Synthesis and Conformational Studies of Regio- and Conformational Isomers Derived from *O*-Benzylation of Tetrahydroxy[3.1.3.1]metacyclophanes

Takehiko Yamato*[a], Yoshiyuki Saruwatari[a], Masashi Yasumatsu[a], and Seiji Ide[b]

Department of Applied Chemistry, Faculty of Science and Engineering, Saga University[a],
Honjo-machi 1, Saga-shi, Saga 840, Japan
Fax: (internat.) + 81(0)952/28-8591
E-mail: yamatot@cc.saga-u.ac.jp

Biotechnology and Food Research Institute, Fukuoka Industrial Technology Center[b],
1465-5 Aikawa, Kurume City, Fukuoka 839, Japan

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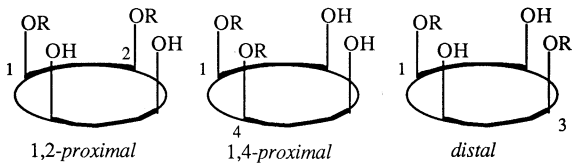
Regioselective *O*-benzylations of [3.1.3.1]metacyclophanes with intraannular OH groups are described. *O*-Benzylation of 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy-[3.1.3.1]metacyclophane **1** with 2 equiv. of benzyl bromide in the presence of Na_2CO_3 leads to exclusive formation of the monosubstituted product **3**. In contrast, use of K_2CO_3 as the base leads to di-*O*-substitution, resulting in the disubstituted product, *distal*-**4**, as the major product, along with some 1,2-*proximal*-**4**, in spite of using a large excess of benzyl bromide. Under the same reaction conditions in the presence of Cs_2CO_3, a mixture of two conformers of the tetra-*O*-benzylated product **2** in a ratio of 80:20 (*cone*-**2**/1,4-*alternate*-**2**) is obtained in 83% yield. Thus, the alkali metal cation plays not only an important role with regard to the regioselectivity, but also in determining the number of *O*-benzylations that occur, as a consequence of the template effect. Regioselective syntheses of dimethoxy- and trimethoxy[3.1.3.1]metacyclophanes are accomplished by a protection-deprotection strategy, using the benzyl residues as protecting groups. The ^{1}H-NMR spectra of these macrocyclic metacyclophanes are also discussed.

The introduction of larger alkyl groups at the phenolic oxygens of calix[4]arenes leads to a situation where the OR groups within the cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation[1][2]. Although there exist four possible conformational isomers for calix[4]-arenes; i.e. *cone*, partial-*cone*, 1,2-*alternate*, and 1,3-*alternate*, five different conformational isomers are expected for tetrahydroxy[3.1.3.1]MCPs (MCP = metacyclophane)[3], the additional possibility being 1,4-*alternate* as a result of the asymmetry introduced by the incorporation of two propane bridges. Recently, we reported[3c] a difference in the inhibition of interconversion between conformers derived from tetrahydroxy[3.1.3.1]MCP **1** by *O*-substitution and those derived from the calix[4]arenes, due to the intramolecular hydrogen bonding between the hydroxy groups of the 1,3-diarylpropane units being weaker than that between the diarylmethane units.

Regioselective *O*-alkylation of hydroxy groups in calixarenes is important for many purposes, in particular for the construction of multiple binding receptors or larger molecules starting from several calixarene units[4]. Shinkai et al. have reported on the specific synthesis of calix[4]arene derivatives in a certain conformation using benzyl residues as protecting groups[5].

In contrast to the two possible regioisomers for *O*-disubstituted calix[4]arenes[4], i.e. *proximal* and *distal*, three different regioisomers are to be expected for tetrahydroxy[3.1.3.1]MCPs, of which two *proximal* isomers; i.e. 1,2-*proximal* and 1,4-*proximal* (Figure 1), arise as a result of the introduction of the propane bridges. The aforementioned difference in the intramolecular hydrogen bonding between the hydroxy groups of the 1,3-diarylpropane units and diarylmethane units is expected to have an effect on the regioselectivity of *O*-alkylations of tetrahydroxy[3.1.3.1]MCPs.

Figure 1. Three possible structures of di-*O*-substituted [3.1.3.1]MCPs with *cone* conformation



Furthermore, the regioisomers that result from internal substitution of tetrahydroxy[*n*.1.*n*.1]MCPs having higher than three methylene bridges are hitherto unknown. Thus, there is substantial interest in investigating the effects of intramolecular hydrogen bonding on the regioselective *O*-benzylation of the flexible tetrahydroxy[3.1.3.1]MCPs.

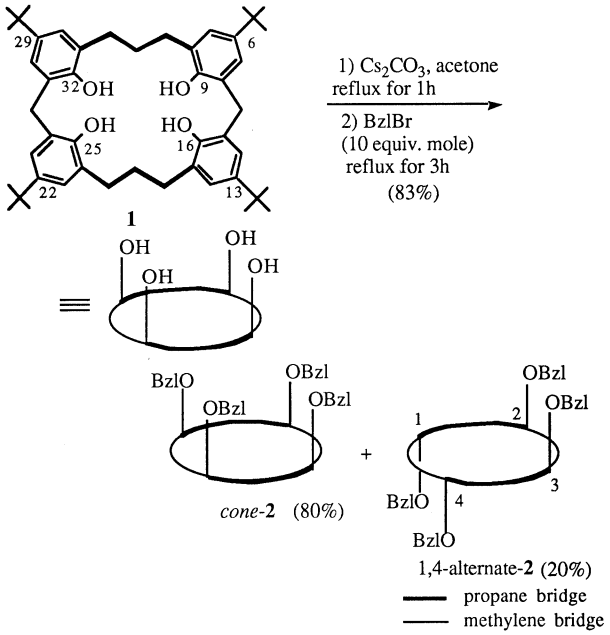
In this paper, we report on the regioselective synthesis of intraannularly *O*-benzylated tetrahydroxy[3.1.3.1]MCP **1** and on its application in the specific synthesis of methoxy-substituted [3.1.3.1]MCPs using the benzyl residues as protecting groups.

  1434−193X/98/0202−0309 $ 17.50+.50/0

Results and Discussion

We previously reported that *O*-benzylation of 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **1**[3a][3b] with 10 equiv. of benzyl bromide in the presence of NaH affords the tetra-*O*-benzylated product *cone*-**2** in 75% yield. No formation of other possible conformers was observed. Under the same reaction conditions in the presence of Cs_2CO_3, a mixture of two conformers of the tetra-*O*-benzylated product **2** in a ratio of 80:20 (*cone*-**2**/1,4-*alternate*-**2**) was obtained in 83% yield.

