Medium-sized cyclophanes. Part 61.† *ipso*-Acylation of *tert*-butyl[*n*.2]metacyclophanes: through-space electronic interactions between two benzene rings

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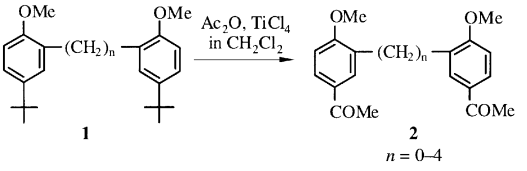
The selective introduction of one or two acetyl groups by direct replacement of *tert*-butyl groups *via* the *ipso* aromatic acetylation of meta-bridged aromatic compounds having two arene rings is described. Acetylation of *syn*- and *anti*-di-*tert*-butyl[*n*.2]metacyclophanes **3** (n = 2,3,4) with acetyl chloride in the presence of $TiCl_4$ gave the *ipso*-acetylation product at the *tert*-butyl group. However, only one *tert*-butyl group is *ipso*-acetylated under mild reaction conditions in the presence of $TiCl_4$ because of deactivation of the second aromatic ring by the introduced acetyl group. Higher yields of monoacetylated product are obtained from the anti-conformer than the syn-conformer. Therefore, the intra-annular interaction might be much more favorable to stabilize the initial σ-complex intermediate than face-to-face overlap in the case of *ipso*-acetylation. On the other hand, acetylation of **3** with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$ afforded the two-fold *ipso*-acetylation product **6** in quantitative yield. Thus, the extent of *ipso*-acetylation at the *tert*-butyl groups of **3** was strongly affected by the activity of the acylation catalyst. The presently developed procedure was further applied to the direct removal of a *tert*-butyl group by electrophilic substitution of *tert*-butyl-8-methoxy[2.2]MCPs **11**, which are prone to give transannular reaction products under electrophilic reaction conditions.

Although the replacement of a *tert*-butyl group by a nitro group in electrophilic aromatic substitutions has frequently been described in the literature,[2,3] generally the yields are mostly modest because of the accompanying side reactions.[4] Only in activated compounds are better yields obtained. However, there have been only a few investigations on other *ipso*-electrophilic aromatic substitutions of *tert*-butylarenes having more than two benzene rings.[5,6] A few years ago we reported[7] that *ipso* aromatic acylation of 1,*n*-bis(5-*tert*-butyl-2-methoxyphenyl) alkanes (**1**) leads to the direct introduction of one or two acetyl groups (Scheme 1), depending on the acylation reagents. However, the mechanistic aspects of *ipso*-attack in electrophilic aromatic substitutions having more than two aromatic rings are still not clear because of the possibility of through-space electronic interactions occurring among the other benzene rings.

On the other hand, we have reported[8] that nitration of 5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**3a**, MCP = metametacyclophane) with various nitrating reagents led to mono-*ipso*-nitration at the *tert*-butyl group to give 5-*tert*-butyl-8,16-dimethoxy-13-nitro[2.2]MCP as well as the corresponding 17-oxa[2.2.1](1,3,2)cyclophane arising from an intramolecular condensation reaction *via* *anti*-*syn*-ring inversion of the nitration intermediate. The latter novel product was found to be obtained owing to the release of the strain in these systems.

Although the parent [2.2]MCP was first reported as early as in 1899 by Pelligrin,[9] the synthesis of *syn*-[2.2]MCP was not realized until 85 years later. Mitchell *et al.*[10] have successfully prepared *syn*-[2.2]MCP at low temperature by using (arene) chromiumcarbonyl complexation to control the stereochemistry. However, *syn*-[2.2]MCP isomerizes readily to the *anti*-isomer above 0 °C. Itô *et al.*[11] have also isolated and characterized *syn*-[2.2]MCP without complexation. On the other hand, the groups of Boekelheide,[12a] Lai[12b] and Staab[13] succeeded in synthesizing intra-annularly substituted *syn*-[2.2]MCPs. However, the internally substituted *anti*- and *syn*-[*n*.2]MCPs can be easily synthesized and well characterized.[14,15] Thus, the through-space electronic interaction could be achieved through the intra-annular positions *via* a σ-complex intermediate **A** in the former conformer, but through face-to-face overlapping among the two benzene rings as in a σ-complex intermediate **B** in the latter conformer (Fig. 1). Therefore, it is possible to investigate the different behavior in the acylation of *anti*- and *syn*-[*n*.2]MCPs and to determine which conformer contributes more strongly to the through-space electronic interaction.



Scheme 1

† Part 60: ref. 1.

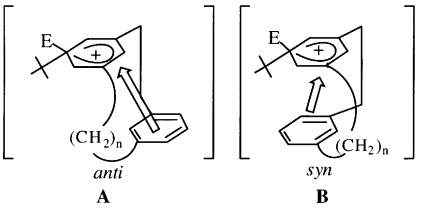


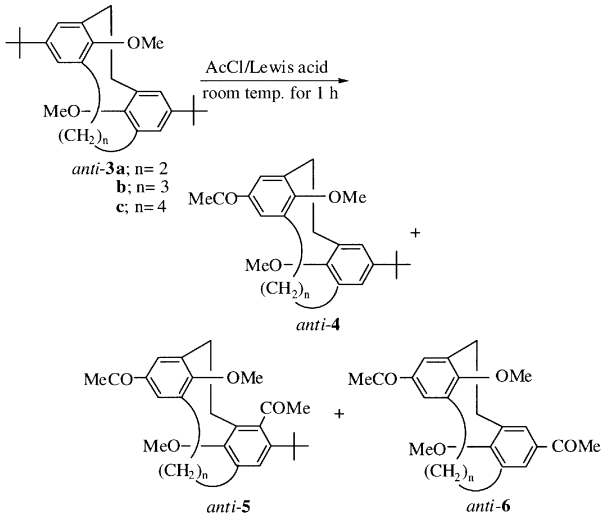
Fig. 1 Two possible through-space electronic interactions of [*n*.2]MCPs.

Thus there is substantial interest in systematically investigating the relationship between neighboring benzene rings in the *ipso* aromatic acylations of larger ring sized *tert*-butyl[*n*.2]MCPs having *anti*- and *syn*-conformations than *tert*-butyl[2.2]MCPs, which might only afford the *ipso*-acylation product at the *tert*-butyl group because of the formation of the intramolecular condensation product *via anti-syn*-ring inversion of the nitration intermediate[8b] being impossible. In this paper we describe the selective introduction of one or two acyl groups by direct replacement of *tert*-butyl groups *via* the *ipso* aromatic acylation of the meta-bridged aromatic compounds, *tert*-butyl[*n*.2]MCPs having two arene rings, to investigate the through-space electronic interactions occurring among other benzene rings.

