Medium-size cyclophanes, 69[1] Synthesis and *ipso*-nitration of di-*tert*-butyl-1,2-dimethyl[2.10]metacyclophan-1-enes

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Syn-5,21-di-*tert*-butyl-1,2-dimethyl[2.10]metacyclophan-1-ene *syn*-**4** was prepared by the McMurry reaction of 1,10-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)decane **3**, and nitrated with fuming nitric acid to give the two-fold *ipso*-nitration product *syn*-**5** in good yield.

Keywords: cyclophanes, [2.10]metacyclophan-1-enes, McMurry reaction, conformation, isomerisation, *ipso*-nitration

In studying the chemistry and spectroscopic properties of the [2.2]MCP-1-enes (MCP = metacyclophane) skeleton,[2,3] attempts have been made to introduce functional groups directly into the benzene rings. These have failed because of novel transannular reactions arising from the electronic interaction between 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.[4] In the case of the larger sized [2.*n*]MCP-1-enes the reactions on the bridged double bonds have been observed under the elecrophilic aromatic substitution conditions.[4,5] There is interest in developing a convenient method of introducing substituents onto the aromatic rings of [2.*n*]MCP-1-enes.

Recently we have reported a convenient preparation of 1,2-disubstituted [2.2]- and [2.3]MCP-1-enes[6,7] using the reductive coupling of carbonyl compounds by low-valent titanium, the McMurry reaction.[8] We report here a convenient preparation of higher methylene bridged *syn*- and *anti*-1,2-dimethyl[2.10] MCP-1-enes **4** by the McMurry reaction and their *ipso*-electrophilic aromatic substitution reactions.

Results and discussion

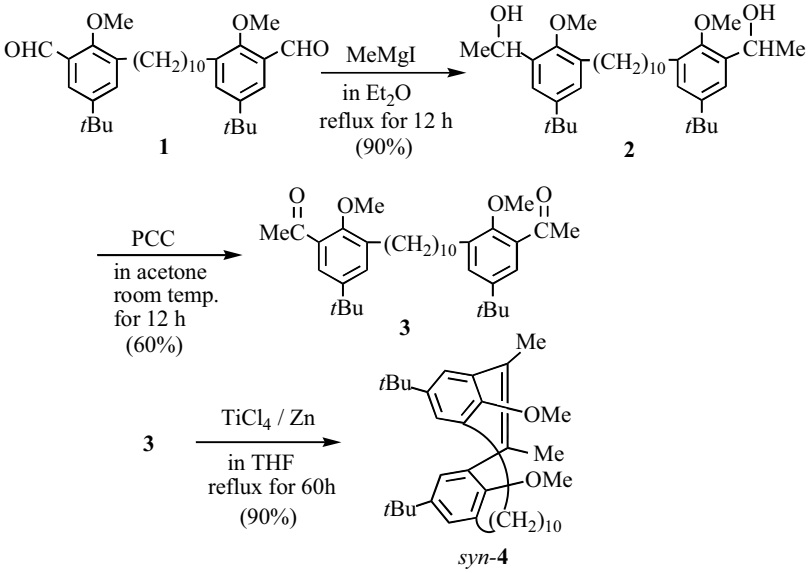
The starting compound 1,10-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)decane (**1**) was prepared as described previously[6b] by using the *tert*-butyl group as a positional protective group on the aromatic ring. The bisformylated compound **1** was converted to the bisalcohol derivative **2** in 90 % yield by the Grignard reaction of **1** with MeMgI in ether. Oxidation of **2** with pyridinium chlorochromate (PCC) afforded bisacetyl derivative **3** in 60 % yield.

1,10-Bis(2-acetyl-5-*tert*-butyl-3-methoxylphenyl)decane (**3**) was subjected to reductive coupling by the McMurry reaction following the improved Grützmacher's procedure[9] (Scheme 1). Thus, the reductive coupling reaction of **3** was carried out using $TiCl_4$–Zn in refluxing THF under the high dilution conditions to afford the desired compound, *syn*-5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]MCP-1-ene (*syn*-**4**), in 90 % yield. None of the corresponding *anti*-isomer was observed under the condition used.

We have previously reported the selective *ipso*-acylation of di-*tert*-butyl[2.*n*]MCPs to afford mono and di-acylation product in good yields depending on the acylation conditions used.[10] However, an attempted *ipso*-acylation of *syn*-**4** with acetyl chloride in the presence of $AlCl_3$ $MeNO_2$ failed to afford the corresponding diacetyl[2.10]MCP-1-ene. Only the *syn*-to-*anti* isomerisation product *anti*-**4** in 60 % yield. In fact treatment of *syn*-**4** with $AlCl_3$ $MeNO_2$ in CH_2Cl_2 under the same conditions also afforded *anti*-**4** in 80 % yield.

