Medium-sized cyclophanes. Part 36.[1] Synthesis and conformational studies of dimethoxy[*m.n*]metacyclophanes

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The synthesis and structure of internally substituted [*m.n*]metacyclophanes are described. The preparation of *tert*-butyl[*n*.2]metacyclophanes **8** was carried out by using the *tert*-butyl group as a positional protecting group on the aromatic ring. The reaction of 1,*n*-bis(3-chloromethyl-2-methoxyphenyl)alkanes **5** with Na_2S in ethanol under high-dilution conditions, followed by oxidation with *m*-chloroperbenzoic acid, afforded the corresponding thia[*n*.3]metacyclophane dioxide **7**. The pyrolysis of *anti*-thia[*n*.3]metacyclophane dioxides **7** gave both the *syn*- and *anti*-[*n*.2]metacyclophane **8** except for the case of *anti*-thia[10.3]metacyclophane dioxide **7f**, which afforded the solely conformationally mobile analogue **8f** at room temperature. The solution conformation of [*m.n*]metacyclophanes is sensitive to the chain length of the bridges. The ring-inversion energy barriers determined by variable-temperature ^1H NMR spectroscopy decrease with increasing length of the bridges. In the case of thia[*n*.3]metacyclophanes **6** and thia[*n*.3]metacyclophane dioxides **7**, [7.3]-analogues **6d** and **7d** are both conformationally rigid below 140 °C, but [8.3]-analogues **6e** and **7e** exhibit conformational flipping with coalescence temperatures of −20 °C ($\Delta G_c^{\ddagger}$ = 12.0 kcal mol^{-1})† and 50 °C ($\Delta G_c^{\ddagger}$ = 15.6 kcal mol^{-1}), respectively. On the other hand, [*n*.2]metacyclophanes **8** are conformationally rigid for [7.2]-**8d** and [8.2]-metacyclophane **8e** below 140 °C, but [10.2]metacyclophane **8f** exhibits conformational flipping above −20 °C ($\Delta G_c^{\ddagger}$ = 11.9 kcal mol^{-1}). Demethylation of dimethoxythia[*n*.3]-**6** and dimethoxy [*n*.2]metacyclophanes **8** with BBr_3 in dichloromethane afforded the corresponding dihydroxythia[*n*.3]-**9** and dihydroxy[*n*.2]metacyclophanes **1**, respectively. Methylation of the hydroxy groups of dihydroxy[*n*.2]metacyclophanes **1** led to the conformationally rigid structures, *i.e.* the fixed conformations such as '*syn*' and '*anti*' conformations. The *syn*:*anti* ratio of the products is strongly governed by the number of the methylene groups in the bridge. Thus the proportion of *syn* conformer increases with increasing number of methylene bridges. The template effect of the sodium cation plays an important role in this alkylation for the higher dihydroxy[*n*.2]metacyclophanes **1c–f** which adopt more flexible conformations. Conversion of the hydroxy groups of dihydroxy[10.2]metacyclophane **1f** into ethoxy and benzyloxy groups afforded exclusively *syn*-conformers *syn*-**10a** and *syn*-**10b**, which are conformationally rigid structures. The assignment of *syn* and *anti* conformations was confirmed by ^1H NMR analysis.

The synthesis and stereochemical aspects of conformationally mobile [*m.n*]MCPs (MCP = metacyclophane) have been of interest for the past decade,[2] particular attention[3] being paid to [2.2]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] Sato *et al.* have also reported on the conformational behaviour of the 2-thia-[3.2]MCPs and their analogues.[2a] While in [3.3]MCP the aromatic rings preferentially appear to adopt the *syn*-arrangement, its lower and higher homologues, *i.e.* [3.2]-, [4.2]- and [4.3]-MCPs, prefer the mobile *anti*-conformation.[5]

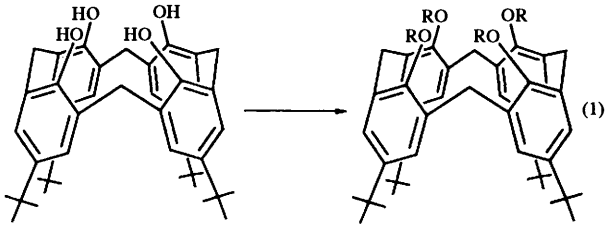
The ring-inversion barriers for the higher [*m.n*]MCPs are estimated and found to decrease with increasing length of the bridges.[5] Most of the reported [*m.n*]metacyclophanes, however, are internally unsubstituted ones. The introduction of intra-annular substituents, such as methyl, increases the barrier to conformational flipping;[6] for example, both *syn*- and *anti*-9,18-dimethyl-2,11-dithia[3.3]MCP exist as discrete conformers, whereas 2,11-dithia[3.3]MCP is conformationally mobile.[7,8] Surprisingly, few of the higher MCPs containing internal methyl substituents have been studied[9] despite the fact that the chemical shift of the methyl group provides a convenient probe for ^1H NMR studies of any possible conformational changes. Hence, the introduction of substituents into the internal positions of higher [*m.n*]MCPs may influence not only the ring inversion but may also give rise to a change of the equilibrium position of *syn* and *anti* conformers.

Recently, we have found[10] that *anti*-11,19-dimethyl[5.2]-MCP and *anti*-12,20-dimethyl[6.2]MCP are both conformationally rigid below 150 °C, but *anti*-14,22-dimethyl[8.2]MCP exhibits conformational flipping at the coalescence temperature of 140 °C, and the estimated energy barrier to flipping is 20.5 kcal mol^{-1} in hexachlorobuta-1,3-diene. The conformation of dihydroxy[*n*.2]MCPs (*n* = 2–6) in solution is also affected by the chain length of the bridges.[11]

On the other hand, Gutsche, Reinhoudt and Shinkai[12,13] have reported that the introduction of substituents onto the hydroxy groups of tetrahydroxy[1.1.1.1]MCP (calix[4]arene) led to the conformationally rigid structures, *i.e.* the fixed conformations such as 'cone,' 'partial cone,' '1,2-alternate' and '1,3-alternate.' A 'cone' shape conformation is shown in equation (1).

However, there was no report concerning the introduction of substituents on the hydroxy groups of dihydroxy[*n*.2]MCPs in spite of the formation of only two conformers, *i.e.*, *syn*- and *anti*-conformer, being possible. In contrast to four possible conformations in calix[4]arenes,[12a] the conformational isomerism in the present system is much more simplified. Furthermore, the conformations regarding internally substituted

† 1 cal = 4.184 J.

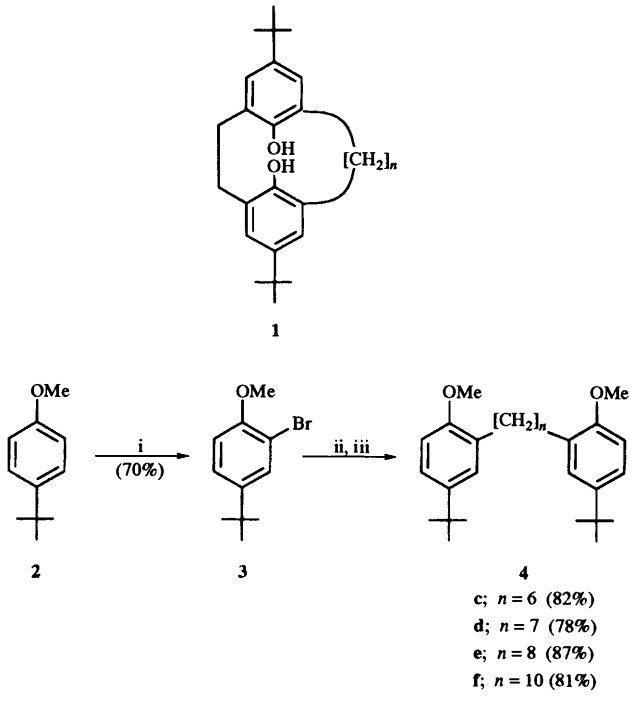


dihydroxy[*m.n*]MCPs having more than seven methylene bridges are so far not known. Thus there is substantial interest in investigating the effects of intra-annular substituents on the conformations of the flexible higher dihydroxy[*n*.2]MCPs.

In this paper we report on the synthesis of intra-annularly *O*-substituted dihydroxy[*n*.2]MCPs, from anisole by using the *tert*-butyl function as a positional protective group,[14] and on the investigation of the ring inversion of these systems.