Scheme 1



In contrast, attempted *O*-benzylation of tetraol **1** with a large excess of benzyl bromide (20 equiv.) in the presence of Li_2CO_3 failed. The starting compound was recovered almost quantitatively. When Na_2CO_3 was used as a base, a mixture of the monosubstituted product **3**, the 1,2-disubstituted product 1,2-*proximal*-**4** and the 1,3-disubstituted product *distal*-**4** was obtained in a ratio of 46:26:28, while the other possible isomer, the 1,4-disubstituted product 1,4-*proximal*-**4**, was not observed. Interestingly, when a similar reaction was carried out with 2 equiv. of benzyl bromide, preferential formation of the monosubstituted product **3** was observed. In contrast, use of K_2CO_3 led to di-*O*-substitution to afford the disubstituted product *distal*-**4** as the major product (*distal*-**4**:1,2-*proximal*-**4**, 70:30). However, attempted *O*-benzylation in the presence of $BaCO_3$ resulted only in quantitative recovery of the starting compound.

The ratio of the products dibenzyloxy[3.1.3.1]MCP **4** and tetrabenzyloxy[3.1.3.1]MCP **2** in the *O*-benzylation of tetrahydroxy[3.1.3.1]MCP **1** is governed by the choice of alkali metal carbonate used as a catalyst, as shown by the results listed in Table 1. Thus, when lithium carbonate is used in this reaction, only recovery of the starting compound is observed. On the other hand, when sodium carbonate is employed, the monobenzylated product **3** is formed in 79% yield. However, in the case of potassium carbonate, selective

Scheme 2

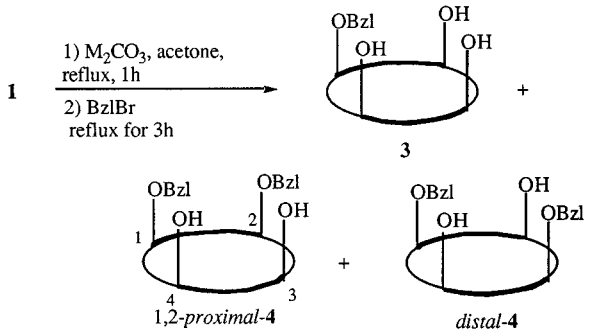


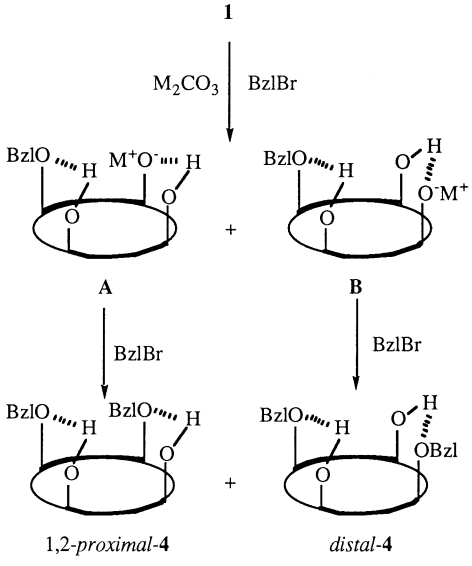
Table 1. *O*-Benzylation reaction of tetraol **1** with benzyl bromide[a]

run	base	BzlBr/**1** [mol/mol]	products (% yield)[b],[c] **3**	1,2-*proximal*-**4**	*distal*-**4**
1	Li_2CO_3 [d]	20	0	0	0
2	Na_2CO_3 [e]	2	83 (79)	10 (8)	7 (6)
3	Na_2CO_3	10	46	26	28
4	K_2CO_3	10	0	30 (22)	70 (63)
5	$BaCO_3$ [d]	48	0	0	0

[a] $[M_2CO_3]$/**1** = 20 [mol/mol]. – [b] Relative yields determined by ^{1}H-NMR spectroscopy. – [c] Isolated yields are shown in parentheses. – [d] Starting compound **1** was recovered quantitatively. – [e] Starting compound **1** was recovered in 15% yield.

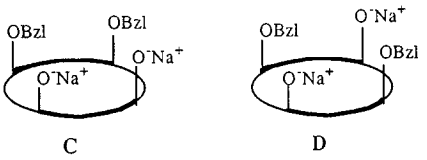
di-*O*-benzylation is observed, affording a mixture of *distal*-**4** and 1,2-*proximal*-**4** in a ratio of 70:30, even when a large excess of benzyl bromide is used. The larger alkali metal cation K^+ is clearly instrumental in forming the di-*O*-benzylation product **4**; use of the much larger Cs^+ ion leads to a decrease in the yield of this product. These results indicate that the alkali-metal cation plays an important role, not only with regard to the regioselectivity as a result of the template effect, but also in determining the degree of *O*-alkylation, as previously observed in the *O*-alkylation of tetraol **1**[3].

Figure 2. Possible intramolecular hydrogen bonds with the dissociated O^- groups



In contrast to the situation with a strong base (e.g. NaH), which leads to complete dissociation to two O^- anions, when a weak base is used (M_2CO_3, M = Na, K), the undissociated OH groups form intramolecular hydrogen bonds with the dissociated O^- groups (intermediates **A**, **B** in Figure 2) rather than undergoing further dissociation to form the metal template intermediates **C** or **D**. Thus, second alkylation is not observed due to these intramolecular hydrogen bonds with the benzyloxy groups. The present template effect is also verified by the observation that *O*-benzylation of the dibenzyloxy[3.1.3.1]MCPs 1,2-*proximal*-**4** and *distal*-**4** using NaH as the base furnishes exclusively the tetrabenzyloxy[3.1.3.1]MCP *cone*-**2** via intermediates **C** and **D** as shown Figure 3.

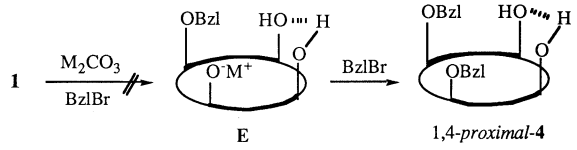
Figure 3. Possible intermediates leading to tetra-*O*-benzylation



O-Benzylation of tetraol **1** in the presence of Na_2CO_3 affords the 1,2-disubstituted products 1,2-*proximal*-**4** and *distal*-**4** in an approximately 1:1 ratio. In contrast, significantly more of the 1,3-di-*O*-substitution product *distal*-**4** results when K_2CO_3 is used as a base, compared to the amount of 1,2-*proximal*-**4**. Thus, the ratio of the products 1,2-*proximal*-**4** and *distal*-**4** in the *O*-benzylation of tetrahydroxy[3.1.3.1]MCP **1** is also governed by the nature of alkali metal carbonate used as catalyst. Although the reason for these observations is not clear from the available results, one might assume the template effect of the larger alkali metal cation K^+ to be responsible. Thus, on steric reasons, the larger alkali metal cation K^+ clearly gives rise to the preferential formation of the *distal* potassium phenoxide intermediate **B** leading to *distal*-**4**, rather than the 1,2-*proximal* intermediate **A** leading to 1,2-*proximal*-**4**, while application of the smaller Na^+ ion leads to a decrease in the steric crowding in the intermediate **A**.