Although the detailed reaction mechanism is not clear from the present data, one might suppose that the *syn*-to-*anti* ring inversion proceeds in acidic media by protonation of the bridged double bond to form the longer bridged single bond.

The structures of **4** were elucidated based on their elemental analyses and spectral data. Especially, the mass spectral data for **4** (M^+ = 518) strongly supports the cyclic structure. The



Scheme 1

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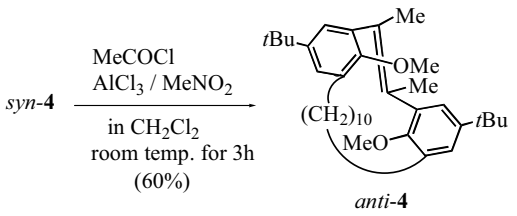


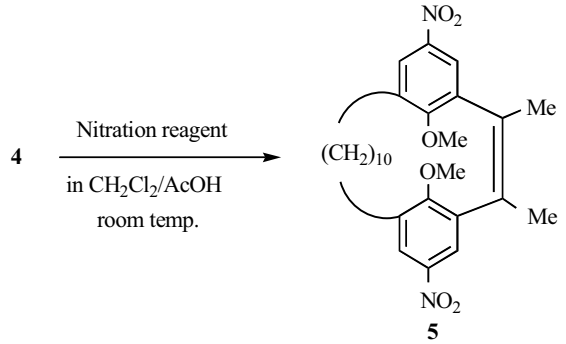
Scheme 2

structures *anti*-**4** and *syn*-**4** were readily apparent from their ^{1}H NMR spectra. Thus, the internal methoxy protons show an upfield shift due to the ring current of the opposite benzene ring.[2] The ^{1}H NMR spectrum of conformer *anti*-**4** and *syn*-**4** respectively shows the methoxy protons at δ 3.44 and 3.65 ppm. The aromatic protons of conformer *syn*-**4** are observed much higher field (δ 6.77, 6.85 ppm) than those of conformer *anti*-**4** at δ 6.97 and 7.19 ppm. The *tert*-butyl protons are also observed a higher field (δ 1.12 ppm) than those of conformer *anti*-**4** at δ 1.32 ppm. The above data distinguish the anti-conformer from the syn conformer and reveal the structure of *syn*-**4** as the *syn*-conformer. And in both *anti*-**4** and *syn*-**4** the double bond stereochemistry adopts *Z*-geometry. It was also found that *anti*-to-*syn*-ring inversion is inhibited for both *anti*-**4** and *syn*-**4**. There was no change of the NMR pattern for the benzyl protons of the decane bridge below 130 °C in $CDBr_3$.

An attempted nitration of *syn*-**4** with 4 equiv. of cupric nitrate in acetic anhydride at room temperature for 24 h failed and the starting material was recovered. Interestingly, when compound *syn*-**4** was treated with excess fuming HNO_3 in CH_2Cl_2 and acetic acid solution at room temperature for 30 min. the two-fold *ipso*-nitration product *syn*-**5** was obtained in 80 % yield.[11] This result is quite different from the nitration of the corresponding *anti*-5,21-di-*tert*-butyl-8,24-dimethoxy[2.10]MCP-1-ene[6b] under the same conditions which afforded an intractable mixture of products. In the present case the bridged 1,2-dimethyl group might protect the system from reaction with nitric acid. Similar treatment with mixed acid (HNO_3: H_2SO_4 1: 1) afforded *syn*-**5** within 10 min. No products derived from reaction at the bridging double bond and *syn*-to-*anti*-isomerisation reaction were observed. In the case of *anti*-**4**, the *ipso*-nitration product *anti*-**5** was also obtained in 85 % yield.

Conclusions

We have demonstrated a convenient preparation of *syn*-1,2-dimethyl[2.10]MCP-1-ene *syn*-**4** by McMurry reaction of 1,10-bis(3-acetyl-5-*tert*-butyl-2-methoxyphenyl)decane(**3**). Acetylation of *syn*-**4** with acetyl chloride in the presence of $AlCl_3$ $MeNO_2$ afforded *anti*-isomer *anti*-**4** in good yield. In contrast treatment of *syn*-**4** and *anti*-**4** with fuming nitric acid or mixed acid led to *ipso*-nitration to give the corresponding dinitration product without cleavage of the bridged double bond. These results provide the opportunity for the synthesis of functionalised MCP-enes. Further studies on the chemical properties of 1,2-dimethyl[2.*n*]MCP-1-enes are now in progress.



Scheme 3

Table 1 Nitration of 1,2-dimethyl[2.10]matacyclophan-1-enes (**4**).

