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Syntheses of All Possible Conformational Isomers of O-Alkyl-p-t-Butylcalix[4]arenes

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Abstract In p-t-butylcalix[4]arene ($1H_4$) and its mono-, di-, tri-, and tetra-O-alkyl derivatives ($1HR_3$, $1H_2R_2$, $1HR_3$, and $1R_4$ respectively), 23 different homologs can exist (including $1H_4$) We found that the OH group in the unmodified phenol unit is permeable through the calix[4]arene ring Thus, several conformational isomers become equivalent after the oxygen-through-the-annulus rotation of the OH group and the number of the possible homologs is reduced to 13 (including $1H_4$). We here report the syntheses of all of these possible conformational isomers by using a protection-deprotection method with a benzyl group and metal template effects The results are very useful for understanding the conformer distribution in $1H_2R_2$, $1HR_3$, and $1R_4$, which has confused calixarene chemists for a long time and is still a matter of discussion

Introduction

Calix[4]arenes are cyclic tetramers made up of phenol and formaldehyde It is known that unmodified calix[4]arenes adopt a cone conformation because of the stabilization by intramolecular hydrogen-bonding interactions [1-7] On the other hand, introduction of four bulky substituents into the OH groups suppresses the oxygen-through-the-annulus rotation and results in conformational isomers [1,3,8-12] We have found that in p-t-butylcalix[4]arene ($1H_4$) the n-propyl group (Pr) is bulky enough to inhibit the rotation Basically, four different conformers can exist they are cone, partial cone, 1,2-alternate, and 1,3-alternate As shown in Table 1, these four conformers can exist in di-, tri-, and tetra-O-propylated stages ($1H_2Pr_2$, $1HPr_3$, and $1Pr_4$, respectively) Furthermore, two different regio-isomers (distal and proximal) exist in the stage of $1H_2Pr_2$ The total number of possible homologs is 23 (including cone-$1H_4$ and cone-$1HPr_3$) It thus seems to be extremely difficult to synthesize all possible conformers listed in Table 1 As described in this paper, however, we found that the OH group in unmodified phenol unit is permeable

Table 1. Conformational isomers possible in $1H_4$ and its O-alkylation derivatives

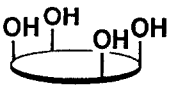
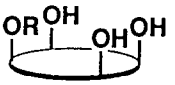
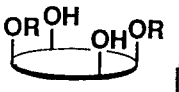
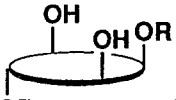
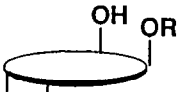
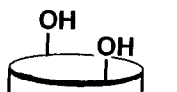
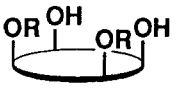
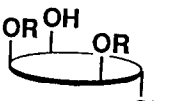
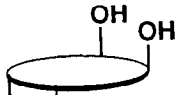
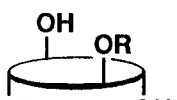
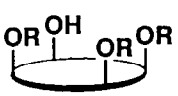
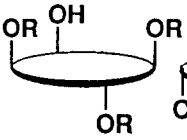
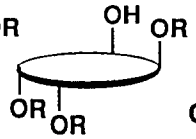
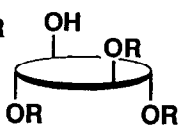
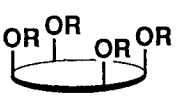
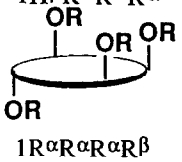
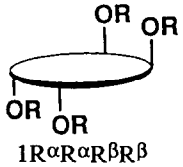
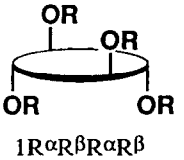
calixarene	conformation			
	cone	partial cone	1,2-alternate	1,3-alternate
$1H_4$				
	$1H^{\alpha}H^{\alpha}H^{\alpha}H^{\alpha}$			
$1H_3R$				
	$1H^{\alpha}H^{\alpha}H^{\alpha}R^{\alpha}$			
distal-$1H_2R_2$				
	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}$ $1H^{\alpha}R^{\alpha}H^{\beta}R^{\alpha}$	$1H^{\alpha}R^{\alpha}H^{\beta}R^{\beta}$	$1H^{\alpha}R^{\beta}H^{\alpha}R^{\beta}$
proximal-$1H_2R_2$				
	$1H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}$	$1H^{\alpha}H^{\beta}R^{\alpha}R^{\alpha}$ $1H^{\alpha}H^{\alpha}R^{\alpha}R^{\beta}$	$1H^{\alpha}H^{\alpha}R^{\beta}R^{\beta}$ $1H^{\alpha}H^{\beta}R^{\beta}R^{\alpha}$	$1H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}$
$1HR_3$				
	$1H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	$1H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}$ $1H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$ $1H^{\beta}R^{\alpha}R^{\alpha}R^{\alpha}$	$1H^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$	$1H^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$
$1R_4$				
	$1R^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	$1R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$	$1R^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$	$1R^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$

