# Direct introduction of bromine onto the bridged methylene of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]metacyclophane[a]

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Treatment of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]metacyclophane **1** with 1,3-dibromo-5,5-dimethylhydantoin (DBMH) in $CH_2Cl_2$ led to the first successful introduction of bromine onto the bridged methylene group.

**Keywords:** cyclophanes, bromination, 1,3-dibromo-5,5-dimethylhydantoin, dihydropyrene, Swern oxidation, cyclophane ketone

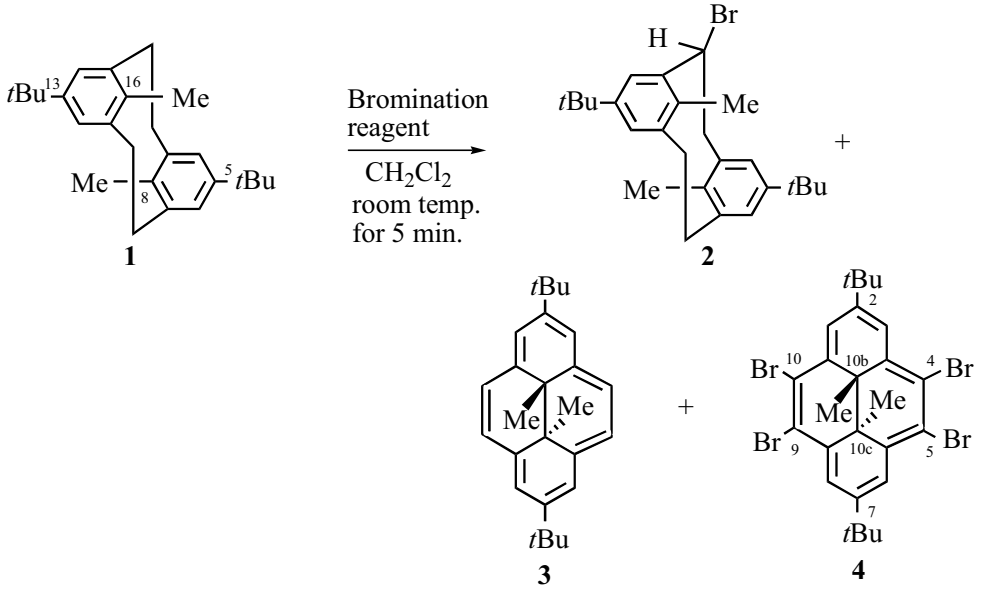
For many years various research groups have been attracted by the chemistry and spectral properties of the [2.2]MCP ([2.2]MCP = [2.2]metacyclophane) skeleton.[2] Its conformation, which was elucidated by X-ray measurements,[3] is frozen into a chair-like non-planar form. Many attempts have been made to introduce functional groups directly into the methylene groups of [2.2]MCPs, but these have failed because of the deviation of the benzyl carbon atom from the plane of the benzene ring.[2,4] We previously reported[5] the first successful introduction of a chlorine onto the methylene groups of 8,16-dimethyl[2.2]MCP involving the reaction of 8,16-dimethyl[2.2]MCP with iodine monochloride.

However, we have not yet succeeded introducing substituents into the methylene groups of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP **1** because of novel transannular reactions arising from the electronic interaction between the two benzene rings, the proximity of the 8,16-positions and the release of the considerable strain energy to form the more stable annulene π-electron system, 10b,10c-dihydropyrene. Recently, we reported the direct photochemical introduction of acetoxy groups onto the bridged methylenes of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP **1**.[6] However, this method was not suitable for the introduction functional groups to the bridged methylenes of 8,16-dimethyl[2.2]MCPs. We undertook the present work in order to extend the novel reaction mentioned above. We now report that treatment of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP **1** with DBMH (DBMH = 1,3-dibromo-5,5-dimethylhydantoin)[7] in $CH_2Cl_2$ led to the first successful introduction of bromine into the methylene group and the formation of the corresponding [2.2]MCP-1-one.

## Results and discussion

Attempted bromination of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP **1**[8] with 0.28 equiv. of DBMH (two atoms of bromine are available) in methylene dichloride at room temperature for 5 min led to bromination at the bridged methylene to afford **2** in 51% yield along with the recovery of the starting compound in 45% yield. Interestingly, when bromination of **1** with 0.55 equiv. of DBMH was carried out under the same reaction conditions, the yield of mono bromination product **2** increased to 83% yield along with a small amount of 2,7-di-*tert*-butyl-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene **3** and 2,7-di-*tert*-butyl-4,5,9,10-tetrabromo-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene **4**.[9] The yield of tetrabrominated product **4** increased with increasing amounts DBMH. Finally in the case of 3.1 equiv. of DBMH only compound **4** was obtained in 98% yield.

