 (CN); δ_H ($CDCl_3$) 1.26, 1.27 (9H, s, *t*Bu), 2.26, 2.27 (3H, s, *Me*), 2.50 (6H, s, *Me*), 3.00–4.52 (6H, m, CH_2, *CH*), 7.16 (2H, s, Ar*H*), 7.46 (4H, d, *J* = 8.3 Hz, Ar*H*) and 7.92 (4H, d, *J* = 8.3 Hz, Ar*H*); *m/z* 562 (M^+) (Found: C, 65.95; H, 6.06; N, 4.73. $C_{31}H_{34}N_2O_4S_2$ (562.75) requires C, 66.17; H, 6.09; N, 4.98%).

Compound **2b** was similarly prepared in 78% yield.

2,6-Bis[2-isocyano-2-(tolylsulfonyl)ethyl]-4-tert-butylanisole (**2b**): Pale brown prisms (hexane), m.p. 150–151 °C (dec.); 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*) and 7.87, 7.93 (4H, d, *J* = 8.3 Hz, Ar*H*); *m/z* 578 (M^+) (Found: C, 64.56; H, 5.87; N, 4.73. $C_{31}H_{34}N_2O_5S_2$ (578.75) requires C, 64.34; H, 5.92; N, 4.84%).

Stepwise cyclisation of TosMIC adduct **2** *and dibromide* **3**; *typical procedure*

To a suspension of NaH (2.1 g, 51 mmol) in DMF (150 mL) a solution of **2b** (4.7 g, 8.5 mmol) and **3b** (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. Conc. 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 *anti*-to-*syn* ratio was determined as 60 : 40 by ^1H NMR spectrum. The residue was chromatographed on silica gel using $CHCl_3$ as eluents to give crude *anti*-**4d** and *syn*-**4d** as a pale yellow solid, respectively. Recrystallisation from hexane afforded *anti*-**4d** (965 mg, 31%) and *syn*-**4d** (712 mg, 23%), respectively.

anti-6-tert-Butyl-9-methoxy-15-methyl[3.3]metacyclophane-2,11-dione (*anti*-**4d**): Colourless prisms (hexane), m.p. 98–100 °C.; ν_{max} (KBr)/cm^{-1} 1697 (C=O); δ_H ($CDCl_3$) 1.34 (9H, s, *t*Bu), 2.22 (3H, s, *Me*), 3.28 (2H, d, *J* = 15.0 Hz, CH_2), 3.36 (3H, s, O*Me*), 3.40 (2H, d, *J* = 13.2 Hz, CH_2), 3.45 (2H, d, *J* = 13.2 Hz, CH_2), 3.76 (2H, d, *J* = 15.0 Hz, CH_2), 5.39 (1H, s, Ar*H*), 6.84 (2H, s, Ar*H*) and 7.36 (2H, s, Ar*H*); *m/z* 364 (M^+) (Found: C, 78.86; H, 7.68. $C_{24}H_{28}O_3$ (364.49) requires C, 79.09; H, 7.74%).

syn-6-tert-Butyl-9-methoxy-15-methyl[3.3]metacyclophane-2,11-dione (*syn*-**4d**): Colourless prisms (hexane), m.p. 172–174 °C; ν_{max} (KBr)/cm^{-1} 1706 (C=O); δ_H ($CDCl_3$) 0.89 (9H, s, *t*Bu), 1.91 (3H, s, *Me*), 3.02 (2H, d, *J* = 13.7 Hz, CH_2), 3.21 (2H, d, *J* = 13.6 Hz, CH_2), 3.55 (2H, d, *J* = 13.7 Hz, CH_2), 3.63 (3H, s, O*Me*), 3.74 (2H, d, *J* = 13.6 Hz, CH_2), 6.61 (2H, s, Ar*H*), 6.97 (2H, s, Ar*H*) and 7.22 (1H, s, Ar*H*); *m/z* 364 (M^+) (Found: C, 78.96; H, 7.63. $C_{24}H_{28}O_3$ (364.49) requires C, 79.09; H, 7.74%).

Compounds *anti*-**4a**–**c** and *anti*-**4e**–**f** were similarly prepared. The yields are listed in Table 1.

anti-6-tert-Butyl-9,15-dimethyl[3.3]metacyclophane-2,11-dione (*anti*-**4a**): Colourless prisms (hexane), m.p.148–151 °C; ν_{max} (KBr)/cm^{-1} 1699 (C=O); δ_H ($CDCl_3$) 0.94 (3H, s, *Me*), 1.37 (9H, s, *t*Bu), 2.14 (3H, s, *Me*), 3.25 (2H, d, *J* = 11.3 Hz, CH_2), 3.46 (2H, d, *J* = 16.5 Hz, CH_2), 3.53 (2H, d, *J* = 11.3 Hz, CH_2), 3.62 (2H, d, *J* = 16.5 Hz, CH_2), 4.80 (1H, s, Ar*H*), 6.86 (2H, s, Ar*H*) and 7.29 (2H, s, Ar*H*); *m/z* 348 (M^+) (Found: C, 82.84; H, 8.06. $C_{24}H_{28}O_2$ (348.49) requires C, 82.72; H, 8.1%).