Results and discussion

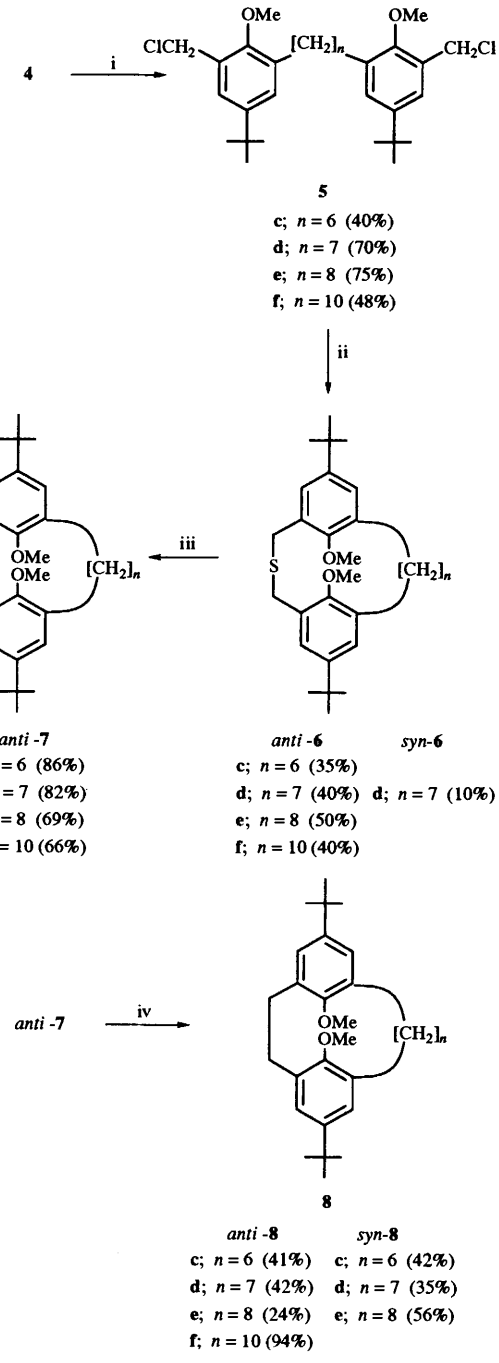
1,*n*-Bis(5-*tert*-butyl-2-methoxyphenyl)alkanes **4** have been prepared according to our previous papers.[10,11,15] Thus, the cross-coupling reactions of 5-*tert*-butyl-2-methoxyphenylmagnesium bromide with 1,*n*-dibromoalkanes have been carried out in the presence of copper(I) bromide as a catalyst in a mixture of hexamethylphosphoric triamide (HMPA) and tetrahydrofuran (THF) at reflux temperature to give the desired 1,*n*-bis(5-*tert*-butyl-2-methoxyphenyl)alkanes **4d–4f** in satisfactory yields (Scheme 1).



Scheme 1 *Reagents and conditions:* i, Br_2CCl_4; ii, Mg, THF; iii, $Br[CH_2]_nBr$, CuBr, HMPA, reflux for 17 h

The chloromethylation of diarylalkanes **4d–4f** with paraformaldehyde in the presence of HCl–H_3PO_4[11] afforded the corresponding bischloromethyl derivatives **5d–5f** in 48–75% yield (Scheme 2).

The cyclization of chlorides **5d–5f** has been carried out under the conditions of high dilution and in ethanolic Na_2S[10,11] to afford the corresponding dimethoxy-15/16/17-thia[*n*.3]MCPs **6d–6f** in 40–50% yield. The ^1H NMR spectrum of dimethoxy-



Scheme 2 *Reagents and conditions:* i, $(HCHO)_x$. HCl, H_3PO_4, AcOH, 90–95 °C for 36 h; ii, Na_2S, EtOH, high dilution; iii, MCPBA, CH_2Cl_2, room temp. for 17 h; iv, 500 °C, 1 mmHg

15-thia[7.3]MCP **6d** showed two kinds of methoxy protons, each as a singlet. Thiacyclophane **6d** has been found to consist of two isomers, *syn*- and *anti*-**6d** by its ^1H NMR spectrum (20 : 80) (Fig. 1). Unfortunately, attempted separation of these isomers as pure compounds failed. They are thermally stable and not interconvertible [at 150 °C in dimethyl sulfoxide (DMSO) solution or at 400 °C in the solid state].

The ^1H NMR spectra of conformers *anti*-**6d** and *syn*-**6d** showed the methoxy protons at δ 3.30 and 3.64, respectively. The aromatic protons of conformer *syn*-**6d** were observed at a much higher field position (δ 6.81 and 7.14) than those of conformer *anti*-**6d** (δ 6.98 and 7.29). It is well known that the internal methoxy protons of *anti*-[2.2]MCPs should show an upfield shift due to the ring current in the opposite aromatic ring.[16] On the other hand, the ^1H NMR spectra of the

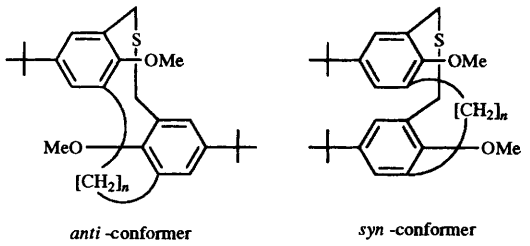


Fig. 1 Schematic drawing of *anti*- and *syn*-conformers of compounds **6**

CH_2SCH_2 bridge of dimethoxy-16/18-thia-[8.3]- **6e** and -[10.3]-MCP **6f** showed a singlet at room temperature due to their flexible conformations. This behaviour strongly suggests that the rate of conformational ring flipping is faster than the NMR time-scale above room temperature.

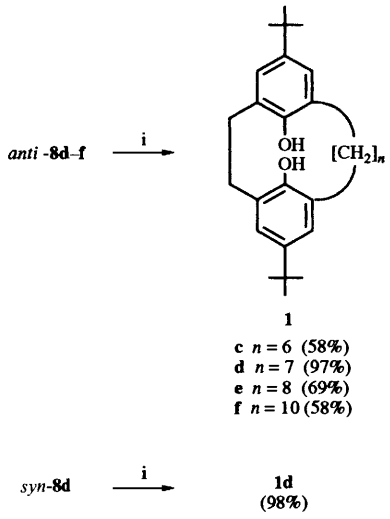
Oxidation of sulfides **6d–6f** with *m*-chloroperbenzoic acid (MCPBA) furnished the corresponding sulfones **7d–7f** in 66–82% yield. There is no exchange between the *syn*- and *anti*-conformers during the oxidation of sulfide **6d** to sulfone **7d**.

Pyrolysis of sulfones **7d–7f** under reduced pressure (1 mmHg) was carried out according to the reported method [17] to yield phanes **8d–8f**, respectively. The ^1H NMR spectrum of compounds **8d** and **8e** showed two kinds of methoxy protons, each as a singlet. By careful column chromatography (silica gel, Wako C-300), two conformers, *anti*-**8d** and *syn*-**8d**, were separated (*syn*:*anti* ratio, 55:45). They were thermally stable and did not interconvert at 150 °C in DMSO solution or at 400 °C in the solid state.

The ^1H NMR spectrum of conformer *anti*-**8d** and *syn*-**8d**, respectively, showed the methoxy protons at δ 3.37 and 3.63. The aromatic protons of conformer *syn*-**8d** were observed at much higher field (δ 6.71, 6.75) than those of conformer *anti*-**8d** at δ 6.77 and 7.20. The above data show that the structure of *anti*-**8d** is the *anti*-conformer, whereas the structure of *syn*-**8d** is the *syn*-conformer. The same phenomenon was obtained in the [8.2]-analogue **8e** (*syn*:*anti* ratio, 30:70); however, the attempted separation of *syn*- and *anti*-conformers as pure compounds failed. On the other hand, the ^1H NMR spectra of the CH_2CH_2 bridge of dimethoxy[10.2]MCP **8f** showed a singlet at room temperature due to its flexible conformations.

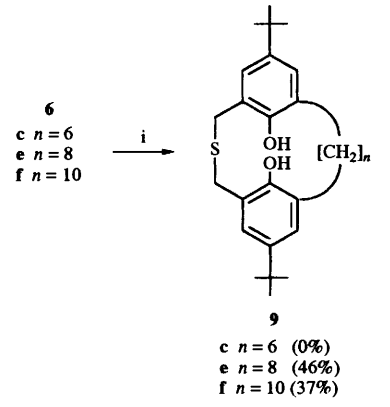
Recently, we have found [10] that only *syn*-8,16-di-*tert*-butyl-11,19-dimethyl[5.2]MCP is obtained by pyrolysis of the corresponding 13-thia[5.3]MCP dioxide, but that other analogues are exclusively converted into the *anti*-[*n*.2]MCPs. In the present work, a mixture of *anti*- and *syn*-conformers **8d**, **8e** was obtained by pyrolysis of the 15/16-thia[*n*.3]MCP dioxides **7d**, **7e**; however, the [10.3]-analogue **7f** gave flexible [10.2]MCP **8f**. It has also been found that the ratio of the *anti*-conformers decreases with increasing length of the methylene bridges. The aromatic π–π interaction of two opposite benzene rings, which may inhibit the formation of the *syn*-conformer decreases with increasing number of methylene groups, and in turn the through-space interaction between the non-bonding electron pairs of the oxygen atoms of the methoxy groups and the opposite aromatic π-electrons of the *anti*-conformer may disfavour the formation of the latter.

Attempted demethylation of *syn*- (*syn*-**8d**) and *anti*-dimethoxy[7.2]MCP (*anti*-**8d**) with BBr_3 in dichloromethane to give the corresponding dihydroxy[7.2]MCPs, *i.e.*, *syn*-**1d** and *anti*-**1d**, failed. In each case only the flexible dihydroxy[7.2]MCP **1d** was obtained, in 97% and 98% yield, respectively. The same result was obtained in the demethylation of a mixture of *syn*- and *anti*-dimethoxy[8.2]MCPs **8e** to give dihydroxy[8.2]MCP **1e** in 69% yield. These findings suggest that ring inversion is possible in the dihydroxy-[7.2]- and -[8.2]-MCPs, which seem to have sufficient space for the conformational flipping to occur as demonstrated by molecular models. The same treatment of dimethoxy[10.2]MCP **8f** gave the corresponding dihydroxy-[10.2]MCPs **1f** in 58% yield (Scheme 3).