Similar treatment of **1** with 1.1 equiv, of BTMA $Br_3$ (BTMA $Br_3$ = benzyltrimethylammonium tribromide)[10] carried out under the same reaction conditions described above afforded the desired 1-bromo[2.2]MCP **2** in 68% yield along with an 18% recovery of the starting material in spite of prolonging the reaction time from 5 min to 1 h. This result indicated




**Scheme 1**

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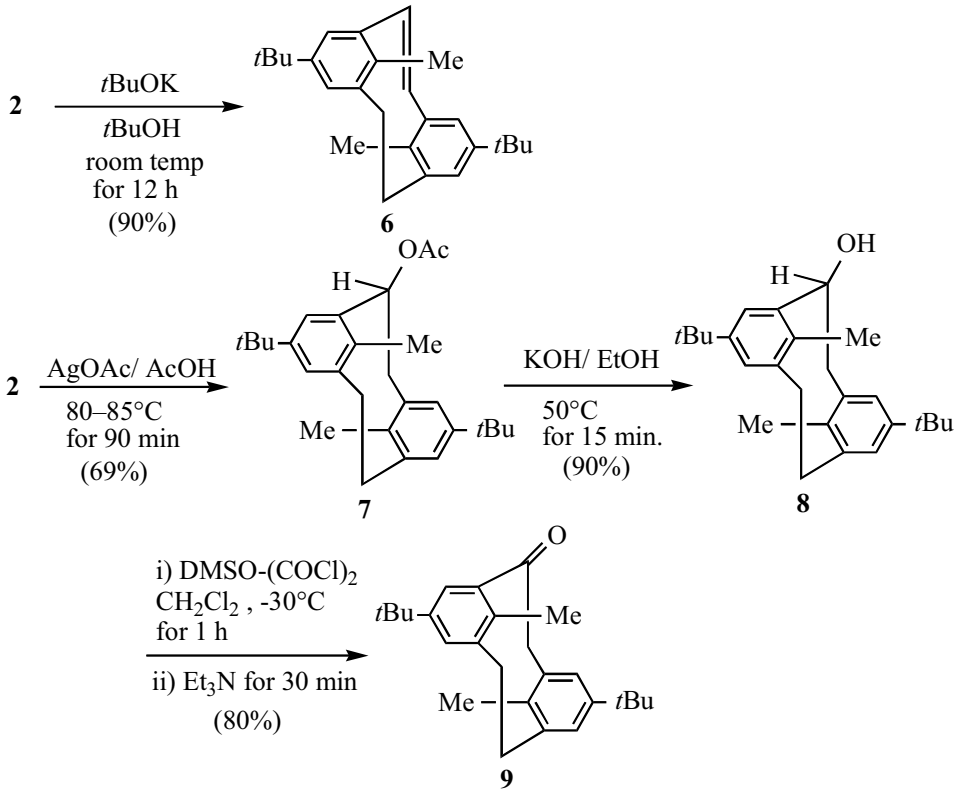
[a] Medium-sized cyclophanes. Part 70.




**Scheme 2**

that DBMH is a more reactive bromination reagent than BTMA $Br_3$ in the present bromination reaction at the bridged methylene of [2.2]MCP **1**.

Although the detailed mechanism of the formation of **2** is not clear in the present results, compound **2** may be an intermediate of the formation of dihydropyrenes **3** and **4** in the present bromination of **1**. In fact, when the compound **2** was treated with 3.1 equiv. of DBMH under the same conditions, tetrabromodihydropyrene **4** was obtained via dihydropyrene **3** in almost quantitative yield.