Results and discussion

Attempted acetylation of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**3a**)[16] with acetyl chloride in the presence of $TiCl_4$ at room temperature for 1 h gave the mono-*ipso*-acetylated product *anti*-5-acetyl-13-*tert*-butyl-8,16-dimethoxy-[2.2]MCP (*anti*-**4a**) in 74% yield as a major product along with *anti*-4-acetyl-13-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**5a**) and *anti*-5,13-diacetyl-8,16-dimethoxy[2.2]MCP (*anti*-**6a**), shown in Scheme 2. No formation of the corresponding 17-oxa[2.2.1](1.2.2)cyclophane arising from an intramolecular condensation reaction *via anti-syn*-ring inversion as in the nitration of 8,16-dimethoxy[2.2]MCP, *anti*-**3a**, was observed.[8b]

While in the acetylation of *anti*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2]MCP (*anti*-**3b**)[15a] under the same reaction conditions the mono-*ipso*-acetylated product *anti*-6-acetyl-14-*tert*-butyl-9,17-dimethoxy[3.2]MCP (*anti*-**4b**) was obtained in 69% yield, two other different acetylation products, *anti*-**5b** and *anti*-**6b**, were obtained in 9 and 11% yields, respectively. A similar result was obtained in the acetylation of *anti*-[4.2]MCP, *anti*-**3c**, to afford the mono *ipso*-acetylated product *anti*-**4c** in 83% yield along with a small amount of *anti*-**5c**. The formation of the two-fold *ipso*-acetylation product, *anti*-7,15-diacetyl-10,18-dimethoxy[4.2]MCP (*anti*-**6c**), was not observed under the reaction conditions used (see Table 1).



Scheme 2

Table 1 Lewis acid catalyzed acetylation of di-*tert*-butyldimethoxy[*n*.2]metacyclophanes *anti*-**3**[a]

Substrate	Number of methylene units, *n*	Lewis acid	Products (% yield)[b] *tab1fnc*
anti-**3a**	2	A	*anti*-**4a** (74) [62], *anti*-**5a** (17) [10], *anti*-**6a** (4)
anti-**3b**	3	A	*anti*-**4b** (69) [43], *anti*-**5b** (9) [5], *anti*-**6b** (11)
anti-**3c**	4	A	*anti*-**4c** (83) [74], *anti*-**5c** (5) [3]
anti-**3a**	2	B	*anti*-**6a** (100) [82]
anti-**3b**	3	B	*anti*-**6b** (95) [78]
anti-**3c**	4	B	*anti*-**6c** (89) [74]

[a] Conditions: A: $TiCl_4$, catalyst/*anti*-**3** = 14 (mol/mol), AcCl/*anti*-**3** = 4 (mol/mol); B: $AlCl_3$–$MeNO_2$, catalyst/*anti*-**3** = 12 (mol/mol), AcCl/*anti*-**3** = 6 (mol/mol). Reaction temperature: room temperature. [b] Yields were determined by GLC analyses. [c] Isolated yields are shown in square brackets.

Interestingly, with varying activity of the acetylation catalyst the ratio of the product arising from mono-*ipso*-acetylation, **4** to the product arising from two-fold *ipso*-acetylation at the *tert*-butyl groups, **6**, changed. When the acetylation catalyst was changed from titanium tetrachloride to the more reactive $AlCl_3$ $MeNO_2$ the yield of di-*ipso*-acylated products **6** increased from 4–11% to quantitative yields (Table 1). Thus, the extent of *ipso*-acetylation at the *tert*-butyl groups of **3** is strongly affected by the activity of the acetylation catalyst, as has been reported for electrophilic aromatic substitution in normal aromatic systems.[17]

From the results of $AlCl_3$–$MeNO_2$ catalyzed acetylation of *anti*-**3** one might suppose that *anti*-**5** is the intermediate for the formation of the di-*ipso*-acetylation product *anti*-**6**. In fact, we have navigated the $AlCl_3$–$MeNO_2$ catalyzed acetylation of *anti*-**3** under milder reaction conditions. Acetylation of *anti*-**3a** with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$ at room temperature for 0.2 h gave the di-acetylation products, *anti*-**5a** and *anti*-**6a**, in 51 and 46% yields, respectively, along with mono-*ipso*-acetylated product *anti*-**4a** in 3% yield. Prolonging the reaction time for 1 h resulted in an increase of the yield of *anti*-**6a** from 46% to 65%. Finally the reaction was completed in 6 h to afford *anti*-**6a** in quantitative yield (Table 2). Similar results were obtained in the case of the [3.2] and [4.2] systems.

Furthermore, acetylation of the mono-*ipso*-acetylated product *anti*-**4a** carried out under the same conditions afforded almost the same ratio of diacetylated products *anti*-**5a** and *anti*-**6a** along with recovery of starting compound. This result strongly suggests that in the first step *ipso*-acetylation at the *tert*-butyl group must occur. In the second step, the different regioselectivity was then observed to exclusively acetylate at positions ortho to the *tert*-butyl group, 4 or 6, because of deactivation of the second aromatic ring by the acetyl group. It was also found that treatment of *anti*-**5a** with $AlCl_3$–$MeNO_2$ in CH_2Cl_2 for 24 h under the same conditions resulted essentially in recovery of the starting compound (Table 3). In contrast, when the same reaction was carried out in the presence of acetyl chloride, the di-*ipso*-acetylation product *anti*-**6a** was obtained in 80% yield along with recovery of starting compound (Scheme 3). Furthermore, acylation of *anti*-**5a** with propionyl chloride carried out under the same conditions afforded *anti*-**6a** in 64% yield. No formation of 5-acetyl-8,16-dimethoxy-13-propionyl[2.2]MCP, *anti*-**6d**, was detected under the reaction conditions used. Similar results were obtained in

Table 2 Acetylation of di-*tert*-butyldimethoxy[*n*.2]metacyclophanes *anti*-**3**[a]

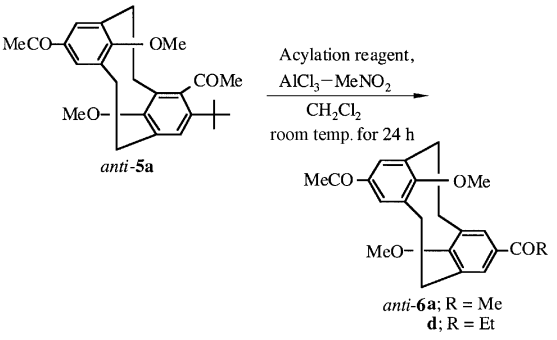
Run	Substrate	Number of methylene units, *n*	Time/h	Products (% yield)[b]		
				anti-**4**	*anti*-**5**	*anti*-**6**
1	*anti*-**3a**	2	0.2	3	51	46
2	*anti*-**3a**	2	1	0	35	65
3	*anti*-**3a**	2	3	0	12	88
4	*anti*-**3a**	2	5	0	5	95
5	*anti*-**3a**	2	6	0	0	100 (90)[c]
6	*anti*-**3b**	3	1	0	44	56
7	*anti*-**3c**	4	1	0	46	54

[a] Conditions: $AlCl_3$–$MeNO_2$, catalyst/*anti*-**3** = 6 (mol/mol), AcCl/*anti*-**3** = 4 (mol/mol). Reaction temperature: room temp. [b] Yields were determined by GLC analyses. [c] Isolated yields.