Table 2. Conformational isomers which become equivalent after the rotation of the OH group

calixarene	basic conformation		equivalent conformation		
distal-$1H_2R_2$	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$	=	$1H^{\alpha}R^{\alpha}H^{\beta}R^{\alpha}$	$1H^{\alpha}R^{\beta}H^{\alpha}R^{\beta}$	
	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}$	=	$1H^{\alpha}R^{\alpha}H^{\beta}R^{\beta}$		
proximal-$1H_2R_2$	$1H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}$	=	$1H^{\alpha}H^{\beta}R^{\alpha}R^{\alpha}$	$1H^{\alpha}H^{\alpha}R^{\beta}R^{\beta}$	$1H^{\beta}R^{\alpha}R^{\alpha}R^{\alpha}$
	$1H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}$	=	$1H^{\alpha}H^{\alpha}R^{\alpha}R^{\beta}$	$1H^{\alpha}H^{\beta}R^{\beta}R^{\alpha}$	
$1HR_3$	$1H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$	=	$1H^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$		
	$1H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}$	=	$1H^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$		

Table 3. Basic conformational isomers remaining after the rotation of the OH group

calixarene	conformation			
	cone	partial cone	1,2-alternate	1,3-alternate
$1H_4$	$1H^{\alpha}H^{\alpha}H^{\alpha}H^{\alpha}$			
$1H_3R$	$1H^{\alpha}H^{\alpha}H^{\alpha}R^{\alpha}$			
distal-$1H_2R_2$	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$	$1H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}$		
proximal-$1H_2R_2$	$1H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}$			$1H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}$
$1HR_3$	$1H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	$1H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}$ $1H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$		
$1R_4$	$1R^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	$1R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$	$1R^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$	$1R^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$

through the calix[4]arene ring (even the OH group in $1HPr_3$) This means that the position of the OH group in these conformers is determined as a consequence of the thermodynamic control As summarized in Table 2, several conformers thus become equivalent to each other after the oxygen-through-the-annulus rotation of the OH group In $1H_2Pr_2$, for example, distal-1,3-alternate-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\beta}H^{\alpha}Pr^{\beta}$)* is equivalent to distal-cone-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$) and distal-1,2-alternate-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\beta}Pr^{\beta}$) is equivalent to distal-partial-cone-$1H_2Pr_2$($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$) In $1HPr_3$, for example, 1,3-alternate-$1HPr_3$ ($1H^{\alpha}Pr^{\beta}Pr^{\alpha}Pr^{\beta}$) is equivalent to distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) and 1,2-alternate $1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\beta}$) is equivalent to proximal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$). Thus, the number of remaining conformers is reduced to 13 (including cone-$1H_4$ and cone-$1H_3Pr$. Table 3) The decrease in the number encouraged us to challenge the syntheses of all possible conformers This challenge is of great significance not only in the development of new calix[4]arene-based conformers but also in the elucidation of reaction mechanisms by which these conformers are formed [13]

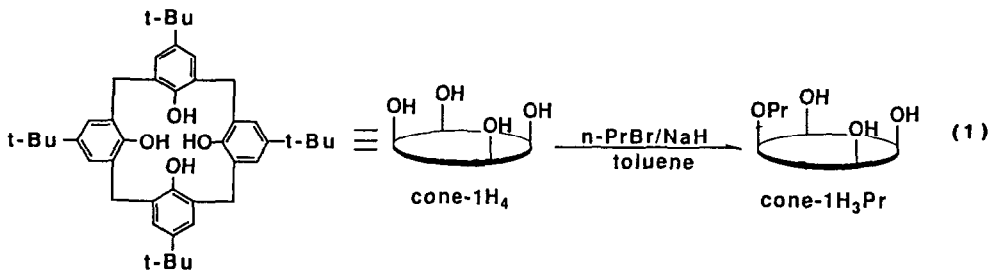
Results and Discussion

Strategies for Syntheses. Through the previous studies[10-14] we have found several versatile methods useful for the syntheses of new conformers (i) mono-O-alkylated p-t-butylcalix[4]arenes ($1H_3R$) can be synthesized in toluene by the control of a $1H_4$/RX (alkyl halides) ratio,[14] (ii) the reaction of $1H_4$ and RX in the presence of M_2CO_3 (M=Na or K) selectively yields distal-cone-$1H_2R_2$,[12,15,16] (iii) the reaction in the presence of Cs_2CO_3 yields either $1HR_3$ or $1R_4$ (depending on a $1H_4$/RX ratio), the product being the mixture of partial cone, 1,2-alternate, and 1,3-alternate,[12,17] (iv) the reaction in the presence of $Ba(OH)_2$ affords only cone-$1HR_3$,[12,18] (v) a benzyl group is useful for protection of the OH group [14] By the combination of these strategies we can now synthesize all possible conformers listed in Table 3.