The structures of the products obtained in the present work were determined from their elemental analyses and spectral data. The structure of **2** was elucidated based on its elemental analysis and spectral data. The mass spectrum of **2** strongly supports the monobrominated structure. The $^1$H NMR spectrum of **2** shows two internal methyl resonances as singlets at δ 0.50, 0.97 ppm and a bridge methine signal as a double doublet ($J$ = 2.4, 6.1 Hz) at δ 5.62 ppm. One of the two methyl protons is in a strongly deshielding region of bromine atom of *exo*-Br on the ethylene bridge resulting in a much larger downfield shift (δ 0.97 ppm) than that of the other one (δ 0.50 ppm). In contrast, the aromatic protons were observed as doublets at δ 7.06, 7.20 and 7.36 ppm, which are almost same as that for the *exo*-Cl arrangement of 1-*exo*-5,13-trichloro-8,16-dimethyl[2.2]MCP (δ 7.0–7.3 ppm).[5] A deshielded aromatic proton due to the *endo*-Br atom on the ethylene bridge was not observed.

When compound **2** was treated with *t*BuOK in *tert*-butyl alcohol, the corresponding MCP-1-ene **6** was obtained in 90% yield. It was also found that acetolysis of **2** with silver acetate in acetic acid at 80–85°C for 90 min afforded the corresponding acetate **7** with complete retention of configuration in 69% yield. On the basis of the spectral data and the chemical conversions, compound **2** is assigned the structure, 1-*exo*-bromo-5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP.

It was also found that acetate **7** was easily converted to the corresponding alcohol **8** by hydrolysis with alcholic KOH at 50°C for 15 min. in almost quantitative yield. Attempted oxidation of alcohol **8** with pyridinium chlorochromate[11] carried out in a methylene dichloride solution at room temparature for 1 h failed. An intractable mixture of products due to ring cleavage was obtained. Fortunately, Swern oxidation[12] of **8** succeeded in affording the desired [2.2]MCP-1-one **9** in 80% yield.

In conclusion, although the detailed mechanism of formation of **2** is not clear in the present stage, it is concluded that the present novel bromination with DBMH leds to the first direct introduction of bromo group into the methylene group of [2.2]MCP **1**. The preparation of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP-1-one **(9)** from **1** through **2** appears to be a usuful route to [2.2]MCP-1-one derivatives. Studies of the scope and limitation of the route are in progress.

## Experiment

All m.p.s are uncorrected. NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference: $J$-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 spectrometer at 75 eV using a direct-inlet system through GC. VPC analyses were performed by a Shimadzu gas chromatograph, GC-14A; Silicone OV-1, 2 m; programmed temperature rise, 12°C min$^{-1}$; carrier gas nitrogen, 25 cm$^3$ min$^{-1}$.

*Materials*

Preparation of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP (**1**)[8] was previously described.

*Bromination of 5,13-di-tert-butyl-8,16-dimethyl[2.2]MCP* (**1**) *with DBMH in methylene dichloride – typical procedure***.**

To a solution of **1** (500 mg, 1.43 mmol) in $CH_2Cl_2$ (15 cm$^3$) was added DBMH (225 mg, 0.787 mmol) at room temperature. The reaction mixture was stirred for 5 min., and poured into 10% sodium hydrogen

**Table 1** Bromination of 5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP **1** with DBMH and $BTMABr_3$ in $CH_2Cl_2$

| Run | Reagent | Reagent/**1b**/mol/mol | Products Yield/%[a,b] | | | Recovery |
|---|---|---|---|---|---|---|
| | | | **2** | **3** | **4** | **1** |
| 1 | DBMH | 0.28 | 51 | 1 | 3 | 45 |
| 2 | DBMH | 0.55 | 83 (70) | 2 | 9 | 6 |
| 3 | DBMH | 0.8 | 60 | 2 | 35 | 3 |
| 4 | DBMH | 1.1 | 28 | 3 | 67 | 2 |
| 5 | DBMH | 3.1 | 0 | 0 | 98 (85) | 0 |
| 6 | $BTMABr_3$[c] | 1.1 | 68 (45) | 1 | 13 | 18 |

[a]Yields were determined by $^1H$ NMR spectra. [b]Isolated yields are shown in parentheses. [c]Reaction time was 1 h.