Scheme 3 *Reagents and conditions:* i, BBr_3, CH_2Cl_2, room temp. for 2 h

Attempted demethylation of dimethoxythia[6.3]MCP **6c** with BBr_3 in CH_2Cl_2 under the same reaction conditions as that of dimethoxy[6.2]MCP **8c** failed to give any of the expected diol **9c**. Only the starting compound was recovered, in quantitative yield. In contrast, demethylation of dimethoxythia[8.3]- **6e** and -[10.3]-MCP **6f** led to the desired demethylated products, **9e** and **9f** in 46 and 37% yield respectively (Scheme 4). To the

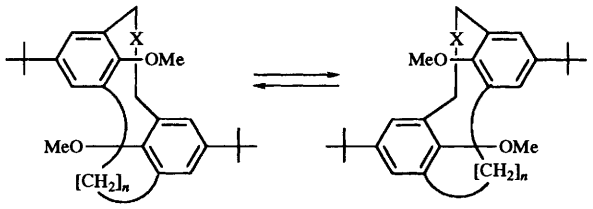


Scheme 4 *Reagents and conditions:* i, BBr_3, CH_2Cl_2 room temp. for 6 h

best of our knowledge, no example of a small-membered methoxythiaMCP being demethylated under the conditions used have been reported. This result may be attributed to the larger ring size of compounds **6e** and **6f**.

The conformations of dimethoxythia[7.3]MCPs, such as **6d** and **7d**, which have been prepared in the present work, in solution are rigid and the signals of the methylene bridges do not coalesce below 150 °C. The energy barriers to flipping are therefore above 25 kcal mol^{-1} (see Table 1). However, as already mentioned, dimethoxy-[8.3]- and -[10.3]-analogues seem to have sufficient space for conformational ring flipping as demonstrated by molecular models. Therefore, we have studied the ring inversion of these systems by using variable-temperature ^1H NMR spectroscopy. The ^1H NMR spectrum of dimethoxythia[8.3]MCP *anti*-**6e** and dimethoxythia[10.3]MCP *anti*-**6f** in $CDCl_3$ at room temperature exhibits a sharp single peak for the protons on the methylene bridge. However, in the case of the [8.3]-system, as the temperature of the solution of the respective compound in $CDCl_3$–CS_2 (1:3) is decreased, a single peak for the benzyl protons splits into a pair of doublets at

Table 1 The coalescence temperatures and energy barriers of (*n* + 8)-thia[*n*.3]MCPs **6** and 2-thia[*n*.3]MCP dioxides **7**[a]



6 X = S
7 X = SO_2

Methylene number *n*	(*n* + 8)-Thia[*n*.3]MCPs **6** $T_c(\Delta G_c^{\ddagger})$	(*n* + 8)-Thia[*n*.3]MCP dioxides **7** $T_c(\Delta G_c^{\ddagger})$
6	> 150	> 150
7	> 150	> 150
8	−20 (12.0)[b]	50 (15.6)
10	< −60[b]	−20 (10.3)[b]

[a] T_c: [°C]; $\Delta G_c^{\ddagger}$: [kcal mol^{-1}]. T_c and $\Delta G_c^{\ddagger}$ were determined in hexachlorobuta-1,3-diene using $SiMe_4$ as reference unless otherwise indicated. [b] Solvent: $CDCl_3/CS_2$ = 1/3.

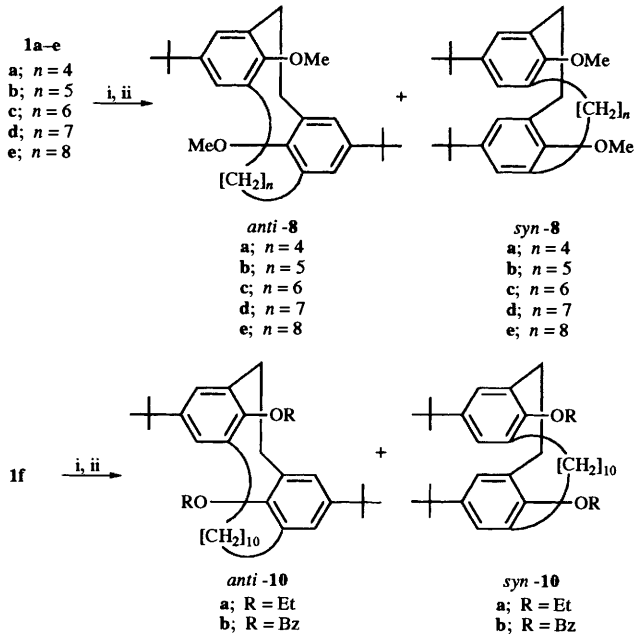
below −20 °C. The energy barrier to the conformational ring flipping estimated from the coalescence temperature (T_c) is 12.0 kcal mol^{-1}. In spite of a decrease in temperature to −60 °C in $CDCl_3$–CS_2 (1 : 3), no change in the spectrum was observed for the [10.3]-system.

The energy barriers for sulfones *anti*-**7e** and *anti*-**7f** were estimated to be 15.6 (T_c = 50 °C) and 10.3 (T_c = −20 °C) kcal mol^{-1}, respectively, and found to be ≈3.6 kcal mol^{-1} larger than those for the corresponding sulfides **6**. The difference could mainly be attributed to the bulkiness of the sulfone group compared with the bivalent sulfur group.[8]

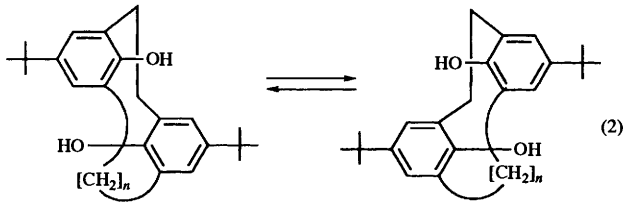
As mentioned previously, the conformations of dihydroxy[2.2]-, -[3.2]- and -[4.2]-MCPs are rigid, but the higher analogues are flexible and exhibit conformational ring flipping.[11] However, there has been no report concerning the introduction of substituents on the hydroxy groups of dihydroxy[*n*.2]MCPs **1** in spite of the formation of only two conformers, *i.e. syn*- and *anti*-conformer, being possible in contrast to four possible conformations in calix[4]arenes.[12,13]

In fact, *O*-alkylation of dihydroxy[*n*.2]MCPs **1a–e** with iodomethane was carried out by using NaH as a base and the ratios of *anti*- to *syn*-conformer are compiled in Table 2. As shown in Table 2, *O*-methylation of *anti*- and *syn*-dihydroxy-[4.2]MCPs **1a** exclusively afforded the corresponding *anti*- and *syn*-dimethoxy[4.2]MCPs **8a**, respectively, because of the rigid structures of these systems (Scheme 5). In contrast, *O*-methylation of *anti*-dihydroxy[5.2]MCP **1b** gave a mixture of *anti*- and *syn*-dimethoxy[5.2]MCPs **8b** in the ratio of 60 : 40. In the case of *O*-methylation of *anti*-dihydroxy[6.2]MCP **1c**, this furnished the formation of only *syn*-dimethoxy[6.2]MCP *syn*-**8c**. No formation of *anti*-dimethoxy[6.2]MCP *anti*-**8c** was observed.

We have previously reported[11] that the conformation of dihydroxy[*n*.2]MCPs in solution is affected by the chain length of the bridges. The ring-inversion barriers for the dihydroxy-[*n*.2]MCPs **1** were estimated and found to decrease with increasing length of the bridge, as expected. The conformations of dihydroxy[4.2]- **1a** and [5.2]-MCP **1b** are rigid above 140 °C in $CDCBr_3$ of hexachlorobuta-1,3-diene, but [6.2]MCPs **1c** are flexible and exhibit conformational ring flipping above 130 °C on the NMR time-scale [see eqn. (2)]. A higher barrier (for dihydroxy[5.2]MCP **1b**) to conformational ring flipping than that for dihydroxy[6.2]MCP **1c** was observed. On the other hand, in polar solvents such as [$^2H_6$]DMSO, CD_3CN or



Scheme 5 (see Table 2). *Reagents and conditions:* i, dimethylformamide (DMF)–THF, room temp. for 1 h; ii, RX, reflux for 3 h



(2)

	n	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
1a	4	>140	>27.5
1b	5	>140	>27.5
1c	6	130	20.6

[$^2H_6$]acetone at room temperature the ^1H NMR spectrum of hydroxy[5.2]MCP **1b** is almost identical with that in $CDCl_3$ and no *syn*-conformer is observed. However, *syn*-conformer was detected at 60 °C in [$^2H_6$]DMSO, and as the temperature was raised the ratio of the *syn*-conformer to the *anti*-conformer increased. This phenomenon indicated that dihydroxy[5.2]-MCP **1b** is mobile but interconverts more slowly than the NMR time-scale. Although the individual peaks of the *anti*- and *syn*-conformers do not coalesce below 140 °C, and the energy barrier to flipping is above 25 kcal mol^{-1} [eqn. (2)], the interconversion between *anti*- and *cone*-conformer could be possible in the [5.2]-system. Therefore the polarity of the solvent may change the equilibrium position of *anti*–*syn* conformers by decreasing the energy difference of *anti*–*syn* conformers by stabilizing the much more polar *syn*-conformer and the intramolecular hydrogen bond of the *syn*-conformer. Since the formation of *syn*-[5.2]MCP phenoxide intermediate **B** (see Scheme 7 below) from *anti*-dihydroxy[5.2]MCP **1b** *via* the oxygen-through-the annulus rotation could be possible in the reaction media, *e.g.* a mixture of dimethylformamide (DMF) and THF, *syn*-dimethoxy[5.2]MCP *syn*-**8b** was obtained in 40% yield along with *anti*-dimethoxy[5.2]MCP *anti*-**8b**. In contrast, *O*-methylation of *anti*-dihydroxy[6.2]MCP **1c** gave exclusively *syn*-dimethoxy[6.2]MCP **8c** because of its more flexible structure than that of [5.2]-analogue **1b**. The same results were observed in the case of the higher [7.2]- and [8.2]-analogues, but the proportion of the *syn*-conformer