Run	Substrate	Nitration reagent	Time/h	Product/%[a]
1	*syn*-**4**	$Cu(NO_3)_2$	24	*syn*-**5** (0)[b]
2	*syn*-**4**	HNO_3	0.5	*syn*-**5** (80)
3	*syn*-**4**	HNO_3/H_2SO_4	0.5	*syn*-**5** (85)
4	*syn*-**4**	HNO_3	0.5	*anti*-**5** (85)

[a]Isolated yields are shown. [b]Starting compound *syn*-**4** was recovered in quantitative yield.

Experiment

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.

Materials. The preparation of 1,10-bis(5-*tert*-butyl-3-formyl-2-methoxyphenyl)decane (**1**) was previously described.[6b]

Preparation of 1,10-bis[5-tert-butyl-3-(1-hydroxyethyl)-2-methoxyphenyl]decane (**2**)**:** To a solution of methylmagnesium iodide [prepared from methyl iodide (14.4 g, 101 mmol) and magnesium (2.05 g, 84.3 mmol)] in Et_2O (45 cm^3) was added a solution of **1** (8.85 g, 16.9 mmol) in tetrahydrofuran (100 cm^3) dropwise under the conditions of gentle refluxing. The reaction mixture was refluxed for an additional 12 h, and then quenched with 10 % ammonium chloride (100 cm^3) and extracted with Et_2O (100 × 3 cm^3). The extract was washed with water (100 cm^3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallised from hexane to afford (12.0 g 90 %) as pale yellow prisms; m.p. 127–129 °C; ν_{max} (KBr)/cm^{-1}: 3418 (OH); δ_H ($CDCl_3$) 1.30 (18 H, s, *t*Bu), 1.20–1.40 (12 H, m, *CH*$_2$), 1.52 (6 H, d, *J* = 6.4, *CH*$_3$), 1.5–1.7 (4 H, m, *CH*$_2$), 2.35 (2 H, broad s, *OH*), 2.60 (4 H, t, *J* = 7.9, *CH*$_2$), 3.87 (6 H, s, *OCH*$_3$), 5.18 (2 H, t, *J* = 6.4, *CH*), 7.12 (2 H, d, *J* = 2.4, Ar*H*), 7.63 (2 H, d, *J* = 2.4, Ar*H*); *m/z*: 554 (M^+) (Found C, 77.65; H, 10.7. $C_{36}H_{58}O_4$ (554.85) requires C, 77.9; H, 10.54 %).

Preparation of 1,10-bis(3-acetyl-5-tert-butyl-2-methoxyphenyl) decane (**3**)**:** To a solution of $C_5H_5NH^+CrO_3Cl^-$ (2.80 g, 12.98 mmol) in acetone (150 cm^3) was added a solution of **2** (3.0 g, 5.41 mmol) in acetone (50 cm^3) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed to silica-gel (Wako, C-300; 500 g) using as eluent $CHCl_3$ to give crude **3**. Recrystallisation from hexane to afford 3 (1.80 g 60 %) as colourless prisms; m.p. 55–56 °C; ν_{max} (KBr)/cm^{-1}: 1686 (C=O); δ_H ($CDCl_3$) 1.30 (18 H, s, *t*Bu), 1.32–1.35 (12 H, m, *CH*$_2$), 1.59–1.66 (4 H, m, ArCH$_2$*CH*$_2$), 2.59–2,66 (4 H, m, Ar*CH*$_2$CH$_2$), 2.63 (6 H, s, *Me*), 3.73 (6 H, s, O*Me*), 7.34 (2 H, d, *J* = 2.4, Ar*H*), 7.41 (2 H, d, *J* = 2.4, Ar*H*); *m/z*: 550 (M^+) (Found C, 78.45; H, 9.8. $C_{36}H_{54}O_4$ (550.82) requires C, 78.5; H, 9.9 %).

McMurry coupling reaction of **3:** The McMurry reagent was prepared from $TiCl_4$ (7.7 cm^3, 70 mmol) and Zn powder (9.8 g, 150 mmol) in 500 cm^3 of dry THF, under nitrogen. A solution of 1,10-bis(5-*tert*-butyl-3-acetyl-2-methoxyphenyl)decane **3** (2.75 g, 5 mmol) in dry THF (100 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 temp., and hydrolysed with aqueous 10% K_2CO_3 (500 cm^3) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (300 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, 500 g) with hexane–benzene (2: 1) as eluents to give *syn*-**4**. Recrystallisation from MeOH to afford *syn*-5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene *syn*-**4** (2.3 g 90 %) as colourless prisms; m.p. 139–140 °C; ν_{max} (KBr)/cm^{-1}: 2962, 1362, 1298, 1212,

1119, 1022, 877, 802, 705, 653; δ_H ($CDCl_3$) 1.12 (18 H, s), 1.10–1.38 (16 H, m), 2.21 (6 H, s), 2.09–2.20 (2 H, m), 2.74–2.88 (2 H, m), 3.65 (6 H, s), 6.77 (2 H, d, *J* = 2.4), 6.85 (2 H, d, *J* = 2.4); *m/z*: 518 (M^+) (Found C, 83.4; H, 10.4. $C_{36}H_{54}O_2$ (518.83) requires C, 83.3; H, 10.5 %).