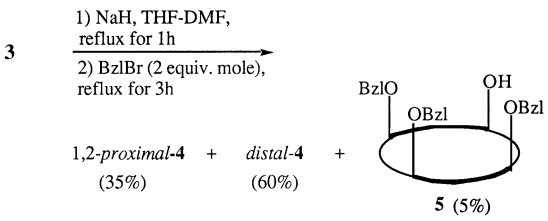
Furthermore, *O*-benzylation of tetraol **1** affords mainly the 1,2- and 1,3-disubstituted products, rather than the other possible isomer, the 1,4-disubstituted product 1,4-*proximal*-**4**. This finding might also be explained in terms of the steric crowding in the potassium phenoxide intermediate **E** at the 1,4-positions, this being less with the smaller alkali metal cation Na^+ (Scheme 3). The differential intramolecular hydrogen bonding between the hydroxyl groups of the 1,3-diarylpropane units and diarylmethane units should have an effect on regioselectivity in the *O*-benzylation of tetrahydroxy[3.1.3.1]MCP **1**.

Scheme 3



In order to study the reaction route from tetraol **1** to the tetra-*O*-benzylated product **2** in more detail, we have attempted to carry out the *O*-benzylation of the possible intermediates with benzyl bromide in the presence of either NaH or Cs_2CO_3. *O*-Benzylation of triol **3** with 10 equiv. of benzyl bromide in the presence of NaH afforded exclusively the *cone*-tetra-*O*-benzylated product *cone*-**2** in 90% yield. It was also found that *O*-benzylation of triol **3** with 2.0 equiv. of benzyl bromide in the presence of NaH afforded a mixture of the di-*O*-benzylated 1,2-*proximal*-**4** and *distal*-**4** as major products in 83% yield, along with the tri-*O*-benzylated product **5** with *cone* conformation in 5% yield. No formation of the other possible conformers was observed.

Scheme 4



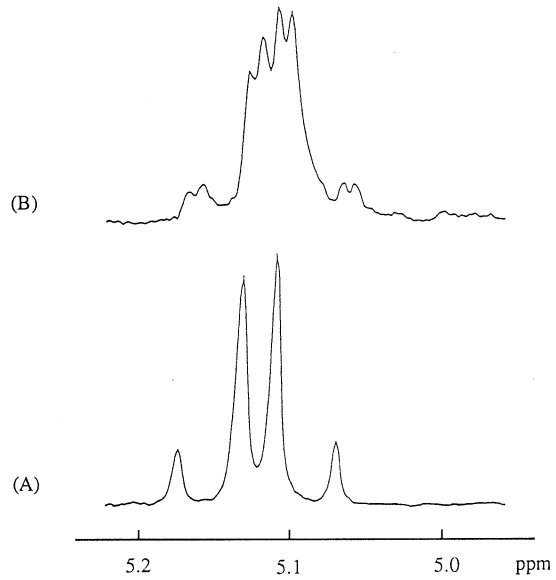
In contrast, when Cs_2CO_3 was used as a base in the *O*-benzylation of triol **3** with benzyl bromide, a mixture of two conformers of the tetra-*O*-benzylated product **2** in a ratio of 80:20 (*cone*-**2**/1,4-*alternate*-**2**) was obtained in quantitative yield. This ratio is the same as that observed in the *O*-benzylation of tetraol **1** under the same reaction conditions. Interestingly, similar reactions of the diols 1,2-*proximal*-**4** and *distal*-**4** carried out in the presence of Cs_2CO_3 afforded exclusively the *cone*-tetra-*O*-benzylated product *cone*-**2**. These results strongly indicate that the diols 1,2-*proximal*-**4** and *distal*-**4** with *cone* conformations could be intermediates in the formation of the *cone*-tetra-*O*-benzylated product *cone*-**2**. Thus, the conformation leading to 1,4-*alternate*-**2** has not been observed upon the complete introduction of a second benzyl group. In other words, formation of 1,4-*alternate*-**2** results only when the second benzyl group enters by ring inversion of the O^- anion on the unmodified phenol unit in triol **3**.

The ^{1}H-NMR spectrum of triol **3** shows three singlets for the *tert*-butyl protons at δ = 1.21, 1.24, and 1.25 (relative intensity 1:1:2), two sets of doublets of equal intensity for the ArCH_2Ar methylene protons at δ = 3.48, 3.56, 4.08 and 4.28 (J = 13.7 Hz), and a set of doublets (J = 11.2 Hz) for the diastereotopic benzyl protons at δ = 5.12 and 5.17. The IR (KBr) spectrum of **3** shows the absorption for the hydroxyl stretching vibration at around 3358 cm^{-1}. The ^{1}H-NMR spectrum (in $CDCl_3$) exhibits signals for the hydroxy groups at around δ = 7.50 and 8.12. These data confirm the existence of the intramolecular hydrogen bonding between the hydroxy groups and benzyloxy groups of the cyclic structure, which may fix the "*cone*" conformation[1][6]. Furthermore, the fact that the ^{1}H-NMR-spectral pattern for the ArCH_2Ar and Ar$CH_2CH_2CH_2$Ar methylene protons of **3** remains unchanged on increasing the temperature up to 150°C in [D_6]DMSO, indicates that ring inversion by

oxygen-through-the-annulus rotation is inhibited. It is quite interesting to note that the introduction of only one benzyl group on a phenolic oxygen in **1** inhibits the ring inversion by oxygen-through-the-annulus rotation, resulting in a rigid conformation for **3**.

Recently, chiral calixarenes have been reported by many groups[7]. Böhmer and co-workers[8] demonstrated the chirality of dissymmetric calix[4]arenes with C_2 and C_4 symmetry by interaction with Pirkle's reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol]. The macrocycle **3** is expected to have a plane of chirality, since the two types of substituents and bridged linkages are fixed in a C_1-symmetrical conformation and no conformational change is observed at room temperature. The ^{1}H-NMR spectrum of compound **3** in the absence and presence of Pirkle's reagent is shown in Figure 4. It can be seen that a pair of doublets due to the benzyl protons of the ArOCH_2Ph moiety of **3** is split into two pairs on addition of Pirkle's reagent.