Table 2 Conformer distribution for the reaction of compounds **1a–f** with alkyl halides[a]

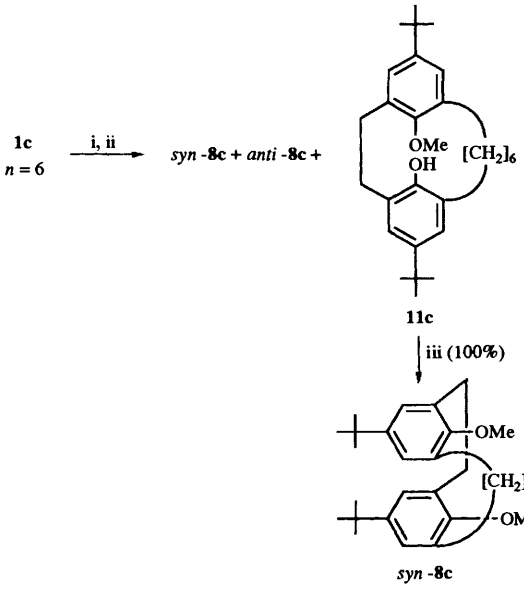
Substrate	Number of methylene bridges, *n*	RX	Yield (%)[b]	Conformer distribution (%)[c]	
				anti-	*syn*-
anti-**1a**	4	MeI	**8a** (100)	100	0
syn-**1a**	4	MeI	**8a** (100)	0	100
anti-**1b**	5	MeI	**8b** (100)	60	40
anti-**1c**	6	MeI	**8c** (100)	0	100
anti-**1d**	7	MeI	**8d** (100)	9	91
anti-**1e**	8	MeI	**8e** (100)	35	65
anti-**1f**	10	EtBr	**10a** (100)	18	82
anti-**1f**	10	BzlBr	**10b** (100)	20	80

[a] The reaction time was 3 h unless indicated otherwise. RX/substrate = 40 (mol/mol). [b] Isolated yields are shown. [c] Relative yields determined by ^{1}H NMR spectroscopy.

decreased with increasing length of the polymethylene bridge as shown in Table 2.

Why did the flexible conformation of dihydroxy[*n*.2]MCPs afford mainly *syn*-dimethoxy[*n*.2]MCP *syn*-**8** instead *anti*-dimethoxy[*n*.2]MCP *anti*-**8** in spite of the latter's thermodynamically more unstable structure? The template effect of an alkaline metal cation plays an important role in the *O*-alkylation of calixarenes to afford the conformational isomers.[13] The same metal template effect operates in *O*-alkylation of dihydroxy-[*n*.2]MCPs **1**. The dihydroxy[6.2]MCP **1c** ring is probably flexible enough so that the $O^- \cdots M^+$ interaction is strong enough to hold two O^- anions on the same side of the ring (intermediate **B** in Scheme 7), resulting in the complete formation of *syn*-conformer **8c**. However, this interaction decreases in the *O*-methylation of dihydroxy[5.2]MCP **1b** due to the higher barrier for dihydroxy[5.2]MCP **1b** to conformational ring flipping than that for dihydroxy[6.2]MCP **1c**. Furthermore, with increasing length of the bridges to more than six methylenes the metal template effect decreases due to the greater distance over which two O^- anions must be held on the same side of the ring, resulting in increased formation of the *anti*-conformer.

The ratio of the products dimethoxy[6.2]MCP **8c** and monohydroxy[6.2]MCP **11c** in the *O*-methylation of dihydroxy[6.2]-MCP **1c** (see Scheme 6) is governed by the nature of the alkali



Scheme 6 (see Table 3). *Reagents and conditions:* i, M_2CO_3, acetone, reflux for 1.5 h; ii, MeI, reflux for 6 h; NaH, DMF–THF, room temp. for 1 h; iii, RX, reflux for 3 h

metal carbonates used as catalyst, as was revealed by the results listed in Table 3. Thus, when lithium carbonate was used in this

Table 3 Conformer distribution for the reaction of 9,17-di-*tert*-butyl-12,20-dihydroxy[6.2]metacyclophane **1c** with iodomethane in the presence of alkali carbonates[a]

Run	Base (mol. equiv. over **1c**)	Products yield (%)[b]			
		8c			Recovery of substrate **1c**
		anti-	*syn*-	**11c**	
1	Li_2CO_3 (10.0)	0	0	0	100
2	Na_2CO_3 (10.0)	0	0	38	62
3	Na_2CO_3 (20.0)	0	0	35	65
4	K_2CO_3 (5.0)	3	4	93	0
5	K_2CO_3 (10.0)	9	12	79	0
6	Cs_2CO_3 (10.0)	36	18	46	0

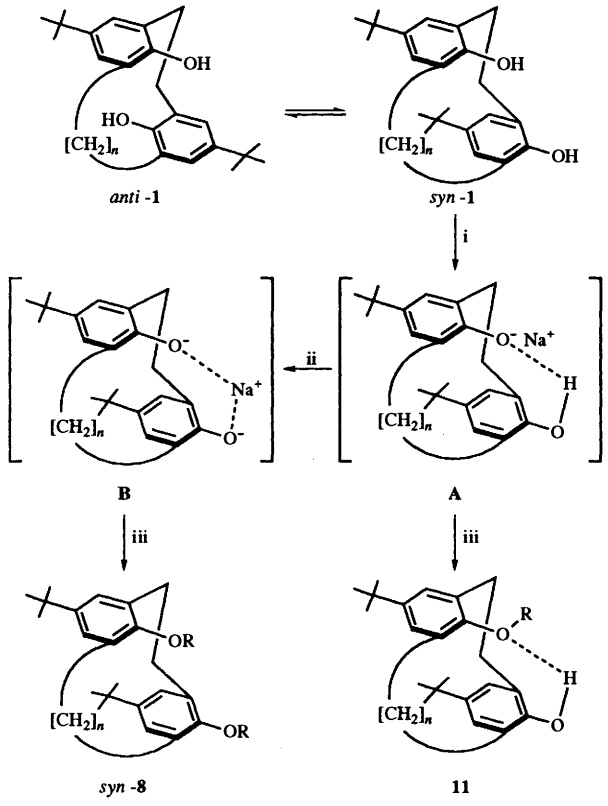
[a] Reflux in acetone for 6 h. [b] Relative yields determined by ^{1}H NMR spectroscopy.

reaction, only recovery of the starting compound was observed. On the other hand, when sodium carbonate was employed, monomethylated product **11c** was formed in 35–38% yield along with recovery of the starting compound in spite of the presence of a large excess of sodium carbonate. However, in the case of potassium carbonate, then selective monomethylation was observed. The larger alkaline metal K^+ obviously increases the yield of a monomethylation product **11c**, while the action of the even larger Cs^+ ion leads to a decrease in the yield of the monomethylation product. These results seem to indicate that the template effects of an alkaline metal cation plays an important role in this *O*-alkylation reaction, as previously observed in the case of the calixarenes.[13d,18]

When a weak base is used (M_2CO_3), the undissociated OH group forms intramolecular hydrogen bonds with the dissociated O^- group (intermediate **A** in Scheme 7) rather than undergoing further dissociation to form the metal template intermediate **B**; this is different from the conditions under the strong base (*e.g.*, NaH) which led to the complete formation of two O^- anions. The same phenomenon might occur in the mono methylated product **11**. Thus, a second alkylation was not observed due to the intramolecular hydrogen bonds with the methoxy group.

The present template effect was also confirmed by the observation of *O*-methylation of monomethoxy[6.2]MCP **11c** under the conditions of NaH as a base to furnish exclusively the *syn*-dimethoxy[6.2]MCP *syn*-**8c**.