Table 3 Acid catalyzed *ipso*-acylation of *anti*-**5a**[a]

Run	Acylation reagent	Products (% yield)[b] *tab3fnc*	
		anti-**6a**	Recovd. *anti*-**5a**
1	None	7	93
2	MeCOCl	80 (68)	20
3	EtCOCl	64 (55)	36

[a] Conditions: AcCl/*anti*-**5a** = 8 (mol/mol); $AlCl_3$–$MeNO_2$/*anti*-**5a** = 12 (mol/mol). Reaction temperature: room temp. [b] Yields were determined by GLC analyses. [c] Isolated yields are shown in parentheses.

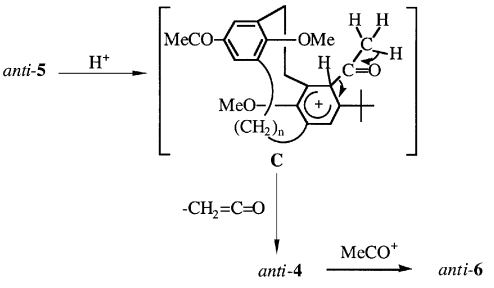


Scheme 3

the case of the [3.2] and [4.2] systems. These results suggest that *anti*-**5** could be an intermediate for the formation of the two-fold *ipso*-acetylation product *anti*-**6**.

Although the mechanism of *ipso*-acetylation of *anti*-**5** to afford *anti*-**6** is not completely clear, we tentatively proposed the reaction pathway illustrated in Scheme 4. The deacetylation[18] of the sterically hindered acetyl group occurs by the protonation at the acetyl group of *anti*-**5**, followed by ellimination of ketene to form *anti*-**4**, from which the *ipso*-acetylation again occurs to afford *anti*-**6**. However, from the presently available data, the reason why the acylation of *anti*-**5a** with propionyl chloride afforded *anti*-**6a**, but not *anti*-**6d**, is pending clarification.

The structures of *anti*-**5** and *anti*-**6** were assigned on the basis of elemental analyses and spectral data. For example, the ^1H NMR spectrum of *anti*-**5c** in $CDCl_3$ shows three singlets at δ 1.37 for *tert*-butyl protons, at δ 3.14 and 3.30 for methoxy protons, and a set of doublets (J = 2.0 Hz) at δ 7.44 and 7.70 for aromatic protons in a strongly deshielded region due to the acetyl group. It was also found that one of the ethano-bridge



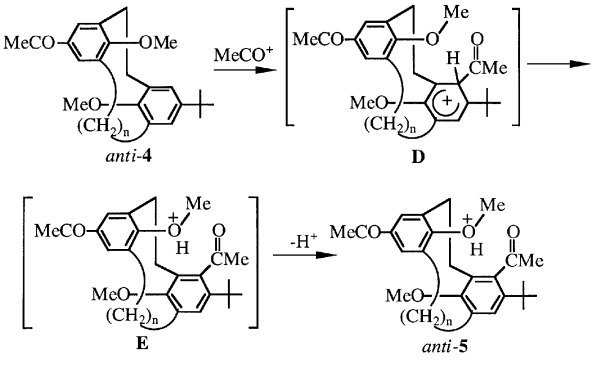
Scheme 4

protons is observed in a deshielded region (δ 2.72–2.92) due to the acetyl group at position 8. As a result, *anti*-**5c** has been assigned to *anti*-8,15-diacetyl-7-*tert*-butyl-10,18-dimethoxy-[4.2]MCP. A similar spectrum was observed for *anti*-**6c** and assigned to *anti*-7,15-diacetyl-10,18-dimethoxy[4.2]MCP.

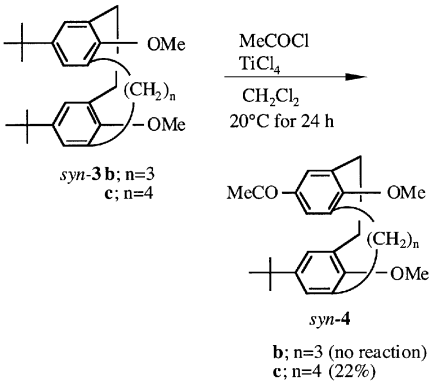
An interesting regioselectivity was observed to exclusively afford the second acetylation product at the 8-position ortho to the *tert*-butyl group of 10,18-dimethoxy[4.2]MCP, *anti*-**3c**. The pseudo-geminal directing effect of the methoxy group might be attributed to the basicity and geometric availability of the oxygen of the methoxy group. The oxygen is probably the strongest base in the medium. In the rate- and product-controlling step, the oxygen accepts a proton from the pseudo-geminal σ-complex (**D**) to form intermediate (**E**), thus producing a pseudo-geminal substituted product *anti*-**5c** as shown in Scheme 5. This result is consistent with Cram's reports[19] that acetyl and nitro groups on the [2.2]paracyclophane nucleus directed acetyl substitution to occur nearly exclusively in the 12-position to give the pseudo-geminal disubstituted hydrocarbon.

Cram *et al.* reported[20] that the rate of acetolysis of [2.2]paracyclophane tosylates was accelerated by the through-space electronic interactions with the opposite aromatic ring. This phenomenon was explained by the stability of the cationic intermediates, which could arise from the through-space electronic interaction with the benzene ring located on the opposite side. The rate increases as the degree of overlapping with the benzene ring increases. In the present [*n*.2]MCPs there are two possible conformers, anti and syn. As shown in Fig. 1, the through-space electronic interaction could occur through the intra-annular positions in the former conformer, but through face-to-face overlapping of the two benzene rings in the latter conformer. The different acylation behaviors of *anti*- and *syn*-[*n*.2]MCPs could give indications on which conformer contributes more strongly to the through-space electronic interaction.