Mono-O-alkylation. It is rather difficult to stop the O-alkylation reaction in the stage of $1H_3R$. We found that $1H_4$ is efficiently mono-O-alkylated when $1H_4$ is

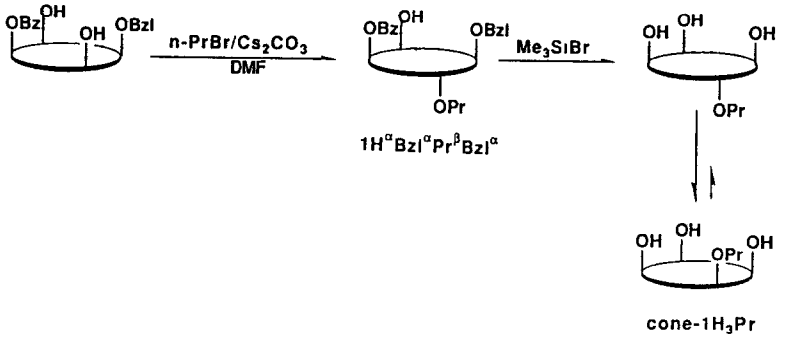
*To distinguish conformational isomers, cone, partial cone, 1,2-alternate, and 1,3-alternate have been used To distinguish the substituent position, distal and proximal have been used However, these two nomenclatures are not enough to distinguish conformational isomers synthesized herein In such cases, we used α and β (for example, $\alpha\alpha\alpha\alpha$ for cone and $\alpha\beta\alpha\beta$ for 1,3-alternate) as used in the nomenclature for porphyrin atropisomers

treated with alkyl halides (such as n-PrBr and BzlBr) in toluene in the presence of NaH In mono-O-benzylation, for example, the yield under the optimum conditions is 67%. In contrast, when polar solvents (such as DMF, acetonitrile, etc.) were used instead of toluene, the product was a mixture of $1HPr_3$, $1H_2Pr_2$, and $1Pr_4$ The excellent selectivity for mono-O-alkylation in toluene is accounted for by two terms. (i) phenoxide anions are deactivated because of the formation of tight ion pairs and (ii) it is energetically favorable to produce monoanionic $1H_3^-$ rather than polyanionic $1H_2^{2-}$, $1H^{3-}$, and 1^{4-} On the other hand, when $Ba(OH)_2$ was used instead of NaH, DMF could be used as solvent for mono-O-alkylation We consider that the reactivity of the phenoxide anions is also suppressed through complexation with Ba^{2+}



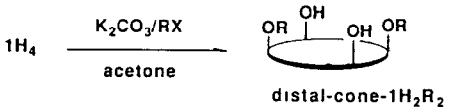
(1)

Compound $1HPr_3$ adopts a cone conformation This is supported by the fact that in ^1H NMR spectroscopy ($CDCl_3$, 25 °C) the $ArCH_2Ar$ methylene protons appear as two pairs of doublets (3 41 and 4 36 ppm for one pair and 3.43 and 4.27 ppm for another pair) and the difference in the chemical shift ($\Delta\delta$ = 0 84-0 95 ppm) is as large as 0 9 ppm [19] This split pattern is commensurate with a cone conformation [19] Is the conformation other than cone really impossible in $1HPr_3$? To answer this question we carried out the following experiment. Mono-O-propylation of distal-cone-$1H_2Bzl_2$ by n-PrBr in DMF in the presence of Cs_2CO_3 gave distal-OPr-inversed partial-cone-$1HPrBzl_2$ ($1H^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$) in 65% yield Treatment of this compound with Me_3SiBr in chloroform should give partial-cone-$1H_3Pr$ ($1H^{\alpha}H^{\alpha}Pr^{\beta}H^{\alpha}$). Actually, however, the compound we recovered in 92% yield was cone-$1H_3Pr$ We consider that three OH groups rotate so that they can form hydrogen-bonds including the OPr group The rotation of the OPr group cannot be ruled out, however Anyway, cone is the sole conformation allowed for $1H_3Pr$.[20]



(2)