The signals of the methylene bridge of dimethoxy-[6.2]- **8c**, -[7.2]-**8d** and -[8.2]-MCP **8e** do not coalesce below 150 °C, and the energy barriers of flipping are both above 25 kcal mol^{-1}. The ^{1}H NMR spectrum of dimethoxy[10.2]MCP **8f** in CS_2–$CDCl_3$ (3:1) below −80 °C shows the *tert*-butyl protons at δ 1.30 and 1.14, the methoxy protons at δ 2.61 and 3.44, and the aromatic protons at δ 6.90, 7.20 and 6.67, 6.85, respectively. On the basis of these data it may be inferred that dimethoxy[10.2]MCP **8f** at this temperature exists as a mixture



Scheme 7 *Reagents:* i, NaH or M_2CO_3; ii, NaH; iii, RX

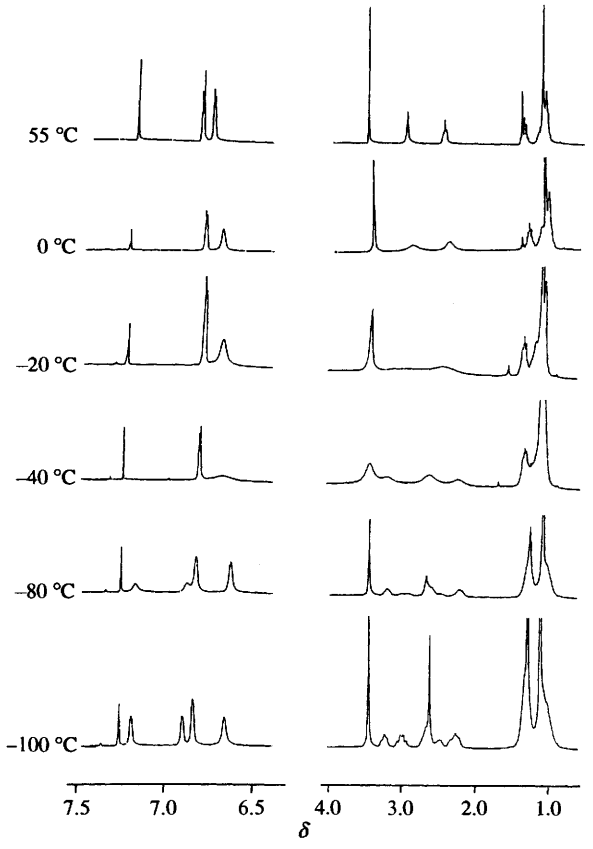


Fig. 2 Dynamic ^1H NMR spectra of compound **8f** [$CDCl_3$–CS_2 (1:3; 270 MHz]

of *anti*- and *syn*-conformers in the ratio of 65:35. However, as the temperature of the solution of the respective compound in CS_2–$CDCl_3$ (3:1) is increased, the individual peaks of the benzyl protons merge and eventually a pair of single peaks is observed above −20 °C (Fig. 2). The energy barrier to the conformational ring flipping estimated from the coalescence temperature (T_c) is 11.9 kcal mol^{-1}.

On the other hand, the signals of the methylene bridge of *anti*-diethoxy[10.2]MCP *anti*-**10a** and *anti*-bis(benzyloxy)-[10.2]MCP *anti*-**10b** do not coalesce below 150 °C, and the energy barriers of flipping are both above 25 kcal mol^{-1}. Thus the ethyl and benzyl groups are bulky enough to inhibit the oxygen-through-the-annulus rotation of species **10**.

The ^1H NMR spectrum of monomethoxy[6.2]MCP **11c** was in accord with its being a mixture of two isomers, *anti*-**11c** and *syn*-**11c** in the ratio 30:70 in $CDCl_3$. Almost the same ratios have been observed in other polar solvents, such as [$^2H_6$]acetone, CD_3CN or [$^2H_6$]DMSO which is different from the situation for the corresponding dihydroxy[6.2]MCP **1c**, in which the portion of the *syn*-conformer increases with increasing dielectronic constant of the solvent.[11] The polarity of the solvent may not change the equilibrium position of *anti*–*syn* conformers by decreasing the energy difference of *anti*–*syn* conformers by stabilizing the much more polar *syn*-conformer and the intramolecular hydrogen bond of the *syn*-conformer. This difference may be attributed mainly to a higher barrier for monomethoxy[6.2]MCP **11c** to conformational ring flipping than that for dihydroxy[6.2]MCP **1c** by introduction of one methyl group onto the phenolic oxygen. Several attempted separations of compound **11c** by column chromatography failed. Only the same ratio mixture of *anti*–*syn* conformers was obtained. From the coalescence of methoxy protons in $CDBr_3$ the barrier for ring inversion was calculated as 17.6 kcal mol^{-1} (T_c = 100 °C), indicating that the introduction of the one methyl group decreased the rigidity of the system by ≈3.0 kcal mol^{-1} {$\Delta G_c^{\ddagger}$ = 20.6 kcal mol^{-1} (T_c = 130 °C) for dihydroxy-[6.2]MCP **1c** in $CDBr_3$}. While the two hydroxy groups in dihydroxy[6.2]MCP **1c** can serve as a donor or an acceptor hydrogen bonds, the OMe group in monomethoxy[6.2]MCP **11c** can serve only as a donor. The decreased rigidity of monomethoxy[6.2]MCP **11c** may be attributed to the loss of an OH···O hydrogen bond in spite of much bulkier OMe substituent compared with an OH group.

Conclusions

In conclusion, we have demonstrated the preparation of intraannularly substituted *anti*- and *syn*-[*n*.2]MCPs having more than seven methylene-group bridges and report their solution conformations for the first time. The solution conformation of [*m.n*]MCPs is sensitive to the chain length of the bridges. The ring-inversion barriers determined by variable-temperature ^1H NMR spectroscopy decrease with increasing length of the bridges. Introduction of alkyl groups on the hydroxy groups of dihydroxy[*n*.2]MCPs **1** led to conformationally rigid structures, *i.e.*, the fixed conformations such as '*syn*' and '*anti*' conformations. The *syn*:*anti* ratio of the products is strongly governed by the length of the polymethylene bridge. Thus the portion of the *syn* conformer increases with increasing length of polymethylene bridges due to the template effect of the alkaline metal cations in the *O*-alkylation reaction for the higher dihydroxy[*n*.2]MCPs **1c–f** which adopt a more flexible conformation. These results will open up new synthetic aspects for cyclophane chemistry. Further studies of the chemical properties of dihydroxy[*n*.2]MCPs **1** and *O*-alkylated [*n*.2]MCPs **8** and **11** are in progress.

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 internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or as a liquid film on NaCl plates in a Nippon Denshi JIR-AQ20M spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC.

Materials

The preparation of 4-*tert*-butylanisole **2** and 2-bromo-4-*tert*-butylanisole **3** was previously described.[19]

Preparation of 1,7-bis(5-*tert*-butyl-2-methoxyphenyl)heptane 4d

To a solution of magnesium (3.4 g, 143 mmol) and a small amount of iodine in THF (5 cm^3) was added a solution of 2-bromo-4-*tert*-butylanisole **3** (17.01 g, 70 mmol) in THF (25 cm^3), and the mixture was refluxed for 12 h. To a gently refluxed solution of 1,7-dibromoheptane (7.74 g, 30 mmol) and CuBr (750 mg, 5.25 mmol) in HMPA (5 cm^3) was added dropwise the above solution of 5-*tert*-butyl-2-methoxyphenylmagnesium bromide. After the reaction mixture had been refluxed for an additional 17 h, it was quenched with 10% aq. ammonium chloride and extracted with CH_2Cl_2 (50 cm^3 × 3). After the combined CH_2Cl_2 extracts had been dried over Na_2SO_4, the solvent was evaporated off under reduced pressure and the residue was recrystallized from hexane to afford the *title compound* **4d** (10.2 g, 78%) as prisms, mp 131–133 °C; $\delta_H(CDCl_3)$ 1.29 (18 H, s), 1.30–1.40 (6 H, m), 1.50–1.62 (4 H, m), 2.55–2.62 (4 H, m), 3.76 (6 H, s), 6.74 (2 H, d, *J* 9.28), 7.14 (2 H, d, *J* 2.44) and 7.15 (2 H, dd, *J* 2.44 and 9.28); *m/z* 272 (M^+) (Found: C, 81.8; H, 10.3. $C_{29}H_{44}O_2$ requires C, 82.02; H, 10.44%).

Compounds **4e** and **4f** were prepared in a similar manner to that described above for **4d**. The yields are compiled in Scheme 1.

1,8-Bis(5-*tert*-butyl-2-methoxyphenyl)octane 4e. *Prisms* (from hexane), mp 83 °C; $\delta_H(CDCl_3)$ 1.30 (18 H, s), 1.34 (6 H, s), 1.56 (6 H, br s), 2.58 (4 H, t, *J* 7.3), 3.79 (6 H, s), 6.77 (2 H, d, *J* 8.8) and 7.14–7.18 (4 H, m); *m/z* 438 (M^+) (Found: C, 82.1; H, 10.5. $C_{30}H_{46}O_2$ requires C, 82.14; H, 10.57%).

1,10-Bis(5-*tert*-butyl-2-methoxyphenol)decane 4f. *Prisms* (from hexane), mp 59–61 °C; $\delta_H(CDCl_3)$, 1.29 (18 H, s), 1.10–1.44 (12 H, m), 1.50–1.64 (4 H, m), 2.59 (4 H, t, *J* 8.0), 3.78 (6 H, s), 6.75 (2 H, d, *J* 9.0) and 7.14–7.17 (4 H, m); *m/z* 466 (M^+) (Found: C, 82.05; H, 10.7. $C_{32}H_{50}O_2$ requires C, 82.35; H, 10.80%).

Preparation of 1,7-bis(5-*tert*-butyl-3-chloromethyl-2-methoxyphenyl)heptane 5d

A vigorously stirred mixture of compound **4d** (10 g, 23.5 mmol), paraformaldehyde (20 g), acetic acid (80 cm^3), H_3PO_4 (85%; 80 cm^3), and conc. HCl (36%; 80 cm^3) was heated at 90–95 °C for 36 h; then the reaction mixture was extracted with benzene (100 cm^3 × 3). The combined extracts were neutralized with an excess of 10% aq. Na_2CO_3, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was recrystallized from hexane to afford the *title compound* **5d** (8.61 g, 70%) as prisms, mp 50–51 °C; $\delta_H(CDCl_3)$ 1.30 (18 H, s), 1.39 (6 H, br s), 1.51–1.63 (4 H, m), 2.61 (4 H, t, *J* 7.9), 3.84 (6 H, s), 4.66 (4 H, s), 7.17 (2 H, d, *J* 2.5) and 7.23 (2 H, d, *J* 2.5); *m/z* 520, 522 and 524 (M^+) (Found: C, 71.0; H, 8.9. $C_{31}H_{46}Cl_2O_2$ requires C, 71.38; H, 8.89%).