Acetylation of *syn*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2]-MCP (*syn*-**3b**)[16] with acetyl chloride in the presence of $TiCl_4$ at room temperature for 24 h led only to recovery of the starting



Scheme 5



Scheme 6

compound. No formation of the desired acetylated compound *syn*-**4b** was detected. In contrast, acetylation of *syn*-[4.2]MCP, *syn*-**3c**, afforded the mono-*ipso*-acetylated product, *syn*-**4c**, in 22% yield along with recovery of the starting compound (Scheme 6). A lower yield of monoacetylated product is obtained with the syn-conformer than with the anti-conformer (83%). The initial σ-complex intermediate would be stabilized by the through-space electronic interaction through face-to-face overlapping with the opposing benzene ring (**B**), thus accelerating the reaction. However, the intra-annular interaction (**A**) might be much more favorable for stabilization of the initial σ-complex intermediate than face-to-face overlapping (**B**) (Fig. 1).

It should be noted that the present *ipso*-acetylation of **3** is quite different from the results of the acetylation of the corresponding internally methyl-substituted *anti*-di-*tert*-butyl[*n*.2]MCPs, *anti*-**7**. For example, *anti*-6,14-di-*tert*-butyl-9,17-dimethyl[3.2]MCP (*anti*-**7b**)[21] with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$ did not afford the desired *anti*-diacetyl[3.2]MCPs *anti*-**8b**, instead only the starting compound was recovered. This result seems to indicate that the methoxy group in **3** plays an important role in the present *ipso*-acetylation reaction. The *ipso*-acylation of **3** is attributed to the highly activated character of the aryl ring and the increased stabilization of the σ-complex intermediate, arising from a dienone-type σ-complex intermediate, which is only possible with a methoxy substituent.

We have reported[7] that similar treatment of 4-*tert*-butyl-2,6-dimethylanisole (**9**) with excess acetyl chloride in the presence of $TiCl_4$ at room temperature gave only quantitative recovery of starting compound. The same treatment of **9** with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$ afforded 4-acetyl-2,6-dimethylanisole (**10**) from *ipso*-acetylation at the *tert*-butyl group in 40% yield only along with the starting compound.

In contrast, as mentioned previously, acetylation of [*n*.2]MCPs **3** with acetyl chloride in the presence of $TiCl_4$ led to *ipso*-acetylation at only one of the *tert*-butyl groups to give **4** in moderate yields, along with the diacetyl products **5** and **6**, thus differing from the acetylation of **9** under the same conditions, which afforded only the starting compound. Cacace *et al.* reported[22] an intramolecular proton shift, namely, a ring-to-ring proton migration, in (β-phenylethyl) arenium ions during the cationic alkylation of 1,2-diphenylethanes, which occurs at a faster rate than the same reaction conducted with toluene in the gas phase. In the present system, an initial σ-complex intermediate would be stabilized by a through-space electronic interaction with the opposing benzene ring, therefore accelerating the reaction, as in the formylation of *tert*-butyl[*n*.2]MCPs.[5c] However, in the presence of $AlCl_3$–$MeNO_2$ two-fold *ipso*-acylation at the *tert*-butyl groups occurred (see Table 4), unlike the similar nitration of *anti*-**3**, which afforded only a mononitration product. These results indicate that

Table 4 Acylation of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane (*anti*-**3a**) with various acylating agents in the presence of Lewis acids[a]

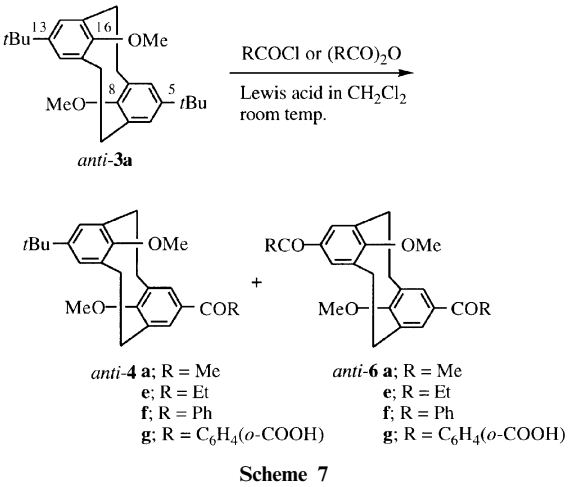
Run	Acylating agent	Catalyst	Reagents/*anti*-**3a** (mol/mol)	Time/h	Product (% yield)[b] *anti*-**4**	*anti*-**6**
1[c]	AcCl	A	3	1	74 (66)	4
2	AcCl	B	6	6	0	100 (81)
3	EtCOCl	B	6	6	0	100 (75)
4	PhCOCl	A	1.2	1	90 (80)	5[d]
5	PhCOCl	B	3	6	0	100 (90)
6	Phthalic anhydride	B	1.2	1	90 (71)	0
7	Phthalic anhydride	B	3	6	95 (80)	0

[a] Conditions: A: $TiCl_4$, catalyst/acylating agents = 4 (mol/mol); B: $AlCl_3$–$MeNO_2$, catalyst/acylating agents = 1.5 (mol/mol). Reaction temperature: room temp. [b] Yields were determined by GLC analysis. Isolated yields are shown in parentheses. [c] Reaction temperature: 0 °C. [d] Starting compound *anti*-**3a** was recovered in 5% yield.

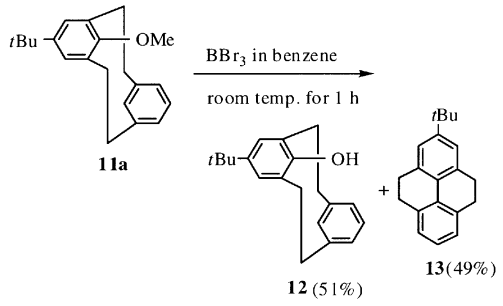
deactivation of the second aromatic ring by the acetyl group might be less than that caused by a nitro group.[8]

Acylation of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**3a**) with benzoyl chloride in the presence of $TiCl_4$ (Scheme 7) led to *ipso*-acylation at only one of the *tert*-butyl groups to give *anti*-5-benzoyl-13-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**4f**) in 80% yield (Table 4). In contrast, acylation of *anti*-**3a** with propionyl chloride or benzoyl chloride in the presence of $AlCl_3$–$MeNO_2$ led to two-fold *ipso*-acylation at the *tert*-butyl groups to give *anti*-5,13-diacyl-8,16-dimethoxy[2.2]MCPs *anti*-**6e** and *anti*-**6f** in 75 and 90% yields respectively. However, in spite of prolonged reaction times and increased amounts of catalyst, the diacylated compound *anti*-**6g** was not obtained in the case of phthalic anhydride, only the monoacylation product *anti*-**4g** being obtained in 80% yield.