Di-O-alkylation. It has bean noticed by Reinhoudt et al ,[15] No et al ,[16] and us[12] that the reaction of $1H_4$ and RX in the presence of M_2CO_3 (M=Na or K) yields di-O-alkylated derivatives (distal-cone-$1H_2R_2$) The reaction stops in the di-O-alkylation stage even in the presence of excess RX For example, the reaction of $1H_4$ and n-PrBr in acetone in the presence of K_2CO_3 yielded distal-cone-$1H_2Pr_2$ in 79% yield [12] Similarly, the reaction of $1H_4$ and benzyl bromide (BzlBr) in acetone in the presence of K_2CO_3 yielded distal-cone-$1H_2Bzl_2$ in 98% yield

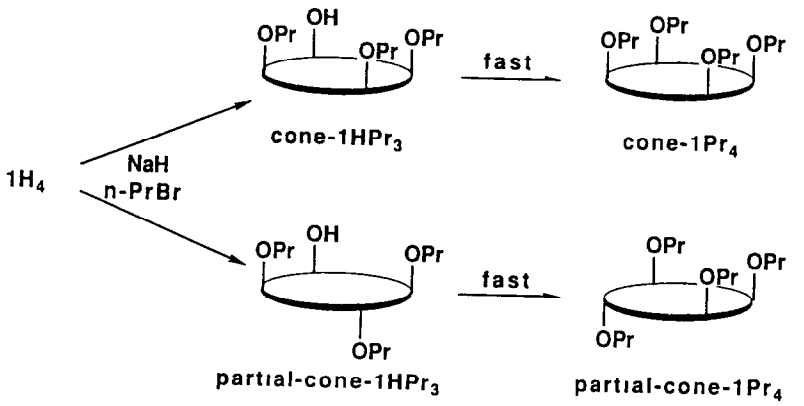


(3)

DMF can be used instead of acetone [12] When Cs_2CO_3 was used instead of Na_2CO_3 or K_2CO_3, on the other hand, further O-alkylation to $1R_4$ took place (vide post) It is known that phenoxide anions having Cs^+ as a countercation is more reactive than those having other alkali metal cations as countercations [21] This is explained by the difference in the ion-pair tightness. Thus, the difference observed between di-O-alkylation in the presence of Na_2CO_3 or K_2CO_3 and tetra-O-alkylation in the presence of Cs_2CO_3 is also explained by the higher reactivity of $1HR_2$-Cs^+ and $1R_3$-Cs^+ due to the formation of the loose ion pairs

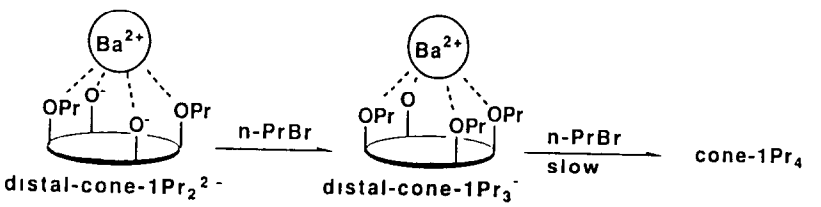
Tri-O-alkylation. The typical base used for O-alkylation of $1H_4$ is NaH [8-11] We followed the progress of the reaction of $1H_4$ and n-PrBr in THF-DMF in the presence of NaH by an HPLC method We found that $1H_2Pr_2$ is accumulated to some extent as an intermediate whereas $1HPr_3$ is detected only as a weak transient peak This implies that the reaction from $1HPr_3$ to $1Pr_4$ is faster than that from $1H_2Pr_2$ to $1HPr_3$ According to an X-ray crystallographic study about distal-cone-$1H_2Me_2$,[22] the two anisole moieties are more or less parallel to each other with the methoxy groups pointing outwards while the two phenol units are flattened with the OH groups pointing inwards On the other hand, the phenol unit in cone-$1HMe_3$ is not so flattened as those in distal-cone-$1H_2Me_2$ [22] Thus, the OH groups in distal-cone-

$1H_2Me_2$ are more buried in the calix[4]arene cavity and therefore become less active toward alkylation reagents.



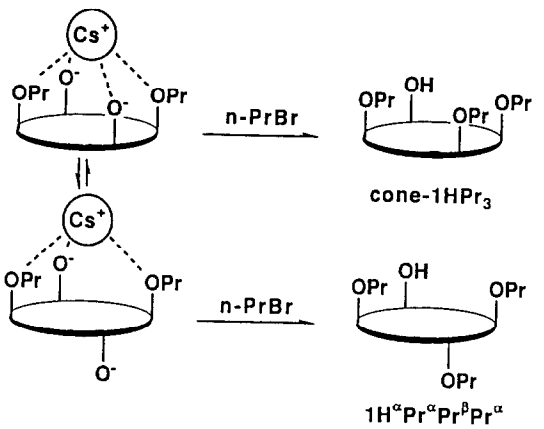
(4)