*Acylation of syn-***4** *with acetyl chloride in the presence of* $AlCl_3$ *–* $MeNO_2$**:** To a solution of *syn*-**4** (20 mg, 0.039 mmol) and acetyl chloride (51 mg, 0.65 mmol) in CH_2Cl_2 (2 cm^3) was added a solution of $AlCl_3$ (92 mg, 0.70 mmol) in $MeNO_3$ (1 cm^3) at 0 °C. After the reaction mixture was stirred at room temp. for 3 h, it was poured into a large amount of ice/water (10 cm^3) and extracted with CH_2Cl_2 (10 cm^3 × 2). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was recrystallised from hexane to afford *anti*-5,21-di-*tert*-butyl-8,24-dimethoxy-1,2-dimethyl[2.10]metacyclophan-1-ene *anti*-**4** (12 mg 60 %) as colourless prisms; m.p. 165–166 °C; ν_{max} (KBr)/cm^{-1}: 2948, 1461, 1203, 1019, 879; δ_H ($CDCl_3$) 0.81–1.20 (16 H, m, *CH*$_2$), 1.32 (18 H, s, *t*Bu), 1.85 (6 H, s, *Me*), 2.17–2.29 (2 H, m, *CH*$_2$), 2.76–2.85 (2 H, m, *CH*$_2$), 3.44 (6 H, s, O*Me*), 6.97 (2 H, d, *J* = 2.4, Ar*H*), 7.19 (2 H, d, *J* = 2.4, Ar*H*); *m/z*: 518 (M^+) (Found C, 83.5; H, 10.5. $C_{36}H_{54}O_2$ (518.83) requires C, 83.3; H, 10.5 %).

*Nitration of syn-***4** *with fuming nitric acid at room temperature*: A solution of *syn*-**4** (20 mg, 0.039 mmol) in CH_2Cl_2 (2.5 cm^3) and AcOH (2.5 cm^3) was added to fuming HNO_3 (0.15 cm^3) at 0 °C. After the reaction mixture had been stirred for 30 min., it was poured into water (10 cm^3). The organic layer was extracted with CH_2Cl_2 (10 cm^3 × 2). The extract was washed with water (10 cm^3), dried (Na_2SO_4), and concentrated. The residue was recrystallised from hexane to afford *syn*-8,24-dimethoxy-1,2-dimethyl-5,21-dinitro[2.10] metacyclophan-1-ene *syn*-**5** (15 mg 80 %) as pale yellow prisms; m.p. 124–125 °C; ν_{max} (KBr)/cm^{-1}: 2929, 2863, 1520, 1336, 1244, 1093, 901, 742, 709; δ_H ($CDCl_3$) 1.12–1.58 (18 H, m, *CH*$_2$), 2.24 (6 H, s, *Me*), 2.75–2.86 (2 H, m, *CH*$_2$), 3.78 (6 H, s, O*Me*), 7.66 (2 H, d, *J* = 2.4, Ar*H*), 7.81 (2 H, d, *J* = 2.4, Ar*H*); *m/z*: 496 (M^+) (Found C, 67.3; H, 7.3. $C_{38}H_{36}N_2O_6$ (496.6) requires C, 67.7; H, 7.3 %).

Similarly, compound *anti*-**5** was obtained in 85 % yield as pale yellow prisms (hexane); m.p. 156–157 °C; ν_{max} (KBr)/cm^{-1}: 2929, 2863, 1520, 1336, 1244, 1093, 901, 742, 709; δ_H ($CDCl_3$) 0.82–1.60 (16 H, m, *CH*$_2$), 1.95 (6 H, s, *Me*), 2.31–2.43 (2 H, m), 2.79–2.88 (2 H, m, *CH*$_2$), 3.61 (6 H, s, O*Me*), 7.96 (2 H, d, *J* = 2.4, Ar*H*), 8.09 (2 H, d, *J* = 2.4, Ar*H*)); *m/z*: 496 (M^+) (Found C, 67.5; H, 7.4. $C_{28}H_{36}N_2O_6$ (496.6) requires C, 67.7; H, 7.3 %).

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