Owing to electronic interaction between the two benzene rings, the proximity of the 8 and 16 positions and the considerable strain energy, [2.2]MCP is prone to give transannular reaction products under electrophilic reaction conditions.[14a,b] In fact, treatment of 5-*tert*-butyl-8-methoxy[2.2]MCP (**11a**) with BBr_3 in benzene at room temperature (Scheme 8) afforded 5-*tert*-butyl-8-hydroxy[2.2]MCP (**12**) in 51% yield along with the transannular reaction product, 2-*tert*-butyl-4,5,9,10-tetrahydropyrene (**13**).[23] This transannular cyclization reaction was also observed when compound **11a** was treated with $TiCl_4$ or $AlCl_3$–$MeNO_2$ in benzene. Therefore, the removal



Scheme 7



Scheme 8

of a *tert*-butyl group by a Lewis acid catalyzed transalkylation is impossible.

Thus, there is substantial interest in investigating the acetylation of the 8-methoxy[2.2]MCPs **11**, which might afford *ipso*-acetylation products because of the deactivation of the transannular cyclization reaction by the introduced acetyl group. *ipso*-Acetylation in the system might compete with the transannular cyclization reaction to afford **13**. In fact, the presently developed procedure was extended to the acetylation of the 8-methoxy[2.2]MCPs **11a–d**. The reaction was carried out under the same conditions as described above and the results are summarized in Table 5.

Acetylation of 5-*tert*-butyl-8-methoxy[2.2]MCP (**11a**) with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$ led to *ipso*-acylation at the *tert*-butyl group to give 5,12-diacetyl-8-methoxy[2.2]MCP (**15a**) and 5,13-diacetyl-8-methoxy[2.2]MCP (**16**) in 80 and 20% yields, respectively (Scheme 9). Similar results were obtained in the case of the 13-methyl derivative **11b** to afford **15b** in 94% yield. However, in the case of the 13-*tert*-butyl derivative **11c**, only the transannular cyclization reaction product **17c** was obtained in quantitative yield. In contrast, compound **11d**, which has an electron-withdrawing group (cyano), afforded only the *ipso*-acetylation product **14d**. These results are consistent with the order of reactivity of **11a–d** to iodine.[24]

Table 5 Acetylation of 8-methoxy[2.2]metacyclophanes **11** with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$[a]

Run	Substrate	R	Products (% yield)[b]
1	**11a**	H	**15a** (80), **16** (20)
2	**11b**	Me	**15b** (94)
3	**11c**	^{t}Bu	**17c** (100)
4	**11d**	CN	**14d** (100)

[a] Conditions: AcCl/**11** = 4 (mol/mol), $AlCl_3$/AcCl = 1.5 (mol/mol). Reaction temperature: 0 °C. [b] Yields were determined by GLC analysis.

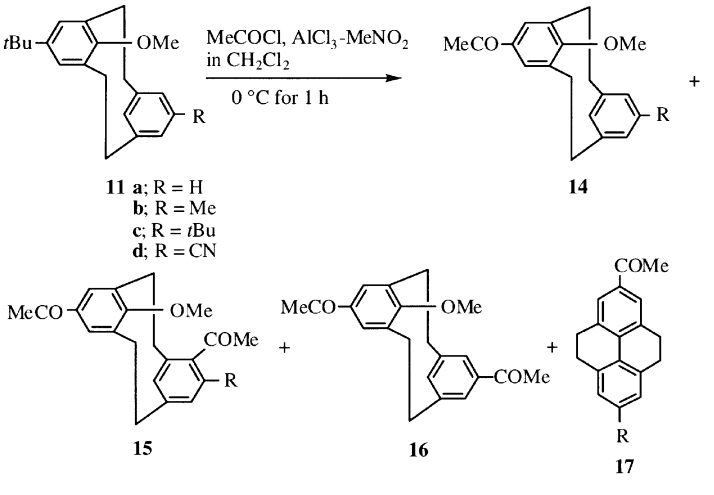
We conclude that the selective *ipso*-acylation of *syn*- and *anti*-di-*tert*-buty[*n*.2]MCPs **3** and **11** led to the direct introduction of one or two acyl group(s) due to a through-space electronic interaction with the opposing benzene ring, similar to the electrophilic aromatic substitution of MCPs. The extent of *ipso*-acylation of **3** has been controlled by the activity of the catalyst used. Especially, the present two-fold *ipso*-acylation with acyl chloride in the presence of $AlCl_3$–$MeNO_2$ provides excellent yields and easy isolation of the products. The presently developped procedure was further applied to the direct removal of a *tert*-butyl group by electrophilic substitution of *tert*-butyl-8-methoxy[2.2]MCPs **11**, which are prone to give transannular reaction products under electrophilic reaction conditions. Further studies on *ipso*-acylation are currently in progress in our laboratory.

Experimental

All mps (Yanagimoto MP-S1) and bps are uncorrected. NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: *J* values are given in Hz. IR spectra were measured on samples as KBr pellets or liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured with a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analyses were performed by Yanaco MT-5. GLC analyses were performed with a Shimadzu gas chromatograph GC-14A; silicone OV-1 2 m column; programmed temperature rise of 12 °C min^{-1}; nitrogen carrier gas flow of 25 mL min^{-1}.

Materials

anti-Dimethoxy[*n*.2]MCPs *anti*-**3a–c**,[15] *syn*-dimethoxy[*n*.2]-MCPs *syn*-**3b,c**,[15] *anti*-6,14-di-*tert*-butyl-9,17-dimethyl[3.2]-MCP (*anti*-**7**)[23] and 8-methoxy[2.2]MCPs **11a–d** were prepared according to the reported procedures.[24]



Scheme 9

General procedure for $TiCl_4$ catalyzed acetylation of di-*tert*-butyldimethoxy[*n*.2]metacyclophane 3

To a solution of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-**3a** (109 mg, 0.286 mmol) and acetyl chloride (0.08 mL, 1.09 mmol) in methylene dichloride (2.2 mL) was added a solution of titanium tetrachloride (0.44 mL, 4.0 mmol) in methylene dichloride (0.5 mL) at 0 °C. After the reaction mixture had been stirred for 1 h at room temp., it was poured into ice-water (20 mL). The organic layer was extracted with CH_2Cl_2 (20 mL × 2). The extract was washed with water (10 mL × 2), dried (Na_2SO_4), and concentrated. The residue was subjected to silica gel (Wako, C-300; 100 g) column chromatography using as eluent benzene–$CHCl_3$, 1:1, and $CHCl_3$ to give *anti*-**4a** (65 mg, 62%), *anti*-**5a** (20 mg, 17%) and *anti*-**6a** (4 mg, 4%).

Compounds *anti*-**4b**, *anti*-**4c**, *anti*-**5b** and *anti*-**5c** were obtained by the acylation of *anti*-**3b** and *anti*-**3c** with acetyl chloride in a similar manner to that described above for *anti*-**3a**. The reaction conditions and yields are compiled in Table 1.