anti-6,15-Di-tert-butyl-9-methyl[3.3]metacyclophane-2,11-dione (*anti*-**4b**): Colourless prisms (hexane), m.p. 144–147 °C; ν_{max} (KBr)/cm^{-1} 1699 (C=O); δ_H ($CDCl_3$) 0.97 (3H, s, *Me*), 1.24 (18H, s, *t*Bu), 3.39 (2H, d, *J* = 11.6 Hz, CH_2), 3.50 (2H, d, *J* = 16.5 Hz, CH_2), 3.61 (2H, d, *J* = 11.6 Hz, CH_2), 3.67 (2H, d, *J* = 16.5 Hz, CH_2), 4.94 (1H, s, Ar*H*), 7.15 (2H, s, Ar*H*) and 7.35 (2H, s, Ar*H*); *m/z* 390 (M^+) (Found: C, 83.28; H, 8.65. $C_{27}H_{34}O_2$ (390.57) requires C, 83.03; H, 8.77%).

anti-6-tert-Butyl-9-methoxy[3.3]metacyclophane-2,11-dione (*anti*-**4c**): Colourless prisms (MeOH), m.p. 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*) and 7.25 (2H, s, Ar*H*); *m/z* 350 (M^+) (Found: C, 78.71; H, 7.48. $C_{23}H_{26}O_3$ (350.46) requires C, 78.83; H, 7.48%).

anti-6,15-Di-tert-butyl-9-methoxy[3.3]metacyclophane-2,11-dione (*anti*-**4e**): Colourless prisms (hexane), m.p. 142–144 °C; ν_{max} (KBr)/cm^{-1} 1688 (C=O); δ_H ($CDCl_3$) 1.27 (9H, s, *t*Bu), 1.36 (9H, s, *t*Bu), 3.26 (3H, s, O*Me*), 3.29 (2H, d, *J* = 15.6 Hz, CH_2), 3.39 (2H, d, *J* = 13.7 Hz, CH_2), 3.51 (2H, d, *J* = 13.7 Hz, CH_2), 3.73 (2H, d, *J* = 15.6 Hz, CH_2), 5.29 (1H, s, Ar*H*), 7.08 (2H, s, Ar*H*) and 7.19 (2H, s, Ar*H*); *m/z* 406 (M^+) (Found: C, 79.75; H, 8.47. $C_{27}H_{34}O_3$ (406.57) requires C, 79.77; H, 8.43%).

anti-6-tert-Butyl-15-bromo-9-methyl[3.3]metacyclophane-2,11-dione (*anti*-**4f**): Colourless prisms (hexane), m.p. 137–139 °C; ν_{max} (KBr)/cm^{-1} 1699 (C=O); δ_H ($CDCl_3$) 1.34 (9H, s, *t*Bu), 3.34 (2H, d, *J* = 15.1 Hz, CH_2), 3.40 (3H, s, O*Me*), 3.45 (2H, d, *J* = 13.2 Hz, CH_2), 3.65 (2H, d, *J* = 13.2 Hz, CH_2), 3.81 (2H, d, *J* = 15.1 Hz, CH_2), 5.58 (1H, s, Ar*H*), 7.18 (2H, s, Ar*H*) and 7.19 (2H, s, Ar*H*); *m/z* 428, 430 (M^+) (Found: C, 64.48; H, 5.65. $C_{23}H_{25}BrO_3$ (429.36) requires C, 64.34; H, 5.87%).

Wolff–Kishner reduction of **5**; *typical procedure*

A mixture of *anti*-**4d** (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, and 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 eluents to give crude *syn*-**5d** as a colourless solid. Recrystallisation from hexane afforded *syn*-6-*tert*-butyl-9-methoxy-18-methyl[3.3]metacyclophane (*syn*-**5d**) (886 mg, 80%) as colourless prisms, m.p. 90–92 °C; δ_H ($CDCl_3$) 1.03 (9H, s, *t*Bu), 1.63–1.68 (2H, m, CH_2), 1.96 (3H, s, *Me*), 2.21–2.29 (2H, m, CH_2), 2.39–2.66 (4H, m, CH_2), 2.90–3.02 (2H, m, CH_2), 3.55–2.68 (2H, m, CH_2), 3.60 (3H, s, O*Me*), 6.26 (2H, s, Ar*H*), 6.48 (2H, s, Ar*H*) and 6.94 (1H, s, Ar*H*); *m/z* 336 (M^+) (Found: C, 85.79; H, 9.52. $C_{24}H_{32}O$ (336.52) requires C, 85.66; H, 9.58%).

Compounds *syn*-**5c** and *syn*-**5e** were similarly prepared in 70 and 80% yields, respectively.

syn-6-tert-Butyl-9-methoxy[3.3]metacyclophane (*syn*-**5c**): Colourless prisms (MeOH), m.p. 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*) and 7.18 (1H, s, Ar*H*); *m/z* 322 (M^+) (Found: C, 85.65; H, 9.39. $C_{23}H_{30}O$ (322.49) requires C, 85.66; H, 9.38%).

syn-6,15-Di-tert-butyl-9-methoxy[3.3]metacyclophane (*syn*-**5e**): Colourless oil; δ_H ($CDCl_3$) 1.06 (9H, s, *t*Bu), 1.14 (9H, s, *t*Bu), 2.25–2.38 (4H, m, CH_2), 2.48–2.65 (4H, m, CH_2), 2.61–2.73 (4H, m, CH_2), 3.66 (3H, s, O*Me*), 6.57 (2H, s, Ar*H*), 6.58 (2H, s, Ar*H*) and 7.10 (1H, s, Ar*H*); *m/z* 378 (M^+) (Found: C, 85.36; H, 9.99. $C_{27}H_{38}O$ (378.6) requires C, 85.66; H, 10.12%).

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