The above finding suggests that the synthesis of $1HR_3$ by the reaction of $1H_4$ and RX in the presence of NaH is rather difficult Gutsche et al [23] reported that $1HMe_3$ is selectively formed by O-methylation of $1H_4$ in the presence of $Ba(OH)_2$ We applied this method to the synthesis of conformationally-immobile $1HPr_3$ Unexpectedly, we found that the product contains only cone-$1HPr_3$ [12,17] After 1 h at 30 °C $1H_4$ was converted to cone-$1HPr_3$ in 100% yield (determined by HPLC isolated yield 63%) When heated for 70 h at 70 °C, we detected cone-$1Pr_4$ in 6% yield (determined by HPLC) The novel cone-selectivity and $1HPr_3$-selectivity are both rationalized in terms of strong Ba^{2+}-phenoxide interactions To form a complex between $1Pr_2^{2-}$ and Ba^{2+} the cone conformation is most favorable because four oxygens can interact with Ba^{2+} Furthermore, the Ba^{2+}-phenoxide interaction is stronger than the Na^+-phenoxide interaction Thus, the reaction occurs with cone-shaped $1Pr_2^{2-}$ to give cone-$1HPr_3$ in 100% selectivity Further O-propylation of cone-$1Pr^{3-}$ is suppressed because of strong coordination of the remaining phenoxide anion to Ba^{2+}



(5)

We also followed the reaction of $1H_4$ and n-PrBr in acetone in the presence of Cs_2CO_3 by HPLC. We observed a new $1HPr_3$ peak other than cone-$1HPr_3$ Under the optimum reaction conditions and reaction time the yield reached 59% We isolated this compound by a TLC method This compound was assigned to be distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) by ^1H NMR spectroscopy.[17] As described above, Cs^+ ion forms loose ion pairs with phenoxide anions. Therefore, it would not exert a strong metal template effect (as Ba^{2+} in Eq. 5) to maintain $1R_2^{2-}$ in a cone conformation. This suggests that in the presence of Cs_2CO_3 $1Pr_2^{2-}$ (or $1HPr_2^-$) exists under an equilibrium between cone and partial cone and the reaction with partial-cone-$1R_2^{2-}$ results in distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$).



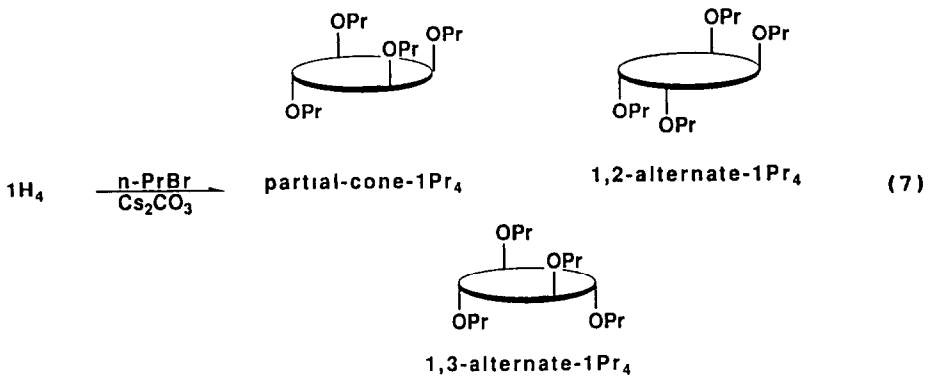
(6)

The ^1H NMR spectra of cone-$1HPr_3$ and distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) were scarcely changed at 0-60 °C After heating these conformers in refluxing THF for 6 h, the products were analyzed by HPLC We confirmed that neither cone-$1HPr_3$ nor distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) isomerizes These findings indicate that the rotation of the PrO group is sterically inhibited while the rotation of the OH group is allowed When cone-$1HPr_3$ was treated with n-PrBr in the presence of NaH, only cone-$1Pr_4$ was recovered in 100% yield When distal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) was treated with n-PrBr in the presence of NaH, we recovered 93% of partial-cone-$1Pr_4$ and 7% of 1,3-alternate-$1Pr_4$ These results establish that when NaH was used as base, the conformer distribution is almost determined in the third O-propylation step The formation of 1,3-alternate-$1Pr_4$ is accounted for by the rotation of the last OH group in $1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$ upon O-propylation In contrast, when cone-$1HPr_3$ was treated with n-PrBr in the presence of Cs_2CO_3, the product was partial-cone-$1Pr_4$ (100% yield) When distal-OPr-inversed partial-cone-$1HPr_3$

($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$) was treated with n-PrBr in the presence of Cs_2CO_3, the product was a mixture of partial-cone-$1Pr_4$ (13%) and 1,3-alternate-$1Pr_4$ (87%) This indicates that the OH group in the unmodified phenol unit is permeable through the calix[4]arene annulus even in the stage of $1HPr_3$. In other words, the observation that in O-propylation with NaH the conformation is apparently immobilized in the stage of $1HPr_3$ is due to the strong metal template effect of Na^+ keeping the OH group in its original position through the Na^+-phenoxide interaction