***anti*-5-Acetyl-13-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-4a.** *anti*-**4a** was obtained as colorless prisms (MeOH), mp 160–163 °C; υ_{max}(KBr)/cm^{-1}: 2951, 2930, 2870, 1673 (C=O), 1588, 1479, 1460, 1413, 1352, 1286, 1191, 1169, 1191, 1169, 1159, 1020; δ_H($CDCl_3$): 1.32 (9 H, s), 2.57 (3 H, s), 2.60–2.81 (8 H, m), 2.90 (3 H, s), 2.98 (3 H, s), 7.05 (2 H, s), 7.69 (2 H, s); *m*/*z*: 366 (M^+). Anal. calcd for $C_{24}H_{30}O_3$ (366.50): C, 78.65; H, 8.25. Found: C, 78.65; H, 8.27.

***anti*-4,13-Diacetyl-5-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-5a.** *anti*-**5a** was obtained as colorless prisms (MeOH), mp 200–201 °C; υ_{max}(KBr)/cm^{-1}: 2933, 1679 (C=O), 1592, 1474, 1352, 1296, 1280, 1246, 1191, 1023; δ_H($CDCl_3$): 1.36 (9 H, s), 2.57 (3 H, s), 2.60–2.90 (8 H, m), 2.66 (3 H, s), 2.90 (3 H, s), 3.09 (3 H, s), 7.16 (1 H, s), 7.67 (2 H, s); *m*/*z*: 408 (M^+). Anal. calcd for $C_{26}H_{32}O_4$ (408.54): C, 76.44; H, 7.9. Found: C, 76.19; H, 7.88.

***anti*-6-Acetyl-14-*tert*-butyl-9,17-dimethoxy[3.2]metacyclophane, *anti*-4b.** *anti*-**4b** was obtained as colorless prisms (MeOH), mp 92–95 °C; υ_{max}(KBr)/cm^{-1}: 2930, 2820, 1677 (C=O), 1592, 1481, 1445, 1289, 1252, 1215, 1192, 1023; δ_H($CDCl_3$): 1.32 (9 H, s), 1.96–2.07 (2 H, m), 2.57 (3 H, s), 2.39–2.77 (8 H, m), 3.02 (3 H, s), 3.08 (3 H, s), 6.98 (1 H, d, *J* 2.4), 7.03 (1 H, d, *J* 2.4), 7.64 (2 H, s); *m*/*z*: 380 (M^+). Anal. calcd for $C_{25}H_{32}O_3$ (380.53): C, 78.91; H, 8.43. Found: C, 78.77; H, 8.34.

***anti*-7,14-Diacetyl-6-*tert*-butyl-9,17-dimethoxy[3.2]metacyclophane, *anti*-5b.** *anti*-**5b** was obtained as colorless prisms (MeOH), mp 169–171 °C; υ_{max}(KBr)/cm^{-1}: 2933, 1691, 1673 (C=O); δ_H($CDCl_3$): 1.37 (9 H, s), 2.00–2.07 (2 H, m), 2.45–2.74 (8 H, m), 2.57 (3 H, s), 2.59 (3 H, s), 3.07 (3 H, s), 3.18 (3 H, s), 7.11 (1 H, s), 7.67 (2 H, s); *m*/*z*: 422 (M^+). Anal. calcd for $C_{27}H_{34}O_4$ (422.57): C, 76.74; H, 8.11. Found: C, 76.36; H, 8.11.

***anti*-7-Acetyl-15-*tert*-butyl-10,18-dimethoxy[4.2]metacyclophane, *anti*-4c.** *anti*-**4c** was obtained as a pale yellow oil; υ_{max}(NaCl)/cm^{-1}: 1675 (C=O); δ_H($CDCl_3$): 1.32 (9 H, s), 1.26–1.37 (4 H, m), 2.03–2.22 (2 H, m), 2.58 (3 H, s), 2.60–2.78 (6 H, m), 3.16 (3 H, s), 3.21 (3 H, s), 6.80 (1 H, d, *J* 2.4), 7.08 (1 H, d, *J* 2.4), 7.45 (1 H, d, *J* 2.4), 7.73 (1 H, d, *J* 2.4); *m*/*z*: 394 (M^+). Anal. calcd for $C_{26}H_{34}O_3$ (394.56): C, 79.15; H, 8.69. Found: C, 78.93; H, 8.55.

***anti*-8,15-Diacetyl-7-*tert*-butyl-10,18-dimethoxy[4.2]metacyclophane, *anti*-5c.** *anti*-**5c** was obtained as colorless prisms (MeOH), mp 126–128 °C; υ_{max}(KBr)/cm^{-1}: 2958, 2920, 2862, 1677 (C=O), 1479, 1297, 1244, 1168, 1015; δ_H($CDCl_3$): 1.37 (9 H, s), 1.18–1.53 (4 H, m), 2.13–2.24 (2 H, m), 2.57 (3 H, s), 2.63 (3 H, s), 2.72–2.92 (6 H, m), 3.19 (3 H, s), 3.30 (3 H, s), 6.92 (1 H, s), 7.44 (1 H, d, *J* 2.0), 7.70 (1 H, d, *J* 2.0); *m*/*z*: 436 (M^+). Anal. calcd for $C_{28}H_{36}O_4$ (436.60): C, 77.03; H, 8.31. Found: C, 77.26; H, 8.11.

General procedure for $AlCl_3$–$MeNO_2$ catalyzed acetylation of *anti*-di-*tert*-butyldimethoxy[*n*.2]metacyclophane, *anti*-3

To a solution of *anti*-**3a** (108.8 mg, 0.286 mmol) and acetyl chloride (0.16 mL, 2.29 mmol) in methylene dichloride (2.2 mL) was added a solution of $AlCl_3$ (457.5 mg, 3.43 mmol) in $MeNO_2$ (1.0 mL) at 0 °C. After the reaction mixture had been stirred at room temperature for 1 h, it was poured into ice-water (10 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL × 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with $CHCl_3$ as eluent to give a solid, which was recrystallized from hexane to yield *anti*-5,13-diacetyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-**6a** (100.8 mg, 82%) as colorless prisms, mp 225–228 °C; υ_{max}(KBr)/cm^{-1}: 2933, 1671 (C=O), 1587, 1412, 1360, 1285, 1236, 1187, 1158, 1012; δ_H($CDCl_3$): 2.58 (6 H, s), 2.65–2.85 (8 H, m), 3.09 (6 H, s), 7.72 (4 H, s); *m*/*z*: 352 (M^+). Anal. calcd for $C_{22}H_{24}O_4$ (352.43): C, 74.98; H, 6.86. Found: C, 74.85; H, 6.92.

Compounds *anti*-**6b** and *anti*-**6c** were obtained by the acylation of *anti*-**3b** and *anti*-**3c** with acetyl chloride in a similar manner to that described above for *anti*-**3a**. The reaction conditions and yields are compiled in Table 1.