Figure 4. Partial ^{1}H-NMR spectra for benzyl protons in **3** in $CDCl_3$, 270 MHz; (A) in the absence of Pirkle's reagent ([**3**] = 1.22 $\times$ 10^{-2} M) and (B) in the presence of Pirkle's reagent (1.2 $\times$ [**3**])



The ^{1}H-NMR spectrum of 1,2-*proximal*-**4** shows two singlets for the *tert*-butyl protons at δ = 1.22 and 1.23, and four doublets (J = 2.4 Hz) of equal intensity for the aromatic protons at δ = 6.88, 6.99, 6.99, and 7.14. Furthermore, the resonance for the ArCH_2Ar methylene protons appears as a pair of doublets (δ = 3.34 and 3.89, J_{AB} = 13.7 Hz, relative intensity 1:1). Similarly, the ^{1}H-NMR spectrum of *distal*-**4** shows two singlets for the *tert*-butyl protons at δ = 1.21 and 1.25, a set of doublets (J = 12.2 Hz) for the benzyl protons at δ = 5.02 and 5.30, and four doublets of equal intensity for the aromatic protons at δ = 6.89, 7.00, 7.09, and 7.16. The benzyl protons are strongly deshielded by the opposite OH groups. Furthermore, the resonance for the ArCH_2Ar methylene protons appears as a pair of doublets (δ = 3.53 and 4.14, J_{AB} = 13.4 Hz, relative intensity 1:1). Although these ^{1}H-NMR signals are very similar for both 1,2-*proximal*-**4** and *distal*-**4**, we have assigned the ^{1}H-NMR signals of *distal*-**4** by comparison with those of *distal*-6,13,22,29-tetra-*tert*-butyl-16,32-dihydroxy-9,25-bis[(2-pyridylmethyl)oxy][3.1.3.1]MCP[9]. Thus, the signals for *distal*-**4** correspond to those of this reference compound except, of course, for those of the pyridine protons.

It was also found that the benzyl methylene protons of the propane bridge ArCH_2CH_2CH_2Ar are observed as four clearly resolved double double doublets for 1,2-*proximal*-**4** at around at δ = 2.24, 2.41, 2.80, and 2.97 (relative intensity 1:1:1:1), but that in the case of *distal*-**4** only two multiplets are observed at around δ = 2.12−2.39 and 2.74−2.96. The former pattern can be assigned to 1,2-*proximal*-**4** because the benzyl methylene protons (*axial*-H and *equatorial*-H) for each of the propane bridges ArCH_2CH_2CH_2Ar are in identical environments, whereas the latter pattern corresponds to *distal*-**4** where these protons are in different environments.

The IR (KBr) spectra of 1,2-*proximal*-**4** and *distal*-**4** both show the absorption for the hydroxyl stretching vibration at around 3376 cm^{-1}. The ^{1}H-NMR spectra (in $CDCl_3$) exhibit signals for hydroxy groups at around δ = 7.40 and 7.85, respectively. The $\tilde{\nu}_{OH}$ and δ_{OH} values for diol **4**, in which two hydroxyl groups are located in 1,2-*proximal* or *distal* positions, show a slightly higher frequency and upfield shift compared to those of parent compound **1** ($\tilde{\nu}_{OH}$ = 3254 cm^{-1} and δ_{OH} = 9.35), which implies that a weaker hydrogen bond is present than that in the corresponding calix[4]arene. Therefore, bis(benzyloxy)[3.1.3.1]MCPs **4** might adopt "*cone*" conformations[1][6] due to the intramolecular hydrogen bonding between the two hydroxy groups and benzyloxy groups. Thus, hydroxy groups and benzyloxy groups can be firmly fixed on the same side of the [3.1.3.1]MCPs 1,2-*proximal*-**4** and *distal*-**4**. Furthermore, as in the case of **3**, no change in the spectral pattern due to the ArCH_2Ar and ArCH_2CH_2CH_2Ar methylene protons is observed on increasing the temperature up to 150°C in [D_6]DMSO, indicating that inversion by oxygen-through-the-annulus rotation is inhibited for 1,2-*proximal*-**4** and *distal*-**4**. Similar findings are observed for the other *O*-benzylated product, monool **5**, as shown in Table 2. The structure of this compound is thus also assigned as a rigid *cone* conformation.

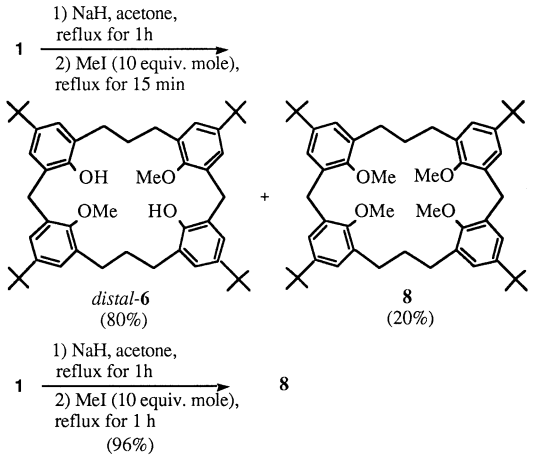
Table 2. Spectral data for *O*-benzylated [3.1.3.1]MCPs **3**, **4**, and **5** [a]

compound	IR, ν_{OH} [cm^{-1}]	methylene-bridge protons *e*	*a*	OH protons
3	3358	3.48 3.56	4.08 4.28	7.50 (2 H) 8.12 (1 H)
1,2-*proximal*-**4**	3376	3.34	3.89	7.40
distal-**4**	3376	3.53	4.14	7.85
5	3323	3.17 3.19	3.65 4.47	7.58

[a] Chemical shifts are expressed in ppm (δ) against TMS as internal standard. Coupling constants are given in Hz; *a* stands for *axial*, *e* for *equatorial*.

In order to use compound **1** as a starting material for the molecular design of functionalized macrocycles, one must fully establish the regioselectivity of derivatization at its phenolic oxygens and the conformational characteristics of the products. In fact, 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **1** was *O*-methylated with MeI in the presence of NaH by refluxing for 15 min. in DMF/THF to yield as a major product one pure regioisomer, namely the 1,3-di-*O*-substitution product *distal*-**6**, along with some of the tetramethoxy derivative **8**, while other possible regioisomers were not observed. Prolonged reaction times led to complete *O*-methylation, affording the tetramethoxy derivative **8** in 96% yield. However, in spite of attempted alkylations under various reaction conditions, the other possible regiospecific products, such as the dimethoxy (*proximal*-**6**) or the trimethoxy (**7**) derivatives, could not be synthesized directly by the reaction of **1** with methyl iodide.