Compounds **5e** and **5f** were prepared in a similar manner to that described above for **5d**. The yields are compiled in Scheme 2.

1,8-Bis(5-*tert*-butyl-3-chloromethyl-2-methoxyphenyl)octane 5e. *Prisms* (from hexane), mp 41–44 °C; $\delta_H(CDCl_3)$ 1.30 (18 H, s), 1.35 (8 H, br s), 1.54–1.60 (4 H, m), 2.61 (4 H, t, *J* 7.9), 3.82 (6 H, s), 4.66 (4 H, s), 7.17 (2 H, d, *J* 2.5) and 7.23 (2 H, d, *J* 2.5); *m/z* 534, 536 and 538 (M^+) (Found: C, 72.0; H, 9.05. $C_{32}H_{48}Cl_2O_2$ requires C, 71.76; H, 9.03%).

1,10-Bis(5-*tert*-butyl-3-chloromethyl-2-methoxyphenyl)decane 5f. *Prisms* (from hexane), mp 83–85 °C; $\delta_H(CDCl_3)$ 1.30 (18 H, s), 1.27–1.60 (16 H, m), 2.62 (4 H, t, *J* 8.0), 3.83 (6 H, s), 4.66 (4 H, s), 7.17 (2 H, d, *J* 2.2) and 7.23 (2 H, d, *J* 2.2); *m/z* 562, 564 and 466 (M^+) (Found: C, 72.7; H, 9.3. $C_{34}H_{52}Cl_2O_2$ requires C, 72.45; H, 9.30%).

Preparation of 10,19-di-*tert*-butyl-13,22-dimethoxy-15-thia-[7.3]metacyclophane 6d

A solution of dichloride **5d** (3.50 g, 6.71 mmol) in ethanol (200 cm^3) and benzene (40 cm^3) and a solution of $Na_2S·9H_2O$ (3.11 g, 12.9 mmol) in ethanol (200 cm^3)–water (40 cm^3) were added separately, but simultaneously, from two Hershberg funnels to boiling ethanol (4 dm^3). When the addition was complete (21 h), the mixture was both refluxed and stirred for 16 h. Then the reaction mixture was concentrated and the residue was extracted with CH_2Cl_2 (200 cm^3 × 3). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 300 g) with benzene–hexane (1:1) as eluent to give the crude *title compound* **6d** (1.30 g, 40%) as solid. The ^1H NMR spectrum of this solid was in accord with its being a mixture of two isomers in the ratio (4:1), and TLC over silica gel showed two closely moving spots. Several attempts at fractional crystallization from hexane failed. Only the same-ratio mixture of *anti*-**6d** and *syn*-**6d** was obtained, as prisms.

***anti*- and *syn*-10,19-Di-*tert*-butyl-13,22-dimethoxy-15-thia-[7.3]metacyclophane *anti*- and *syn*-6d**. *Prisms* (from hexane), mp 66–70 °C; $\delta_H(CDCl_3)$ *anti*-**6d**: 1.18–1.30 (8 H, m), 1.31 (18 H, s), 1.50–1.64 (2 H, m), 2.19–2.31 (2 H, m), 2.60–2.75 (2 H, m), 3.30 (6 H, s), 3.43 (2 H, d, *J* 14.2), 3.78 (2 H, d, *J* 14.2), 6.98 (2 H, d, *J* 2.4) and 7.29 (2 H, d, *J* 2.4); *syn*-**6d**: 1.00–1.44 (10 H, m), 1.13 (18 H, s), 2.04–2.17 (2 H, m), 2.59–2.69 (2 H, m), 3.64 (6 H, s), 3.75 (2 H, d, *J* 15.6), 4.27 (2 H, d, *J* 15.6), 6.81 (2 H, d, *J* 2.4) and 7.14 (2 H, d, *J* 2.4); *m/z* 482 (M^+) (Found: C, 77.0; H, 9.3. $C_{31}H_{46}O_2S$ requires C, 77.13; H, 9.60%).

Compounds *anti*-**6e** and **6f** were prepared in a similar manner to that described above in 50 and 40% yield, respectively.

***anti*-11,20-Di-*tert*-butyl-14,23-dimethoxy-16-thia[8.3]metacyclophane-*anti*-6e**. *Prisms* (from MeOH), mp 95–97 °C; $\delta_H(CDCl_3)$ 1.06 (4 H, m), 1.22 (4 H, m), 1.30 (18 H, s), 1.52 (4 H, m), 2.53 (4 H, br s), 3.39 (6 H, s), 3.72 (4 H, br s), 7.00 (2 H, d, *J* 2.2) and 7.30 (2 H, d, *J* 2.2; *m/z* 496 (M^+) (Found: C, 77.2; H, 9.6. $C_{32}H_{48}O_2S$ requires C, 77.37; H, 9.74%).

13,22-Di-*tert*-butyl-16,25-dimethoxy-18-thia[10.3]metacyclophane 6f. *Prisms* (from hexane), mp 137 °C; $\delta_H(CDCl_3)$ 1.29 (18 H, s), 1.17–1.56 (16 H, m), 2.53 (4 H, t, *J* 7.3), 3.30 (6 H, s), 3.72 (4 H, s), 7.00 (2 H, d, *J* 2.4) and 7.23 (2 H, d, *J* 2.4); *m/z* 524 (M^+) (Found: C, 78.0; H, 10.2. $C_{34}H_{52}O_2S$ requires C, 77.81; H, 9.99%).

Preparation of 10,19-di-*tert*-butyl-13,22-dimethoxy-15-thia-[7.3]metacyclophane 15,15-dioxide 7d

To a solution of sulfide **6d** (998 mg, 2.07 mmol) in CH_2Cl_2 (100 cm^3) was added MCPBA (894 mg, 5.2 mmol). After the reaction mixture had been stirred at room temperature for 17 h, it was washed successively with 10% $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure to leave crude dioxide **7d** (875 mg, 82%) as a solid. Recrystallization from hexane gave the *title compound* **7d** as prisms, whose ^1H NMR spectrum was in accord with its being a mixture of stereoisomers *anti*-**7d** and *syn*-**7d** in the ratio 6:1.

***anti*- and *syn*-10,19-Di-*tert*-butyl-13,22-dimethoxy-15-thia-[7.3]metacyclophane 15,15-dioxide *anti*- and *syn*-7d**. *Prisms* (from hexane), mp 162–164 °C; $\delta_H(CDCl_3)$ *anti*-**7d**: 1.33 (18 H, s), 1.34–1.41 (8 H, m), 1.59–1.72 (2 H, m), 2.18–2.33 (2 H, m), 2.67–2.78 (2 H, m), 3.24 (6 H, s), 3.90 (2 H, d, *J* 15.1), 4.52 (2 H, d, *J* 15.1), 7.12 (2 H, d, *J* 2.7) and 7.65 (2 H, d, *J* 2.7 Hz); *syn*-**7d**:

1.12 (18 H, s), 1.00–1.40 (10 H, m), 2.09–2.20 (2 H, m), 2.57–2.70 (2 H, m), 3.62 (6 H, s), 4.09 (2 H, d, *J* 14.7), 4.89 (2 H, d, *J* 14.7), 6.96 (2 H, d, *J* 2.4) and 7.33 (2 H, d, *J* 2.4); *m/z* 514 (M^+) (Found: C, 72.2; H, 8.8. $C_{31}H_{46}O_4S$ requires C, 72.33; H, 9.01%).

Compounds *anti*-**7e** and **7f** were prepared in a similar manner to that described above in 69 and 66% yield, respectively.

***anti*-11,20-Di-*tert*-butyl-14,23-dimethoxy-16-thia[8.3]metacyclophane 16,16-dioxide *anti*-7e**. *Prisms* (from hexane), mp 200–202 °C; $\delta_H(CDCl_3)$ 0.82–0.91 (2 H, m), 1.00–1.12 (4 H, br s), 1.27 (18 H, s), 1.46–1.70 (6 H, m), 2.32–2.83 (4 H, m), 3.35 (6 H, s), 4.31 (4 H, s), 7.16 (2 H, d, *J* 2.45) and 7.35 (2 H, d, *J* 2.45); *m/z* 528 (M^+) (Found: C, 72.9; H, 9.15. $C_{32}H_{48}O_4S$ requires C, 72.69; H, 9.15%).

13,22-Di-*tert*-butyl-16,25-dimethoxy-18-thia[10.3]metacyclophane 18,18-dioxide 7f. *Prisms* (from hexane), mp > 300 °C; $\delta_H(CDCl_3)$ 1.14–1.22 (10 H, m,), 1.28 (18 H, s), 1.52–1.55 (6 H, m), 2.59 (4 H, t, *J* 6.72), 3.41 (6 H, s), 4.30 (4 H, s), 7.17 (2 H, d, *J* 2.45) and 7.36 (2 H, d, *J* 2.45); *m/z* 556 (M^+) (Found: C, 73.5; H, 9.7. $C_{34}H_{52}O_4S$ requires C, 73.34; H, 9.41%).