***anti*-6,14-Diacetyl-9,17-dimethoxy[3.2]metacyclophane, *anti*-6b.** *anti*-**6b** was obtained as colorless prisms (MeOH), mp 167–169 °C; υ_{max}(KBr)/cm^{-1}: 2938, 1656 (C=O), 1587, 1359, 1275, 1212, 1166, 906, 740, 613; δ_H($CDCl_3$): 2.00–2.10 (2 H, m), 2.59 (6 H, s), 2.46–2.76 (4 H, m), 3.07 (6 H, s), 2.56–2.81 (4 H, m), 7.65 (2 H, d, *J* 2.0), 7.67 (2 H, d, *J* 2.0); *m*/*z*: 366 (M^+). Anal. calcd for $C_{23}H_{26}O_4$ (366.46): C, 75.38; H, 7.15. Found: C, 75.16; H, 7.20.

***anti*-7,15-Diacetyl-10,18-dimethoxy[4.2]metacyclophane, *anti*-6c.** *anti*-**6c** was obtained as colorless prisms (hexane–benzene, 1 : 1), mp 150–151 °C; υ_{max}(KBr)/cm^{-1}: 2962, 2927, 2872, 1676 (C=O), 1595, 1478, 1460, 1418, 1359, 1289, 1191, 1165, 1086, 1010; δ_H($CDCl_3$): 1.18–1.53 (4 H, m), 2.13–2.24 (2 H, m), 2.59 (6 H, s), 2.72–2.89 (6 H, m), 3.21 (6 H, s), 7.47 (2 H, d, *J* 2.4), 7.76 (2 H, d, *J* 2.4); *m*/*z*: 380 (M^+). Anal. calcd for $C_{24}H_{28}O_4$ (380.49): C, 75.76; H, 7.42. Found: C, 76.56; H, 7.66.

General procedure for $AlCl_3$–$MeNO_2$ catalyzed acetylation of di-*tert*-butyldimethoxy[*n*.2]metacyclophane *anti*-3 to afford *anti*-5

To a solution of *anti*-**3a** (380.6 mg, 1.0 mmol) and acetyl chloride (0.283 mL, 4.0 mmol) in methylene dichloride (20 mL) was added a solution of $AlCl_3$ (800 mg, 6.0 mmol) in $MeNO_2$ (1.6 mL) at 0 °C. After the reaction mixture had been stirred at room temp. for 1 h, it was poured into ice-water (20 mL). The organic layer was extracted with CH_2Cl_2 (20 mL × 2). The extract was washed with water (10 mL × 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with $CHCl_3$ as eluent to give a mixture of *anti*-**4a** and *anti*-**5a** as a colorless solid, which was recrystallized from methanol to yield *anti*-**5a** (77.0 mg, 20%) as colorless prisms.

Compounds *anti*-**5b** and *anti*-**5c** were obtained by the acylation of *anti*-**3b** and *anti*-**3c** with acetyl chloride in a similar

manner to that described above for *anti*-**3a**. The reaction conditions and yields are compiled in Table 2.

General procedure for acylation of *anti*-3a with acylation reagents in the presence of Lewis acids

To a solution of *anti*-**3a** (108.8 mg, 0.286 mmol) and propionyl chloride (0.12 mL, 1.72 mmol) in methylene dichloride (2.2 mL) was added a solution of $AlCl_3$ (344.0 mg, 2.58 mmol) in $MeNO_2$ (1.0 mL) at 0 °C. After the reaction mixture had been stirred at room temp. for 6 h, it was poured into ice-water (10 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL × 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with $CHCl_3$as eluent to give a solid, which was recrystallized from hexane to yield the desired 8,16-dimethoxy-5,13-dipropionyl[2.2]metacyclophane, *anti*-**6e** (100.8 mg, 75%) as colorless prisms, mp 208–210 °C; υ_{max}(KBr)/cm^{-1}: 1677 (C=O); δ_H($CDCl_3$): 1.24 (6 H, d, *J* 7.3), 2.63–2.86 (8 H, m), 2.86 (6 H, s), 2.98 (4 H, q, *J* 7.3), 7.72 (4 H, s); *m*/*z*: 380 (M^+). Anal. calcd for $C_{24}H_{28}O_4$ (380.49): C, 75.76; H, 7.42. Found: C, 75.81; H, 7.25.

Compounds *anti*-**4f** and *anti*-**6f** were obtained by the acylation of *anti*-**3a** with benzoyl chloride in a similar manner to that described above. The reaction conditions and yields are compiled in Table 4.

***anti*-5-Benzoyl-13-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-4f.** *anti*-**4f** was obtained as colorless prisms (hexane), mp 166–170 °C; υ_{max}(KBr)/cm^{-1}: 1648 (C=O); δ_H($CDCl_3$): 1.33 (9 H, s), 2.60–2.79 (8 H, m), 2.98 (3 H, s), 3.02 (3 H, s), 7.06 (2 H, s), 7.60 (2 H, s), 7.49–7.82 (5 H, m); *m*/*z*: 428 (M^+). Anal. calcd for $C_{29}H_{32}O_3$ (428.8): C, 81.27; H, 7.53. Found: C, 81.15; H, 7.44.

***anti*-5,13-Dibenzoyl-8,16-dimethoxy[2.2]metacyclophane, *anti*-6f.** *anti*-**6f** was obtained as colorless prisms (hexane), mp > 300 °C; υ_{max}(KBr)/cm^{-1}: 1651 (C=O); δ_H($CDCl_3$): 2.66–2.85 (8 H, m), 3.08 (6 H, s), 7.59 (4 H, s), 7.45–7.84 (10 H, m); *m*/*z*: 476 (M^+). Anal. calcd for $C_{32}H_{28}O_4$ (476.58): C, 80.65; H, 5.92. Found: C, 80.80; H, 5.96.

Acylation of *anti*-3a with phthalic anhydride in the presence of $AlCl_3$–$MeNO_2$

To a solution of *anti*-**3a** (190.3 mg, 0.50 mmol) and phthalic anhydride (89.0 mg, 0.60 mmol) in methylene dichloride (3.0 mL) was added a solution of $AlCl_3$ (239.5 mg, 1.8 mmol) in $MeNO_2$ (0.4 mL) at 0 °C. After the reaction mixture had been stirred at room temperature for 1 h, it was poured into ice-water (10 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL × 2), dried (Na_2SO_4), and concentrated. The residue was recrystallized from benzene to yield the desired 5-*tert*-butyl-13-(2-carboxybenzoyl)-8,16-dimethoxy[2.2]metacyclophane, *anti*-**4g** (167.8 mg, 71%) as colorless prisms, mp 280 °C; υ_{max}(KBr)/cm^{-1}: 1685 (C=O); δ_H($CDCl_3$): 1.28 (9 H, s), 2.46–2.59 (4 H, m), 2.67–2.79 (4 H, m), 2.90 (3 H, s), 2.97 (3 H, s), 7.04 (2 H, s), 7.29–7.31 (1 H, m), 7.35 (2 H, s), 7.59–7.69 (2 H, m), 7.96–7.99 (1 H, m); *m*/*z*: 472 (M^+). Anal. calcd for $C_{30}H_{32}O_5$ (472.59): C, 76.25; H, 6.83. Found: C, 76.63; H, 7.00.