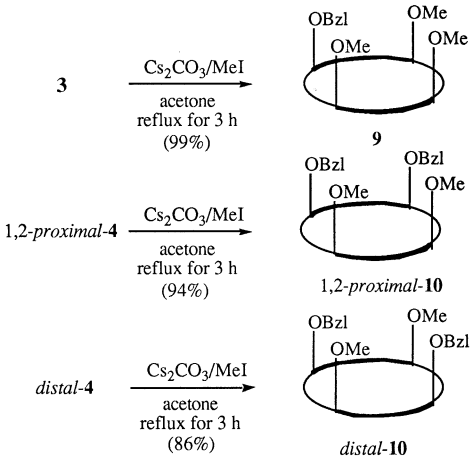
Scheme 5



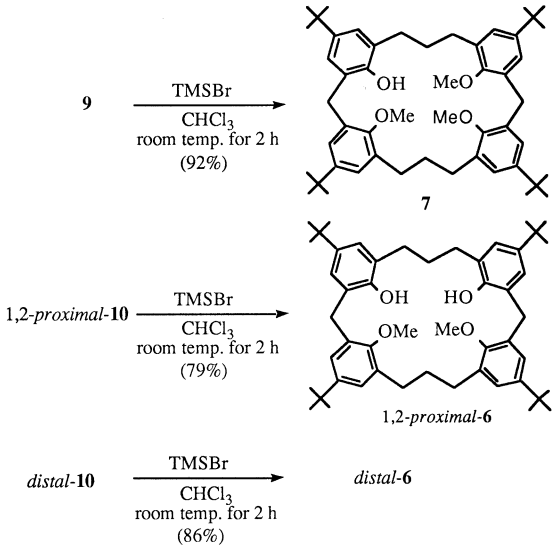
We thus utilized a protection-deprotection method using benzyl as a protecting group[10]. The aforementioned conformational isomers could then be synthesized according to the reaction route shown in Scheme 6. Reaction of the monobenzylated compound **3** with methyl iodide in acetone in the presence of Cs_2CO_3 as base yielded **9**, with a *cone* conformation, in 99% yield. The benzyl group was then removed by treatment with Me_3SiBr in $CHCl_3$ at room temperature for 2 h, to afford the desired trimethoxy derivative **7** in 92% yield. Similarly, the dimethoxy derivatives 1,2-*proximal*-**6** and *distal*-**6** could be prepared via the methylation of diols **4** followed by deprotection with Me_3SiBr in $CHCl_3$. These results demonstrate the utility of the protection-deprotection method as a strategy for the synthesis of these regioisomers.

The observation of a singlet signal for each proton in the ^{1}H-NMR spectrum of tetramethoxy[3.1.3.1]MCP **8**, even at low temperature (−60°C in $CDCl_3/CS_2$, 1:3), indicates that the methoxy groups rotate rapidly through the annulus, compared to the situation in tetrahydroxy[3.1.3.1]MCP **1** ($\Delta G_c^{\neq}$ = 12.5 kcal/mol, T_c = 0°C in $CDCl_3$). Interestingly, the ^{1}H-NMR spectra of the trimethoxy- (**7**) and dimethoxy- (1,2-*proximal*-**6**, *distal*-**6**) derivatives were all found to be temperature-independent: the individual resonances of the

Scheme 6



Scheme 7



ArCH_2Ar methylene protons did not coalesce even at about −60°C (in $CDCl_3/CS_2$, 1:3). Thus, the methyl group is too small to fix the conformation of the [3.1.3.1]MCP ring and each benzene unit can rotate at a speed comparable to the NMR time-scale, in spite of the possibility of intramolecular hydrogen bonding between the OH and OMe groups. Thus, while the four hydroxy groups in tetrahydroxy[3.1.3.1]MCP **1** can serve as donors or acceptors of hydrogen bonds, the OMe groups in dimethoxy- and trimethoxy[3.1.3.1]MCP can serve only as donors. The decreased rigidity of these compounds, in spite of the OMe substituent being much bulkier than an OH group, may be attributed to the loss of an OH···O hydrogen bond.

Conclusions

We have demonstrated for the first time that regioselective *O*-benzylation of the flexible macrocycle **1** can be achieved using benzyl bromide in the presence of alkali metal carbonates in refluxing acetone. When *O*-benzylation of **1** is carried out with 2 equiv. of benzyl bromide in the

presence of Na_2CO_3, exclusive formation of the monosubstituted product **3** is observed. In contrast, use of K_2CO_3 leads to di-*O*-substitution to afford the 1,2-disubstituted 1,2-*proximal*-**4** as a major product, along with *distal*-**4**, in spite of using a large excess of benzyl bromide. Under the same reaction conditions in the presence of Cs_2CO_3, a mixture of two conformers of the tetra-*O*-benzylated product **2** in a ratio of 80:20 (*cone*-**2**/1,4-*alternate*-**2**) is obtained in 83% yield. As a result of the template effect, the alkali metal cation plays an important role, not only with regard to the regioselectivity, but also in determining the degree of *O*-benzylation. The different intramolecular hydrogen bonding between the hydroxyl groups of the 1,3-diarylpropane units and diarylmethane units has an effect on the regioselectivity of di-*O*-alkylations of tetrahydroxy[3.1.3.1]MCPs.

Regioselective syntheses of dimethoxy- and trimethoxy[3.1.3.1]MCPs have been accomplished by a protection-deprotection method using benzyl residues as protecting groups.

Experimental Section

All melting points are uncorrected. − IR (KBr or NaCl): Nippon Denshi JIR-AQ2OM. − ^{1}H NMR: Nippon Denshi JEOL FT-270 in $CDCl_3$, TMS as reference. − UV: Shimadzu 220A spectrophotometer. − MS: Nippon Denshi JMS-01SA-2. − Elemental analysis: Yanaco MT-5.

Materials: The preparation of 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]metacylophane **1** has been described previously[3].

Benzylation of **1** *with Benzyl Bromide in the Presence of Na_2CO_3:* A mixture of **1** (400 mg, 0.567 mmol) and sodium carbonate (1.20 g, 11.4 mmol) in dry acetone (36 ml) was heated to reflux for 1 h under nitrogen. Then, benzyl bromide (0.63 ml, 5.67 mmol) was added and the mixture was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under reduced pressure in a kugelrohr apparatus to remove the excess unreacted benzyl bromide. The ^{1}H-NMR spectrum of the residue was in accord with its being a mixture of **3**, 1,2-*proximal*-**4** and *distal*-**4** in a ratio of 83:10:7. The residue was chromatographed on silica gel with hexane/benzene (1:1), benzene/chloroform (1:1), and ethanol as eluents to give *distal*-**4** (30 mg, 6.0%), 1,2-*proximal*-**4** (40 mg, 8.0%), and **3** (357 mg, 79.1%), respectively.