Pyrolysis of sulfones 7 to give phanes 8

Typical procedure. The sulfone *anti*-**7d** (677 mg, 1.32 mmol) was pyrolysed at 500 °C/1 mmHg according to the literature.[17] The sublimed product was collected, and chromatographed on silica gel (Wako, C-300; 100 g) with a mixture of hexane–benzene (1:1) as eluent to give compounds *anti*-**8d** (247 mg, 42%) and *syn*-**8d** (205 mg, 35%).

***anti*-10,18-Di-*tert*-butyl-13,21-dimethoxy[7.2]metacyclophane *anti*-8d**. *Prisms* (from MeOH), mp 146–149 °C; $\delta_H(CDCl_3)$ 0.88–0.97 (4 H, m), 1.00–1.06 (4 H, m), 1.22–1.35 (2 H, m), 1.30 (18 H, s), 1.91–1.99 (2 H, m), 2.74–2.85 (2 H, m), 2.80 (2 H, d, *J* 9.0), 3.10 (2 H, d, *J* 9.0), 3.37 (6 H, s), 6.77 (2 H, d, *J* 2.7) and 7.20 (2 H, d, *J* 2.7); *m/z* 450 (M^+) (Found: C, 82.5; H, 10.0. $C_{31}H_{46}O_2$ requires C, 82.61; H, 10.29%).

***syn*-10,18-Di-*tert*-butyl-13,21-dimethoxy[7.2]metacyclophane *syn*-8d**. *Prisms* (from MeOH), mp 106–109 °C; $\delta_H(CDCl_3)$ 0.90–0.96 (2 H, m), 1.04–1.13 (3 H, m), 1.15 (18 H, s), 1.22–1.30 (2 H, m), 1.38–1.42 (2 H, m), 2.05–2.15 (2 H, m), 2.60–2.74 (2 H, m), 2.63 (2 H, d, *J* 5.4), 3.47–3.57 (1 H, m), 3.51 (2 H, d, *J* 5.4), 3.63 (6 H, s), 6.71 (2 H, d, *J* 2.4) and 6.75 (2 H, d, *J* 2.4); *m/z* 450 (M^+) (Found: C, 82.52; H, 10.16%).

Compounds *anti*-**8e**, *syn*-**8e** and **8f** were prepared in a similar manner to that described above. The yields are compiled in Scheme 2.

***anti*- and *syn*-11,19-Di-*tert*-butyl-14,22-dimethoxy[8.2]metacyclophane *anti*- and *syn*-8e**. The reaction mixture was treated as described above to afford the crude product, which was chromatographed on silica gel (Wako, C-300; 100 g) with a mixture of hexane–benzene (1:1) as eluent to give a mixture of products *anti*- and *syn*-**8e** (232.4 mg, 80%) as an oil. The ^1H NMR spectrum of this oil was in accord with it being a mixture of two isomers, *anti*-**8e** and *syn*-**8e**, in the ratio 30:70, and TLC over silica gel showed to closely moving spots. Several attempted separations failed. Only the same-ratio mixture of stereoisomers *anti*- and *syn*-**8e** was obtained, as an oil; $\delta_H(CDCl_3)$ *anti*-**8e**: 0.80–1.16 (12 H, m), 1.29 (18 H, s), 2.10–2.21 (2 H, m), 2.67–2.73 (2 H, m), 2.87 (2 H, d, *J* 9.8), 3.18 (2 H, d, *J* 9.8), 3.29 (6 H, s), 6.87 (2 H, d, *J* 2.4) and 7.23 (2 H, d, *J* 2.4); *syn*-**8e**: 0.80–1.60 (12 H, m), 1.16 (18 H, s), 2.20–2.30 (2 H, m), 2.58–2.70 (2 H, m), 2.72–2.84 (2 H, m), 3.40 –3.52 (2 H, m), 3.63 (6 H, s), 6.77 (2 H, d, *J* 2.4) and 6.81 (2 H, d, *J* 2.4); *m/z* 464 (M^+) (Found: C, 82.2; H, 10.4. $C_{32}H_{48}O_2$ requires C, 82.70; H, 10.41%).

13,21-Di-*tert*-butyl-16,24-dimethoxy[10.2]metacyclophane 8f. *Prisms* (from MeOH); mp 67–69 °C; $\delta_H(CDCl_3$; 27 °C) 1.11–1.34 (12 H, m), 1.19 (18 H, s), 1.39–1.46 (4 H, m), 2.48 (4 H, br s), 2.99 (4 H, br s), 3.50 (6 H, s), 6.80 (2 H, d, *J* 2.4) and 6.88 (2 H, d, *J* 2.4); $\delta_H[CS_2$–$CDCl_3$ (3:1); −100 °C] *anti*-**8f**: 1.30 (18 H, s), 1.0–1.4 (16 H, m), 2.2–3.3 (8 H, m), 2.61 (6 H, s), 6.91 (2 H, br s) and 7.20 (2 H, br s); *syn*-**8f**: 1.14 (18 H, s), 1.0–1.4 (16 H, m), 2.2–3.3 (8 H, m), 3.44 (6 H, s), 6.67 (2 H, br s) and 6.85 (2 H, br s); *m/z* 492 (M^+) (Found: C, 82.4; H, 11.0. $C_{34}H_{52}O_2$ requires C, 82.87; H, 10.64%).

Demethylation of ethers 8 to give phenols 1

Typical procedure. To a solution of *anti*-**8d** (450 mg, 1 mmol) in dry CH_2Cl_2 (10 cm^3) at 0 °C was gradually added a solution of BBr_3 (0.4 cm^3, 4 mmol) in CH_2Cl_2 (2 cm^3) over a period of 15 min. After the reaction mixture had been stirred at room temp. for 2 h, it was poured into ice–water, washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with benzene–hexane (1:1) as eluent to give the crude *title compound* **1d** (409 mg, 97%) as a solid. Recrystallization from methanol gave 10,18-*di*-tert-*butyl*-13,21-*dihydroxy*[7.2]*metacyclophane* **1d** as prisms, mp 115–117 °C; ν_{max}(KBr)/cm^{-1} 3386 (OH); $\delta_H(CDCl_3)$ 1.13–1.34 (10 H, m), 1.30 (18 H, s), 2.42 (4 H, br s), 2.98 (4 H, s), 3.79 (2 H, s, replaced by D_2O), 6.87 (2 H, d, *J* 2.2) and 7.11 (2 H, d, *J* 2.2); *m/z* 422 (M^+) (Found: C, 82.6; H, 10.1. $C_{29}H_{42}O_2$ requires C, 82.41; H, 10.02%).

Phenols **1e** and **1f** were prepared in a similar manner to that described above. The yields are listed in Scheme 3. However, attempted demethylation of *syn*-dimethoxy[7.2]metacyclophane *syn*-**8d** to give *syn*-dihydroxy[7.2]metacyclophane *syn*-**1d** failed. Only the flexible dihydroxy[7.2]metacyclophane **1d** was obtained, in 98% yield.

11,19-Di-*tert*-butyl-14,22-dihydroxy[8.2]metacyclophane 1e. *Prisms* (from MeOH), mp 131–136 °C; ν_{max}(KBr)/cm^{-1} 3366 (OH); $\delta_H(CDCl_3)$ 1.07–1.77 (4 H, m), 1.23 (18 H, s), 1.25 (4 H, br s), 1.40–1.50 (4 H, m), 2.47 (4 H, t, *J* 6.7), 3.02 (4 H, s), 4.40 (2 H, s, replaced by D_2O), 6.88 (2 H, d, *J* 2.4) and 6.93 (2 H, d, *J* 2.4); *m/z* 436 (M^+) (Found: C, 82.55; H, 10.2. $C_{30}H_{44}O_2$ requires C, 82.30; H, 9.87%).

13,21-Di-*tert*-butyl-16,24-dihydroxy[10.2]metacyclophane 1f *Prisms* (from hexane), mp 143–145 °C; ν_{max}(KBr)/cm^{-1} 3502 and 3460 (OH); $\delta_H(CDCl_3)$ 1.18 (18 H, s), 1.20–1.54 (16 H, m), 2.45 (4 H, br s), 2.95 (4 H, s), 4.20 (2 H, s, replaced by D_2O), 6.71 (2 H, d, *J* 2.2) and 6.91 (2 H, d, *J* 2.2); *m/z* 464 (M^+) (Found: C, 82.8; H, 10.7. $C_{32}H_{48}O_2$ requires C, 82.70; H, 10.41%).

Demethylation of ethers 6 to phenols 9

To a solution of *anti*-**6e** (231 mg, 0.465 mmol) in dry CH_2Cl_2 (5.6 cm^3) at 0 °C was gradually added a solution of BBr_3 (0.25 cm^3, 2.5 mmol) in CH_2Cl_2 (1 cm^3) over a period of 15 min. After the reaction mixture has been stirred at room temperature for 6 h, it was poured into ice–water, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue which, after column chromatography on silica gel (Wako, C-300; 100 g) with benzene as eluent, afforded 11,20-*di*-tert-*butyl*-14,23-*dihydroxy*-16-*thia*[8.3]*metacyclophane* **9e** as an oil (100 mg, 46%); ν_{max}(NaCl)/cm^{-1} 3428 (OH); $\delta_H(CDCl_3)$ 1.26 (18 H, s), 1.10–1.41 (10 H, m), 1.54–1.63 (2 H, m), 2.59 (4 H, m), 3.77 (4 H, s), 5.40 (2 H, s, replaced by D_2O), 6.94 (2 H, d, *J* 2.4) and 7.05 (2 H, d, *J* 2.4); *m/z* 468 (M^+) (Found: C, 76.6; H, 9.6. $C_{30}H_{44}O_2S$ requires C, 76.87; H, 9.46%).