sulfate (10 $cm^3$). The reaction mixture was extracted with $CH_2Cl_2$ (10 $cm^3$). The combined extracts were washed with water, dried with $Na_2SO_4$ and concentrated. The residue was washed and filtered with a small amount of hexane to give crude **2** as a brown solid. Recrystallisation from hexane gave 1-*exo*-bromo-5,13-di-*tert*-butyl-8,16-dimethyl[2.2] MCP (**2**) as pale yellow prisms (428 mg, 70%), m.p. 169–171°C; $\delta_H$ ($CDCl_3$): 0.50 (3 H, s, *Me*), 0.97 (3 H, s, *Me*), 1.27 (9 H, s, *t*Bu), 1.33 (9 H, s, *t*Bu), 2.76–2.98 (4 H, m, $CH_2CH_2$), 3.41 (1 H, d, $J$ = 15.3, $CH_2$), 3.62 (1 H, dd, $J$ = 6.1, 15.3 $CH_2$), 5.62 (1 H, dd, $J$ = 2.4, 6.1, *CH*), 7.06 (1 H, d, $J$ = 1.9, Ar–*H*), 7.20 (2 H, d, $J$ = 1.9, Ar–*H*), 7.36 (1 H, d, $J$ = 1.9, Ar–*H*); *m/z*: 426, 428 ($M^+$). Anal. calcd. for $C_{26}H_{35}Br$ (427.47): C, 73.05; H, 8.25. Found: C, 72.9; H, 8.2%.

Similarly, bromination of **1** with DBMH and BTMA $Br_3$ was carried out in the same manner as described above under the various conditions. The yields are compiled in Table 1. The formation of 2, 7-di-*tert*-butyl-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene **3** was determined by $^1H$ NMR in comparison with the authentic sample. [9a] 4,5,9,10-Tetrabromo-2,7-di-*tert*-butyl-*trans*-10b,10c-dimethyl-10b, 10c-dihydropyrene **4** was obtained as deep green prisms (hexane); m.p. 228°C (lit.[9a] m.p. 230°C).

*Reaction of* **2** *with tBuOK*: To a solution of **2** (94 mg, 0.22 mmol) in *t*BuOK (10 $cm^3$) was added *t*BuOK (250 mg, 2.23 mmol) at room temperature. The reaction mixture was stirred for 12 h, poured into water (10 $cm^3$). The reaction mixture was extracted with $CH_2Cl_2$ (10 $cm^3 \times 2$). The combined extracts were washed with water, dried with $Na_2SO_4$ and concentrated. The residue was recrystallised from hexane gave 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP-1-ene (**6**) as pale yellow prisms (61 mg, 90%); m.p. 210–211°C (lit.[9a] m.p. 210–211°C).

*Preparation of 1-exo-acetoxy-5,13-di-tert-butyl-8,16-dimethyl[2.2] MCP* (**7**): A solution of **2** (1.0 g, 2.34 mmol) in glacial acetic acid (100 $cm^3$) containing silver acetate (2.5 g, 15.0 mmol) was heated at 85–90°C for 90 min. The resulting suspension was concentrated and then extracted with $CH_2Cl_2$ (30 $cm^3 \times 3$). After the dichloromethane solution had been washed successively with 10% aqueous sodium hydrogencarbonate and water, the extract was dried over anhydrous sodium sulfate and concentrated. The residue was subjected to silica-gel (Wako, C-300; 100 g) column chromatography using as eluent hexane–benzene (1: 1) to give a colourless solid. Recrystallisation from hexane afforded 1-*exo*-acetoxy-5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP (**7**) (657 mg, 69%) as colourless prisms (hexane); m.p. 154–158°C; $\delta_H$ ($CDCl_3$): 0.54 (3 H, s, *Me*), 0.77 (3 H, s, *Me*), 1.27 (9 H, s, *t*Bu), 1.31 (9 H, s, *t*Bu), 2.07 (3 H, s, *Me*), 2.77–3.07 (6 H, m, $CH_2$), 6.20–6.22 (1 H, m, *CH*), 7.12–7.20 (4 H, m, Ar–*H*); $\delta_C$ ($CDCl_3$): 14.14, 14.36, 21.30, 29.69, 31.31, 33.89, 36.03, 36.32, 41.75, 80.50, 123.07, 124.94, 125.68, 126.24, 132.15, 133.21, 136.60, 136.89, 139.80, 140.88, 146.24, 146.52, 170.06; *m/z*: 406 ($M^+$). Anal. calcd. for $C_{28}H_{38}O_2$ (406.61): C, 82.71; H, 9.42. Found: C, 82.88; H, 9.35%.