9-Benzyloxy-6,13,22,29-tetra-tert-butyl-16,25,32-trihydroxy-[3.1.3.1]metacyclophane (**3**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. 144−149°C. − IR (KBr): $\tilde{\nu}$ = 3358 cm^{-1} (OH), 3852 (OH), 2980, 2867, 1485, 1392, 1234, 1231, 1207. − ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 9 H), 1.24 (s, 9 H), 1.25 (s, 18 H), 1.70−1.83 (m, 1 H), 2.07−2.58 (m, 7 H), 2.64−2.83 (m, 2 H), 2.95−3.06 (m, 2 H), 3.48 (d, *J* = 13.7 Hz, 1 H), 3.56 (d, *J* = 13.7 Hz, 1 H), 4.08 (d, *J* = 13.7 Hz, 1 H), 4.28 (d, *J* = 13.7 Hz, 1 H), 5.12 (d, *J* = 11.2 Hz, 1 H), 5.17 (d, *J* = 11.2 Hz, 1 H), 6.87 (d, *J* = 2.4 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 2.4 Hz, 1 H), 7.06 (d, *J* = 2.4 Hz, 1 H), 7.10 (d, *J* = 2.4 Hz, 1 H), 7.12 (d, *J* = 2.4 Hz, 2 H), 7.19 (d, *J* = 2.4 Hz, 1 H), 7.23−7.78 [m, 7 H, ArH (5 H), OH (2 H)], 8.12 (s, 1 H, OH). − MS (75 eV): *m*/*z* = 794 [M$^+$]. − $C_{55}H_{70}O_4$·MeOH (827.2): calcd. C 81.31, H 9.02; found C 81.66, H 8.76.

1,2-proximal-9,25-Bis(benzyloxy)-6,13,22,29-tetra-tert-butyl-16,32-dihydroxy[3.1.3.1]metacyclophane (1,2-*proximal*-**4**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. 270−274°C. − IR (KBr): $\tilde{\nu}$ = 3376 cm^{-1} (OH), 2958, 1457, 1484, 1363, 1208, 1135. − ^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 18 H), 1.23 (s, 18 H), 1.8−1.95 (m, 2 H), 2.0−2.15 (m, 2 H), 2.24 (ddd, *J* = 4.9, 12.2, 12.7 Hz, 2 H), 2.41 (ddd, *J* = 4.9, 12.2, 12.7 Hz, 2 H), 2.80 (ddd, *J* = 4.9, 12.2, 12.7 Hz, 2 H), 2.97 (ddd, *J* = 4.9, 12.2, 12.7 Hz, 2 H), 3.34 (d, *J* = 13.7 Hz, 2 H), 3.89 (d, *J* = 13.7 Hz, 2 H), 4.93 (d, *J* = 12.5 Hz, 2 H), 5.06 (d, *J* = 12.5 Hz, 2 H), 6.88 (d, *J* = 2.4 Hz, 2 H), 6.99 (d, *J* = 2.4 Hz, 4 H), 7.14 (d, *J* = 2.4 Hz, 2 H), 7.35−7.50 [m, 12 H, ArH (10 H), OH (2 H)]. − MS (75 eV): *m*/*z* = 884 [M$^+$]. − $C_{62}H_{76}O_4$ (885.3): calcd. C 84.12, H 8.65; found C 84.24, H 8.74.

distal-9,32-Bis(benzyloxy)-6,13,22,29-Tetra-tert-butyl-16,25-dihydroxy[3.1.3.1]metacyclophane (*distal*-**4**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. 261−265°C. − IR (KBr): $\tilde{\nu}$ = 3376 cm^{-1} (OH), 2956, 1484, 1208, 1196. − ^{1}H NMR ($CDCl_3$): δ = 0.86−0.91 (m, 4 H), 1.21 (s, 18 H), 1.25 (s, 18 H), 2.12−2.39 (m, 4 H), 2.74−2.96 (m, 4 H), 3.53 (d, *J* = 13.4 Hz, 2 H), 4.14 (d, *J* = 13.4 Hz, 2 H), 5.02 (d, *J* = 12.2 Hz, 2 H), 5.30 (d, *J* = 12.2 Hz, 2 H), 6.89 (d, *J* = 2.4 Hz, 2 H), 7.00 (d, *J* = 2.4 Hz, 2 H), 7.09 (d, *J* = 2.4 Hz, 2 H), 7.16 (d, *J* = 2.4 Hz, 2 H), 7.19−7.27 (m, 6 H), 7.61 (d, *J* = 6.8 Hz, 4 H), 7.85 (s, 2 H, OH). − MS (75 eV): *m*/*z* = 884 [M$^+$]. − $C_{62}H_{76}O_4$ (885.3): calcd. C 84.12, H 8.65; found C 83.86, H 8.69.

Benzylation of **1** *with Benzyl Bromide in the Presence of K_2CO_3:* A mixture of **1** (400 mg, 0.567 mmol) and sodium carbonate (1.20 g, 11.4 mmol) in dry acetone (36 ml) was heated to reflux for 1 h under nitrogen. Then, benzyl bromide (0.63 ml, 5.67 mmol) was added and the mixture was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under the reduced pressure in a kugelrohr apparatus to remove the excess unreacted benzyl bromide. The ^{1}H-NMR spectrum of the residue was in accord with its being a mixture of 1,2-*proximal*-**4** and *distal*-**4** in a ratio of 30:70. The residue was chromatographed on silica gel with hexane/benzene (1:1) and benzene/chloroform (1:1) as eluents to give *distal*-**4** (315 mg, 62.8%) and 1,2-*proximal*-**4** (110 mg, 22.0%), respectively.