Acylation of *syn*-3c with acetyl chloride in the presence of $TiCl_4$

To a solution of *syn*-**3c** (116.9 mg, 10.29 mmol) and acetyl chloride (0.08 mL, 1.1 mmol) in methylene dichloride (2.2 mL) was added a solution of $TiCl_4$ (0.44 mL, 4.0 mmol) in methylene dichloride (0.5 mL) at 0 °C. After the reaction mixture had been stirred at 20 °C for 24 h, it was poured into ice-water (10 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL × 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with $CHCl_3$ as eluent to give *syn*-7-acetyl-15-*tert*-butyl-10,18-dimethoxy[4.2]-metacyclophane, *syn*-**4c**, as a colorless oil; υ_{max}(NaCl)/cm^{-1}: 1677 (C=O); δ_H($CDCl_3$): 1.05 (9 H, s), 1.08–1.36 (2 H, m), 1.90–2.16 (4 H, m), 2.40 (3 H, s), 2.65–2.84 (4 H, m), 3.46–3.60 (2 H, m), 3.58 (3 H, s), 3.60 (3 H, s), 6.45 (1 H, d, *J* 2.4), 6.49 (1 H, d, *J* 2.4), 7.12 (1 H, d, *J* 2.4), 7.30 (1 H, d, *J* 2.4); *m*/*z*: 394 (M^+). Anal. calcd for $C_{26}H_{34}O_3$ (394.56): C, 79.15; H, 8.69. Found: C, 79.36; H, 8.71.

General procedure for acylation of 8-methoxy[2.2]metacyclophanes 11 with acetyl chloride in the presence of $AlCl_3$–$MeNO_2$

To a solution of 5-*tert*-butyl-8-methoxy-13-methyl[2.2]metacyclophane (**11b**; 80.0 mg, 0.26 mmol) and acetyl chloride (0.083 mL, 1.04 mmol) in methylene dichloride (2.0 mL) was added a solution of $AlCl_3$ (208.0 mg, 1.56 mmol) in $MeNO_2$ (0.4 mL) at 0 °C. After the reaction mixture had been stirred at 0 °C for 1 h, it was poured into ice-water (10 mL). The organic layer was extracted with CH_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL × 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with $CHCl_3$ as eluent to give a solid, which was recrystallized from methanol to yield the desired 5,12-diacetyl-8-methoxy-13-methyl[2.2]metacyclophane (**15b**) (65.0 mg, 74%) as colorless prisms, mp 74–76 °C; υ_{max}(KBr)/cm^{-1}: 1696 (C=O); δ_H($CDCl_3$): 1.91–2.22 (2 H, m), 2.26 (3 H, s), 2.52 (3 H, s), 2.61 (3 H, s), 2.65–3.30 (6 H, m), 3.15 (3 H, s), 4.10 (1 H, s), 6.90 (1 H, s), 7.69 (2 H, s); *m*/*z*: 336 (M^+). Anal. calcd for $C_{22}H_{24}O_3$ (336.43): C, 78.54; H, 7.19. Found: C, 78.22; H, 7.29.

Compounds **15a**, **16**, **17c**, and **14d** were obtained by the acetylation of **11** with acetyl chloride in a similar manner to that described above for **15b**. Attempted separation of the products **15a** and **16** in the ratio 80:20 (NMR spectrum) failed. The reaction conditions and yields are compiled in Table 5.

5,12-Diacetyl-8-methoxy[2.2]metacyclophane, 15a and 5,13-diacetyl-8-methoxy[2.2]metacyclophane, 16. A mixture of **15a** and **16** was obtained as colorless prisms (methanol), mp 130–134 °C; υ_{max}(KBr)/cm^{-1}: 1681 (C=O); δ_H($CDCl_3$) for **15a**: 1.74–1.84 (1 H, m), 2.09–2.30 (1 H, m), 2.61–3.18 (5 H, m), 2.61 (3 H, s), 2.63 (3 H, s), 3.30 (3 H, s), 3.93–4.00 (1 H, m), 4.32 (1 H, d, *J* 1.95), 7.12 (1 H, dd, *J* 7.81, 1.95), 7.59 (1 H, d, *J* 7.81), 7.70 (1 H, d, *J* 1.95), 7.74 (1 H, d, *J* 1.95); δ_H($CDCl_3$) for **16**: 1.74–1.84 (1 H, m), 2.09–2.30 (1 H, m), 2.61–3.18 (6 H, m), 2.61 (3 H, s), 2.64 (3 H, s), 3.03 (3 H, s), 4.38 (1 H, s), 7.73 (4 H, s); *m*/*z*: 322 (M^+). Anal. calcd for $C_{21}H_{22}O_3$ (322.41): C, 78.23; H, 6.88. Found: C, 78.10; H, 6.96.

2-Acetyl-7-*tert*-butyl-4,5,9,10-tetrahydropyrene, 17c. 17c was obtained as colorless prisms (methanol), mp 106–108 °C; υ_{max}(KBr)/cm^{-1}: 1676 (C=O); δ_H($CDCl_3$): 1.35 (9 H, s), 2.60 (3 H, s), 2.92 (8 H, s), 7.13 (2 H, s), 7.67 (2 H, s); *m*/*z*: 304 (M^+). Anal. calcd for $C_{22}H_{24}O$ (304.44): C, 86.8; H, 7.95. Found: C, 86.57; H, 8.03.

5-Acetyl-13-cyano-8-methoxy[2.2]metacyclophane, 14d. 14d was obtained as colorless prisms [hexane–benzene (5 : 1)], mp 174–179 °C; υ_{max}(KBr)/cm^{-1}: 2223 (CN), 1677 (C=O); δ_H($CDCl_3$): 2.10–2.22 (4 H, s), 2.55–2.65 (1 H, m), 2.63 (3 H, s), 2.85–3.00 (2 H, m), 3.07 (3 H, s), 3.05–3.17 (1 H, m),

4.39 (1 H, s), 7.38 (2 H, d, *J* 1.5), 7.73 (2 H, s); *m*/*z*: 305 (M^+). Anal. calcd for $C_{20}H_{19}O_2N$ (305.38): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.83; H, 6.46; N, 4.27.

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