*Preparation of 5,13-di-tert-butyl-1-exo-hydroxy-8,16-dimethyl [2.2]MCP* (**8**): To a solution of **7** (100 mg, 0.246 mmol) in EtOH (30 $cm^3$) was added a solution of KOH (500 mg, 8.91 mmol) in water (3 $cm^3$) at room temperature. After the reaction mixture had been heated at 50°C for 15 min., it was concentrated under reduced pressure, and extracted with $CH_2Cl_2$ (30 $cm^3 \times 3$). After the dichloromethane solution had been washed successively with water, the extract was dried over anhydrous sodium sulfate and concentrated. The residue was subjected to silica-gel (Wako, C-300; 100 g) column chromatography using as eluent hexane-benzene (1:1) to give a colourless solid. Recrystallisation from hexane afforded 5,13-di-*tert*-butyl-*exo*-1-hydroxy-8,16-dimethyl[2.2]MCP (**8**) (81 mg, 90%) as colourless prisms (hexane); m.p. 258–259°C; $\nu_{max}$(KBr)/$cm^{-1}$: 3580 ($\nu_{OH}$); $\delta_H$ ($CDCl_3$): 0.52 (3 H, s, *Me*), 0.86 (3 H, s, *Me*), 1.27 (9 H, s, *t*Bu), 1.30 (9 H, s, *t*Bu), 2.01 (1 H, broad s, *OH*, exchange with $D_2O$), 2.73–3.13 (6 H, m, $CH_2$ and $CH_2CH(OH)$), 5.34 (1 H, dd, $J$ = 2.2, 4.6, $CHOH$), 7.01 (1 H, d, $J$ = 2.0, Ar-*H*), 7.18–7.21 (3 H, m, Ar–*H*); $\delta_C$ ($CDCl_3$): 14.03, 14.34 (q, $CH_3$), 31.30, 31.34 (q, $C(CH_3)_3$), 33.84, 33.89 (s, $C(CH_3)_3$), 35.83, 36.34 (t, $CH_2CH_2$), 44.56 (t, $CH_2CH(OH)$), 80.66 (d, CH(OH)), 122.73, 124.98, 125.21, 125.80 (d, Ar*CH*), 133.65, 135.22, 136.71, 136.94, 139.66, 140.77, 146.23, 146.34 (s, Ar*C*); *m/z*: 364 ($M^+$, 100). Anal. calcd. for $C_{26}H_{36}O$ (364.58) $C_{26}H_{36}O$: C, 85.66; H, 9.95C. Found: C, 85.35; H, 9.78%.

*Swern oxidation of* **8**: To a solution of of oxalyl chloride (0.25 $cm^3$, 2.75 mmol) in $CH_2Cl_2$ (25 $cm^3$) was added DMSO (0.126 $cm^3$, 1.65 mmol) and then compound **8** (120 mg, 0.329 mmol) in $CH_2Cl_2$ (15 $cm^3$) at –30°C under nitrogen. After the reaction mixture had been stirred at –30°C for 1 h, triethylamine (380 mg, 3.75 mmol) was added. The temperature of the reaction mixture was maintained at –30°C for 30 min. under nitrogen and then allowed to warm to room temp. and stirred for an additional 1 h. Water (10 $cm^3$) was added and the reaction mixture was extracted with $CH_2Cl_2$ (10 $cm^3 \times 3$). The dichloromethane solution was washed with water, dried over $Na_2SO_4$, and evaporated *in vacuum* to a residue, which was crystallised by adding a small amount of hexane to give a colourless solid. Recrystallisation from hexane afforded *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP-1-one (**9**) (95 mg, 80%) as colourless prisms; m.p. 227–228°C; $\nu_{max}$(KBr)/$cm^{-1}$: 1701 (C=O); $\delta_H$ ($CDCl_3$): 0.55 (3 H, s, *Me*), 0.68 (3 H, s, *Me*), 1.28 (9 H, s, *t*Bu), 1.29 (9 H, s, *t*Bu), 2.62–2.70 (2 H, m, $CH_2$), 2.96–3.00 (2 H, m, $CH_2$), 3.73 (1 H, d, $J$ = 16.1, $CH_2$), 3.95 (1 H, d, $J$ = 16.1, $CH_2$), 7.02 (1 H, d, $J$ = 2.4, Ar–*H*), 7.08 (1 H, d, $J$ = 2.4, Ar–*H*), 7.21 (1 H, d, $J$ = 2.4, Ar–*H*), 7.26 (1 H, d, $J$ = 2.4, Ar–*H*); *m/z*: 362 ($M^+$, 100). Anal. calcd. for $C_{26}H_{34}O$ (362.56): C, 85.66; H, 9.95. Found: C, 85.35; H, 9.78%.

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