Tetra-O-alkylation. We previously reported that tetra-O-propylation of $1H_4$ with n-PrBr in the presence of NaH yields cone-$1Pr_4$ and partial-cone-$1Pr_4$ approximately in a 1 1 ratio [10] As described above, the precursors of cone-$1Pr_4$ and partial-cone-$1Pr_4$ are cone-$1HPr_3$ and distal-OPr-inversed partial-cone-$1HPr_3$($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$), respectively

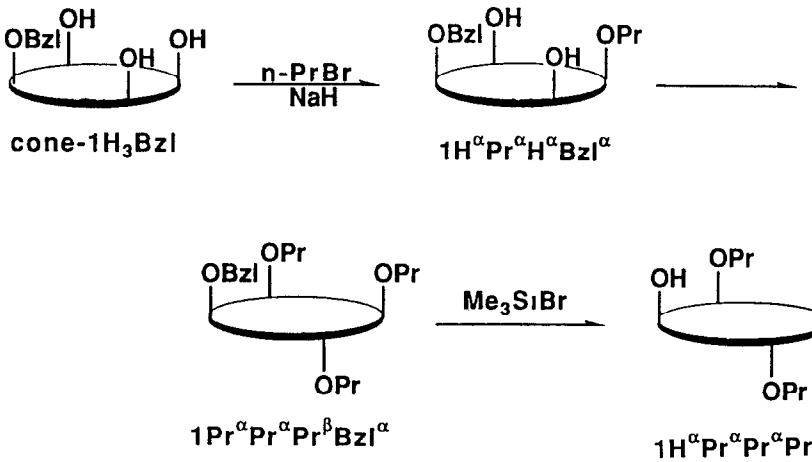
In contract, when $1H_4$ was tetra-O-alkylated with n-PrBr in DMF in the presence of Cs_2CO_3, the product was a mixture of partial-cone-$1Pr_4$ (34%), 1,2-alternate-$1Pr_4$ (9%), and 1,3-alternate-$1Pr_4$ (57%) [12] Clearly, inversion of phenol units occurs easily because of the formation of loose Cs^+-phenoxide ion-pairs



Syntheses Using a Protection-Deprotection Method. In Table 3, there exist four conformers which have not yet been synthesized. They are distal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$), proximal-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$), proximal-1,3-alternate-$1H_2Pr_2$ ($1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) or proximal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$), and proximal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$) Since the syntheses of these conformers in one step were difficult, we developed a new method using a benzyl group as a protecting group.

Proximal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$) was synthesized from cone-$1H_3Bzl$ via OPr-inversed partial-cone-$1Pr_3Bzl$ ($1Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$). The reaction of cone-$1H_3Bzl$ with n-PrBr in THF-DMF in the presence of NaH gave OPr-

inversed partial-cone-$1Pr_3Bzl$ ($1Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$) The examination with ^1H NMR spectroscopy established that the propyl group proximal to the benzyl group is inversed (see Experimental) Conceivably, the first propyl group is introduced to the position distal to the benzyl group and gives distal-cone-$1H_2PrBzl$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Bzl^{\alpha}$) Further O-propylation is similar to di-O-propylation of distal-cone-$1H_2Bzl_2$ ($1H^{\alpha}Bzl^{\alpha}H^{\alpha}Bzl^{\alpha}$) in the presence of NaH which finally yields OPr-inversed partial-cone-$1Pr_2Bzl_2$ ($1Pr^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$: vide post) Debenzylation of $1Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ with Me_3SiBr results in proximal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$) in 69% yield.



(8)

Among three remaining $1H_2Pr_2$, distal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$) was synthesized from distal-cone-$1H_2Bzl_2$ via OPr- inversed partial-cone-$1Pr_2Bzl_2$ ($1Pr^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$) The reaction of distal-cone-$1H_2Bzl_2$ with n-PrBr in THF-DMF in the presence of NaH afforded OPr-inversed partial-cone-$1Pr_2Byl_2$ ($1Pr^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$) in 67% yield As described above, tetra-O-alkylation of $1H_4$ in the presence of NaH results in cone-$1R_4$ and partial-cone-$1R_4$ approximately in a 1 1 ratio We found that in di-O-propylation of distal-cone-$1H_2Bzl_2$ ($1H^{\alpha}Bzl^{\alpha}H^{\alpha}Bzl^{\alpha}$) distal-cone-$1Pr_2Bzl_2$ ($1Pr^{\alpha}Bzl^{\alpha}Pr^{\alpha}Bzl^{\alpha}$) is also yielded in addition to OPr-inversed partial-cone-$1Pr_2Bzl_2$ ($1Pr^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$) We thus isolated $1Pr^{\alpha}Bzl^{\alpha}Pr^{\beta}Bzl^{\alpha}$ by a preparative TLC method. Debenzylation of this compound with Me_3SiBr yielded distal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$) in 90% yield.