Compound **9f** was similarly prepared in 37% yield.

13,22-Di-*tert*-butyl-16,25-dihydroxy-18-thia[10.3]metacyclocyclophane 9f. *Oil*; ν_{max}(NaCl)/cm^{-1} 3428 (OH); $\delta_H(CDCl_3)$ 1.27 (18 H, s), 1.28–1.35 (14 H, m), 1.50–1.68 (2 H, m), 2.58 (4 H, m), 3.79 (4 H, s), 5.62 (2 H, s, replaced by D_2O), 6.95 (2 H, d, *J* 2.4) and 7.06 (2 H, d, *J* 2.4); *m/z* 496 (M^+) (Found: C, 77.5; H, 9.4. $C_{32}H_{48}O_2S$ requires C, 77.37; H, 9.74%).

Methylation of phenols 1

Typical procedure. To a suspension of NaH (1.08 g, 45.0

mmol) in THF (5 cm^3) was added a solution of compound **1c** (408.6 mg, 1.0 mmol) in a mixture of DMF (5 cm^3) and THF (15 cm^3) under nitrogen and the mixture was stirred at room temperature for 1 h. Then MeI (5.67 g, 40.0 mmol) was added and the mixture was heated at reflux for 3 h. After cooling of the reaction mixture to room temperature, it was quenched with water, and extracted with CH_2Cl_2 (200 cm^3 × 2). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (Wako, C-300; 100 g) with hexane–benzene (1 : 1) as eluent to give *syn*-9,17-di-*tert*-butyl-12,20-dimethoxy[6.2]metacyclophane *syn*-**8c** as a solid (436.7 mg, 100%). Recrystallization from methanol afforded *anti*-**8c** as prisms, mp 97–99 °C (lit.,[11] 97–99 °C).

Similarly, methylation of substrates **1a–f** was carried out as described above. The yields are compiled in Table 2. The products *anti*- and *syn*-**8a–f** were readily identified by comparison with authentic materials (ref.11 and this work).

Alkylation of compound 1f

Typical procedure. To a suspension of NaH (1.08 g, 45.0 mmol) in THF (5 cm^3) was added a solution of compound **1f** (464.7 mg, 1.0 mmol) in a mixture of DMF (5 cm^3) and THF (15 cm^3) under nitrogen, and the mixture was stirred at room temperature for 1 h. Then EtBr (4.36 g, 40.0 mmol) was added and the mixture was heated at reflux for 3 h. After cooling of the reaction mixture to room temperature, it was quenched with water, and extracted with CH_2Cl_2 (200 × 2 cm^3). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane–benzene (1 : 1) as eluent to give a mixture of bis-ethyl ethers *anti*- and *syn*-**10a** (520.8 mg, 100%) as an oil. The ^1H NMR spectrum of this oil was in accord with its being a mixture of two isomers, *anti*-**10a** and *syn*-**10a**, in the ratio 18 : 82, and TLC over silica gel showed two closely moving spots. Several attempted separations by column chromatography failed. Only the same-ratio mixture was obtained, as an oil.

***anti*- and *syn*-13,21-Di-*tert*-butyl-16,24-diethoxy[10.2]metacyclophane *anti*- and *syn*-10a**. Oil; $\delta_H(CDCl_3)$ *anti*-**10a**: 0.85 (6 H, t, *J* 7.0), 1.00–1.60 (16 H, m), 1.30 (18 H, s), 2.20–2.30 (2 H, m), 2.71–2.80 (2 H, m), 2.82–2.90 (2 H, m), 3.08–3.20 (2 H, m), 3.45 (4 H, q, *J* 7.0), 6.91 (2 H, d, *J* 2.9) and 7.20 (2 H, d, *J* 2.9); *syn*-**10a**: 1.16 (18 H, s), 1.04–1.50 (16 H, m,), 1.36 (6 H, t, *J* 7.0), 2.11–2.27 (2 H, m), 2.50–2.66 (2 H, m), 2.67–2.97 (2 H, m), 3.24–3.37 (2 H, m), 3.72 (4 H, q, *J* 7.0), 6.69 (2 H, d, *J* 2.4) and 6.86 (2 H, d, *J* 2.4); *m/z* 520 (M^+) (Found: C, 82.75; H, 10.8. $C_{36}H_{56}O_2$ requires C, 83.02; H, 10.84%).

Benzylation of the phenol **1f** with benzyl bromide afforded a mixture of *anti*- and *syn*-**10b** as a solid in quantitative yield. The ^1H NMR spectrum of this solid was in accord with it being a mixture of two isomers, *anti*-**10b** and *syn*-**10b**, in the ratio 20 : 80, and TLC over silica gel showed two closely moving spots. Several attempted fractional recrystallizations from hexane gave syn-16,24-*dibenzyloxy*-13,21-*di*-tert-*butyl*[10.2]*metacyclophane syn*-**10b** as prisms, mp 160–163 °C; $\delta_H(CDCl_3)$ 0.98 (10 H, br s), 1.18 (18 H, s), 1.30–1.40 (6 H, m), 2.20–2.30 (2 H, m), 2.67–2.84 (4 H, m), 3.40–3.51 (2 H, m), 4.70 (4 H, d, *J* 4.88), 6.76 (2 H, d, *J* 2.44), 6.90 (2 H, d, *J* 2.44), 7.28–7.30 (5 H, m) and 7.43–7.47 (5 H, m); *m/z* 644 (M^+) (Found: C, 85.3; H, 9.3. $C_{46}H_{60}O_2$ requires C, 85.66; H, 9.38%).

Methylation of 9,17-Di-*tert*-butyl-12,20-dihydroxy[6.2]metacyclophane 1c in the presence of alkaline metal carbonates

Typical procedure. A mixture of substrate **1c** (102.2 mg, 0.25 mmol) and potassium carbonate (86.4 mg, 1.25 mmol) in dry acetone (16 cm^3) was heated at reflux for 1.5 h under nitrogen. Then iodomethane (0.16 cm^3, 2.5 mmol) was added and the mixture was heated at reflux for 6 h. After cooling of the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give an oil, which was then chromatographed over silica gel (Wako, C-300; 100 g) with hexane–benzene (1 : 1) as eluent to give a mixture of hydroxy ethers *anti*- and *syn*-**11c** (92.0 mg, 87.2%) as an oil. The ^1H NMR spectrum of this oil in [$^2H_6$]DMSO was in accord with it being a mixture of two isomers, *anti*-**11c** and *syn*-**11c**, in the ratio 30 : 70, and TLC over silica gel showed two closely moving spots. Several attempted separations by column chromatography failed. Only the same-ratio mixture of stereoisomers *anti*-**11c** and *syn*-**11c** was obtained, as an oil.

***anti*- and *syn*-9,17-Di-*tert*-butyl-12-hydroxy-20-methoxy-[6.2]metacyclophane *anti*- and *syn*-11c**. Oil; ν_{max}(NaCl)/cm^{-1} 3521 (OH); $\delta_H(CDCl_3)$ *anti*-**11c**: 1.29 (9 H, s), 1.34 (9 H, s), 0.80–3.42 (24 m), 3.09 (1 H, s), 3.18 (3 H, s), 6.87 (1 H, d, *J* 2.4), 6.99 (1 H, d, *J* 2.0), 7.14 (1 H, d, *J* 2.4) and 7.24 (1 H, d, *J* 2.0); *syn*-**11c**: 1.09 (9 H, s), 1.18 (9 H, s), 0.80–3.42 (24 H, m), 3.81 (3 H, s), 6.45 (1 H, s), 6.59 (1 H, d, *J* 2.4), 6.68 (1 H, d, *J* 2.0), 6.80 (1 H, d, *J* 2.4) and 6.90 (1 H, d, *J* 2.0); *m/z* 422 (M^+) (Found: C, 82.3; H, 10.1. $C_{29}H_{42}O_2$ requires C, 82.41; H, 10.02%).

Methylation of *anti*- and *syn*-9,17-di-*tert*-butyl-12-hydroxy-20-methoxy[6.2]metacyclophane *anti*- and *syn*-11c

To a suspension of NaH (90 mg, 3.75 mmol) in THF (3 cm^3) was added a solution of the phenol **11c** (42 mg, 0.10 mmol) in a mixture of DMF (1 cm^3) and THF (3 cm^3) under nitrogen, and the mixture was stirred at room temperature for 1 h. Then MeI (0.52 cm^3) was added and the mixture was heated at reflux for 3 h. After cooling of the reaction mixture to room temperature, it was quenched with water, and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane–benzene (1 : 1) as eluent to give compound *syn*-**8c** (43.6 mg, 100%) as an oil.

Estimation of the activation energy of the ring flipping

The rate constant (k_c) of the observed conformational interconversion at the coalescence temperature (T_c) can be calculated by using equation (3).[20] The free energy of activation

$$k_c = \pi/2^{\frac{1}{2}}(\Delta\nu^2 + 6J^2)^{\frac{1}{2}} \quad (3)$$

($\Delta G_c^{\ddagger}$) for the coalescence can be estimated by using the Eyring equation [eqn. (4)].[20]

$$\Delta G_c^{\ddagger} = 2.303RT_c(10.32 + \log T_c - \log k_c) \quad (4)$$

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Paper 4/06852A
Received 9*th November* 1994
Accepted 20*th December* 1994