Benzylation of **3** *with Benzyl Bromide in the Presence of NaH:* A mixture of **3** (400 mg, 0.503 mmol) and NaH (454.0 mg, 11.35 mmol) in dry tetrahydrofuran (THF, 90 ml) and *N*,*N*-dimethylformamide (DMF, 9 ml) was stirred at room temperature for 1 h under nitrogen. Then, benzyl bromide (0.119 ml, 1.01 mmol) was added and the mixture was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was acidified with 1 N HCl (10 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined extracts were washed with water (2 × 50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a yellow oil, which was then distilled under reduced pressure in a kugelrohr apparatus to remove the excess unreacted benzyl bromide. The ^{1}H-NMR spectrum of the residue was in accord with its being a mixture of 1,2-*proximal*-**4**, *distal*-**4**, and *cone*-**5** in a ratio of 35:60:5. The residue was chromatographed on silica gel with hexane/benzene (1:1) and benzene/chloroform (1:1) as eluents to give *cone*-**5** (19 mg, 3.9%) and a mixture of *distal*-**4** and 1,2-*proximal*-**4** (370 mg, 83%), respectively.

cone-9,16,25-Tris(benzyloxy)-6,13,22,29-tetra-tert-butyl-32-hydroxy[3.1.3.1]metacyclophane (*cone*-**5**): Colorless prisms [hexane/benzene (1:1)], m.p. 180−183°C. − IR (KBr): $\tilde{\nu}$ = 3323 cm^{-1} (OH), 3031, 2963, 1501, 1476, 1415, 1392, 1361, 1295, 1212, 1123, 1023, 958, 930, 915, 789, 868, 820, 755, 732. − ^{1}H NMR ($CDCl_3$): δ = 1.17 (s, 9 H), 1.18 (s, 9 H), 1.22 (s, 9 H), 1.24 (s, 9 H), 1.83−1.93 (m, 4 H), 2.24−2.33 (m, 4 H), 2.53−2.90 (m, 4 H), 3.17

(d, J = 13.18 Hz, 1 H), 3.19 (d, J = 13.18 Hz, 1 H), 3.65 (d, J = 13.18 Hz, 1 H), 4.47 (d, J = 13.18 Hz, 1 H), 4.64 (d, J = 12.21 Hz, 1 H), 4.67 (d, J = 11.48 Hz, 1 H), 4.73 (d, J = 11.48 Hz, 1 H), 4.86 (d, J = 12.21 Hz, 1 H), 4.91 (d, J = 12.21 Hz, 1 H), 4.96 (d, J = 12.21 Hz, 1 H), 6.87 (d, J = 2.44 Hz, 1 H), 6.89 (d, J = 2.44 Hz, 1 H), 6.91 (d, J = 2.44 Hz, 1 H), 6.94 (d, J = 2.44 Hz, 1 H), 6.96 (d, J = 2.44 Hz, 1 H), 7.04 (d, J = 2.44 Hz, 1 H), 7.10 (d, J = 2.44 Hz, 1 H), 7.58 (s, 1 H, OH), 7.12−7.35 (m, 14 H), 7.52−7.55 (m, 2 H). − MS (75 eV): m/z = 974 [M^+]. − $C_{69}H_{82}O_4$ (975.4): calcd. C 84.97, H 8.47; found C 84.93, H 8.58.

Methylation of **1** *with Methyl Iodide in the Presence of NaH:* A mixture of **1** (400 mg, 0.567 mmol) and NaH (454.0 mg, 11.35 mmol) in dry THF (90 ml) and DMF (9 ml) was stirred at room temperature for 1 h under nitrogen. Then, methyl iodide (1.29 ml, 14.18 mmol) was added and the mixture was heated under reflux for an additional 15 min. After cooling to room temperature, the reaction mixture was acidified with 1 N HCl (10 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined extracts were washed with water (2 × 50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a yellow solid. The ^{1}H-NMR spectrum of the product was in accord with its being a mixture of two components, *distal*-**6** and **8** in a ratio of 80:20. The residue was chromatographed on silica gel with benzene as eluent to give *distal*-**6** (300 mg, 72%) and **8** (76 mg, 17%), respectively.

distal-6,13,22,29-Tetra-tert-butyl-9,25-dihydroxy-16,32-dimethoxy[3.1.3.1]metacyclophane (*distal*-**6**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. >300°C. − IR (KBr): $\tilde{\nu}$ = 3413 cm^{-1} (OH), 2960, 2866, 1482, 1459, 1363, 1298, 1208, 1169, 1105, 990, 880. − ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 18 H), 1.25 (s, 18 H), 1.43−1.61 (br. s, 4 H), 2.61−2.69 (br. s, 8 H), 3.78 (s, 4 H), 3.97 (s, 6 H), 6.92 (d, J = 2.4 Hz, 2 H), 6.98 (d, J = 2.4 Hz, 2 H), 7.06 (d, J = 2.4 Hz, 2 H), 7.11 (d, J = 2.4 Hz, 2 H), 7.77 (s, 2 H, OH). − MS (75 eV): m/z = 732 [M^+]. − $C_{50}H_{68}O_4$ (733.1): calcd. C 81.92, H 9.35; found C 81.55, H 9.24.

6,13,22,29-Tetra-tert-butyl-9,16,25,32-tetramethoxy[3.1.3.1]metacyclophane (**8**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. >300°C. − ^{1}H NMR ($CDCl_3$): δ = 1.24 (s, 36 H), 1.75−1.81 (m, 4 H), 2.53 (t, J = 7.3 Hz, 8 H), 3.14 (s, 12 H), 3.83 (s, 4 H), 6.97 (d, J = 2.4 Hz, 4 H), 7.01 (d, J = 2.4 Hz, 4 H). − MS (75 eV): m/z = 760 [M^+]. − $C_{52}H_{72}O_4$ (761.2): calcd. C 82.06, H 9.53; found C 81.86, H 9.44.

Methylation of **3** *and* **4** *with Methyl Iodide in the Presence of Cs_2CO_3. − Typical Procedure:* A mixture of **3** (200 mg, 0.252 mmol) and cesium carbonate (1.64 g, 5.03 mmol) in dry acetone (18 ml) was heated to reflux for 1 h under nitrogen. Then, methyl iodide (0.16 ml, 2.52 mmol) was added and the mixture was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated to give a colorless solid, which was washed with hexane to afford *9-benzyloxy-6,13,22,29-tetra-tert-butyl-16,25,32-trimethoxy-[3.1.3.1]metacyclophane* (**9**) (208 mg, 99.0%) as a colorless powder. Recrystallization from MeOH/$CHCl_3$ (1:1) gave **9**: Colorless prisms, m.p. 187−190°C. − IR (KBr): $\tilde{\nu}$ = 2963 cm^{-1}, 2863, 1479, 1455, 1382, 1111, 1020, 1009. − ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 18 H), 1.27 (s, 9 H), 1.29 (s, 9 H), 1.50−1.90 (m, 4 H), 2.14−2.35 (m, 4 H), 2.54−3.05 (m, 4 H), 2.789 (s, 3 H), 2.794 (s, 3 H), 3.25 (d, J = 14.0 Hz, 1 H), 3.38 (d, J = 14.0 Hz, 1 H), 3.38 (s, 3 H), 4.33 (d, J = 14.0 Hz, 1 H), 4.41 (d, J = 14.0 Hz, 1 H), 4.74 (s, 2 H), 6.85 (d, J = 2.4 Hz, 1 H), 6.90 (d, J = 2.4 Hz, 1 H), 6.96 (d, J = 2.4 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H), 7.02−7.07 (m, 3 H), 7.14 (d, J = 2.4 Hz, 1 H), 7.15−7.23 (m, 3 H), 7.28−7.31 (m, 2 H). − MS (75 eV): m/z = 836 [M^+]. − $C_{58}H_{76}O_4$·MeOH (869.29): calcd. C 81.52, H 9.28; found C 81.30, H 9.16.