Proximal-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$) was synthesized from cone-$1H_2Bzl$ via cone-$1HPr_2Bzl$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Bzl^{\alpha}$) The reaction of cone-$1H_3Bzl$ with n-PrBr in the presence of $Ba(OH)_2$ (specific metal for the synthesis of cone-$1HR_3$) gave cone-$1HPr_2Bzl$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Bzl^{\alpha}$) in 67% yield Debenzylation of this compound with Me_3SiCl yielded proximal-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$) in 78% yield We here used

Me_3SiCl instead of Me_3SiBr because Me_3SiBr cleaved not only the benzyl group but also the propyl groups Me_3SiCl selectively cleaved the benzyl group and gave proximal-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$) in a good yield

The synthesis of proximal-1,3-alternate-$1H_2Pr_2$ ($1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) is more complicated We first considered the synthesis of proximal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$) which becomes equivalent to proximal-1,3-alternate-$1H_2Pr_2$ ($1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) after the rotation of one OH group. Di-O-propylation of cone-$1H_3Bzl$ in the presence of Cs_2CO_3 afforded OPr-inversed partial-cone-$1HPr_2Bzl$ in 79% yield However, there are two possible stereomers in OPr-inversed partial-cone-$1HPr_2Bzl$ they are $1H^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ and $1H^{\alpha}Pr^{\beta}Pr^{\alpha}Bzl^{\alpha}$ These two compounds cannot be distinguished by ^1H NMR spectroscopy As mentioned above about the synthesis of proximal-OPr-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$), the first propyl group should be introduced into the position distal to the benzyl group to give distal-cone-$1H_2PrBzl$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Bzl^{\alpha}$) Thus, the inversion of the phenol unit occurs when the second propyl group enters This allows a presumption that the isolated compound would be $1H^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ that is, the propyl group proximal to the benzyl group is inversed Debenzylation of this compound should give proximal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$) (another stereomer $1H^{\alpha}Pr^{\beta}Pr^{\alpha}Bzl^{\alpha}$ also gives $1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$ after debenzylation) However, the ^1H NMR spectrum ($CDCl_3$, 25 °C) indicated that this compound adopts a proximal-1,3-alternate conformation ($1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) that is, one OH group in proximal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$) rotates to thermodynamically more stable proximal-1,3-alternate-$1H_2Pr_2$ ($1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$)

On the Favorable Conformations after the Oxygen-through-the-annulus Rotation of the OH Group. We have synthesized four different isomers of $1H_2Pr_2$ and three different isomers of $1HPr_3$ listed in Table 2 The ^1H NMR spectra of these compounds were scarcely changed by heating at 60 °C for 1 h in THF One can thus consider that these are stable conformational isomers This finding leads to two important conclusions Firstly, we previously found that the oxygen-through-the-annulus rotation in $1R_4$ is inhibited by R greater than ethyl in other words, propyl is the smallest group to inhibit the rotation [10,17] The present finding indicates that this is also the case in $1H_2R_2$ and $1HR_3$ Secondly, the rotation of the OH group is allowed This means that in Table 2, 6 conformers listed in the left column are thermodynamically more stable than 9 conformers listed in the right column Recent theoretical calculations by Reinhoudt et al [22] predict that calix[4]arene derivatives adopt a conformation so that the intramolecular hydrogen-bonds can be formed most efficiently. In Table 2, for example, the OH groups in distal-cone-$1H_2R_2$ ($1H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$) can form the intramolecular hydrogen-bonds with the proximal OR groups more efficiently than those in OH- inversed distal-partial-cone-$1H_2R_2$ ($1H^{\alpha}R^{\alpha}H^{\beta}R^{\alpha}$) and distal-1,3-alternate-$1H_2R_2$ ($1H^{\alpha}R^{\beta}H^{\alpha}R^{\beta}$)