Compounds 1,2-*proximal*-**10** and *distal*-**10** were synthesized from 1,2-*proximal*-**4** and *distal*-**4** in the same manner as described above for **9** in 94 and 86% yields, respectively.

1,2-proximal-9,32-Bis(benzyloxy)-6,13,22,29-tetra-tert-butyl-16,25-dimethoxy[3.1.3.1]metacyclophane (1,2-*proximal*-**10**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. 210−213°C. − IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1492, 1489, 1385, 1374, 1362, 1292, 1247, 1210, 1149, 1118, 1079, 1019, 873, 859, 739. − ^{1}H NMR ($CDCl_3$): δ = 1.08 (s, 18 H), 1.28 (s, 18 H), 1.21−1.34 (m, 2 H), 1.67−1.76 (m, 2 H), 1.92−2.08 (m, 2 H), 2.30−2.53 (m, 4 H), 2.74 (s, 6 H), 3.00−3.09 (m, 2 H), 3.43 (d, J = 14.6 Hz, 2 H), 4.46 (d, J = 14.6 Hz, 2 H), 4.81 (d, J = 11.7 Hz, 2 H), 4.92 (d, J = 11.7 Hz, 2 H), 6.76 (d, J = 2.3 Hz, 2 H), 6.91 (d, J = 2.3 Hz, 2 H), 7.01 (d, J = 2.3 Hz, 2 H), 7.10 (d, J = 2.3 Hz, 2 H), 7.24−7.36 (m, 6 H), 7.44−7.48 (m, 4 H). − MS (75 eV): m/z = 912 [M^+]. − $C_{64}H_{80}O_4$ (913.3): calcd. C 84.16, H 8.83; found C 84.04, H 8.85.

distal-9,25-Bis(benzyloxy)-6,13,22,29-tetra-tert-butyl-16,32-dimethoxy[3.1.3.1]metacyclophane (*distal*-**10**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. 220−224°C. − IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1481, 1363, 1292, 1243, 1119, 1194, 759, 730. − ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 18 H), 1.17 (s, 18 H), 1.53−1.93 (m, 4 H), 2.33−2.46 (m, 4 H), 2.53−2.67 (m, 2 H), 2.72 (s, 6 H), 2.78−2.92 (m, 2 H), 3.30 (d, J = 13.9 Hz, 2 H), 4.32 (d, J = 13.9 Hz, 2 H), 4.74 (d, J = 11.7 Hz, 2 H), 4.84 (d, J = 11.7 Hz, 2 H), 6.88 (d, J = 2.4 Hz, 2 H), 6.90−6.97 (m, 4 H), 7.04 (d, J = 2.4 Hz, 2 H), 7.18−7.20 (m, 6 H), 7.36−7.40 (m, 4 H). − MS (75 eV): m/z = 912 [M^+]. − $C_{64}H_{80}O_4$ (913.3): calcd. C 84.16, H 8.83; found C 83.87, H 8.77.

Debenzylation of **9** *and* **10** *with Trimethylsilyl Bromide. − Typical Procedure:* A solution of compound **9** (100 mg, 0.120 mmol) in chloroform (6 ml) was treated with Me_3SiBr (0.079 ml, 0.597 mmol) at room temperature for 2 h under nitrogen. The mixture was then diluted with water, and extracted with CH_2Cl_2 (2 × 10 ml). The combined extracts were washed with water (2 × 10 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a pale-yellow solid. The crude product was washed with a small amount of hexane to afford *6,13,22,29-tetra-tert-butyl-9-hydroxy-16,25,32-trimethoxy[3.1.3.1]metacyclophane* (**7**) (82 mg, 92%) as a colorless powder. Recrystallization from MeOH/$CHCl_3$ (1:1) gave **7**: Colorless prisms, m.p. >300°C. − IR (KBr): $\tilde{\nu}$ = 3387 cm^{-1} (OH), 2885, 1438, 1392, 1382, 1199, 1194, 1188, 990, 929, 822. − ^{1}H NMR ($CDCl_3$): δ = 1.20, 1.22, 1.25 (3 × s, 36 H), 1.48−1.72 (m, 4 H), 2.51−2.71 (m, 8 H), 3.78 (s, 4 H), 3.97 (s, 9 H), 6.92 (d, J = 2.4 Hz, 2 H), 6.98 (d, J = 2.4 Hz, 2 H), 7.06 (d, J = 2.4 Hz, 1 H), 7.11 (d, J = 2.4 Hz, 2 H), 7.15 (d, J = 2.4 Hz, 1 H), 7.96 (s, 1 H, OH). − MS (75 eV): m/z = 746 [M^+]. − $C_{51}H_{70}O_4$ (747.1): calcd. C 81.99, H 9.44; found C 81.89, H 9.23.

Compounds 1,2-*proximal*-**6** and *distal*-**6** were synthesized from 1,2-*proximal*-**10** and *distal*-**10** in the same manner as described above for **7**, 79 and 86% yields, respectively.

6,13,22,29-Tetra-tert-butyl-9,32-dihydroxy-16,25-dimethoxy-[3.1.3.1]metacyclophane (1,2-*proximal*-**6**): Colorless prisms [MeOH/$CHCl_3$ (1:1)], m.p. >300°C. − IR (KBr): $\tilde{\nu}$ = 4160 cm^{-1}, 3852, 3398, 2958, 1482, 1458, 1393, 1362, 1297, 1207, 990, 667. − ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 18 H), 1.53−1.64 (br. s, 4 H), 1.25 (s, 18 H), 2.63−2.67 (br. s, 8 H), 3.78 (s, 4 H), 3.97 (s, 6 H), 6.92 (d, J = 2.4 Hz, 2 H), 6.98 (d, J = 2.4 Hz, 2 H), 7.06 (d, J = 2.4 Hz, 2 H), 7.11 (d, J = 2.4 Hz, 2 H), 7.73 (br. s, 2 H, OH). − MS (75 eV): m/z = 732 [M^+]. − $C_{50}H_{68}O_4$ (733.1): calcd. C 81.92, H 9.35; found C 81.78, H 9.35.

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