Similarly, the superiority of the favorable conformations in the left column to other unfavorable conformations in the right column is mostly explained on the same basis Compound $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$ is exceptional, however. Obviously, $1H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\beta}$ which can be readily derived by the rotation of one OH group should form the intramolecular hydrogen-bonds more efficiently than $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$. In ^1H NMR ($CDCl_3$, 25 °C) the $ArCH_2Ar$ protons of this compound appeared as four separate peaks at 3.73 (doublet), 3.77 (singlet), 3.91 (doublet), and 3 98 (singlet) ppm It is known that H_{exo} and H_{endo} with the chemical shift difference of ca 0 9 ppm result when two neighboring phenol units employ a syn conformation whereas the chemical shift difference between these two protons is relatively small when two neighboring phenol units employ an anti conformation.[1-3] Thus, the above splitting pattern (without H_{exo} and H_{endo}) is consistent only with a 1,3-alternate conformation (i.e., $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) Then, is this conformation stabilized without any intramolecular hydrogen-bonding interactions ? We previously found that the δ_{OH} in ^1H NMR ($CDCl_3$, 25 °C) shifts to lower magnetic field and the ν_{OH} in IR (nujol) shifts to lower frequency when the strong intramolecular hydrogen-bond is formed for example, δ_{OH}=10.34 ppm for $1H_4$, 9 54 and 10.13 ppm for $1H_3Me$, 7.19 ppm for distal-$1H_2Me_2$, and 6.20 ppm for $1HMe_3$, ν_{OH}=3170 cm^{-1} for $1H_4$, 3150 and 3280 cm^{-1} for $1H_3Me$, 3450 cm^{-1} for distal-$1H_2Me_2$, and 3470 cm^{-1} for $1HMe_3$ [7] The δ_{OH} and ν_{OH} for $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$ appeared at 7.99 (singlet) ppm and 3380 cm^{-1}, respectively This suggests that the OH groups in $1H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$ form "relatively" strong intramolecular hydrogen-bonds We consider that the OH groups form the intramolecular hydrogen-bonds with the distal OPr groups through which this conformation is stabilized

More interesting is the ^1H NMR spectrum of distal-partial-cone-$1H_2Pr_2$ ($1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$. $CDCl_3$, 25 °C) The $ArCH_2Ar$ protons appear as a pair of doublets at 3 74 and 3 96 ppm and the difference in the chemical shifts ($\Delta\delta$=0 22 ppm) is relatively small According to Gutsche,[1-3] the $\Delta\delta$ becomes smaller when the phenol unit is flattened. Hence, the spectrum suggests the idea that two unalkylated phenol units are flattened, probably, to form intramolecular hydrogen bonds (as in Figure 1) In Figure 1, the four methylene groups are all equivalent and result in a pair of doublets

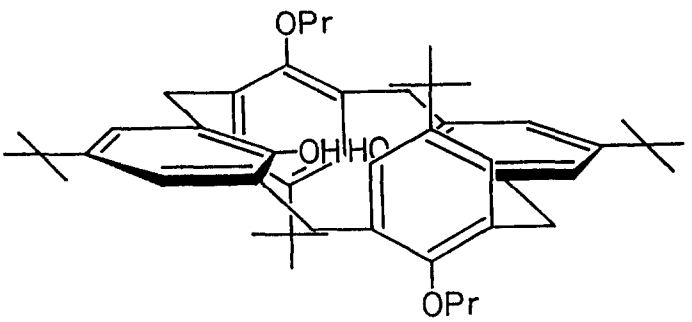


Figure 1. Flattened conformation proposed for $1H^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\beta}$

Conclusions. We here demonstrated that a number of conformational isomers can be derived from $1H_4$. The results consistently indicate that metal cations used as base play a crucial role in determining the conformer distribution. We believe that the present results are very useful for the selective syntheses of desired conformers in high yields.

Experimental

Materials

25-Propoxy-26,27,28-trihydroxy-p-t-butylcalix[4]arene (cone-$1H_3Pr$). Compound $1H_4$ (1.0 g, 1.35 mmol) and n-PrBr (0.17 ml, 1 85 mmol) were dissolved in DMF (20 ml), and the solution was stirred at room temperature for 21 h in the presence of $Ba(OH)_2\,8H_2O$ (486 mg, 1 54 m mol) and BaO (236 mg, 1 54 mmol) The reaction mixture was diluted with water and extracted with chloroform The chloroform layer was separated and dried over $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The residue was recrystallized from chloroform-methanol white powder, mp 238-239 °C, yield 78%: IR (nujol) ν_{OH} 3180 and 3300 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ 1 18, 1 20, and 1 21 (t-Bu, s each, 9H, 18H, and 9H, respectively), 1 24 (CH_3, t, 3H), 2 13-2 22 ($CH_2(CH_3)$, m, 2H), 3 41, 3 43, 4 27, and 4 36 ($ArCH_2Ar$, d each, 2H each), 4 10 (CH_2O, t, 2H), 6 99, 7 04, 7 06, and 7 09 (ArH, d, s, d, and s, respectively, 2H each) 9 57 and 10 15 (OH, s each, 1H and 2H, respectively) Anal. Calcd for $C_{47}H_{62}O_4\,CH_3OH$. C, 79 74, H, 9 20% Found C, 80 02, H, 9 34%.

25-Benzyloxy-26,27,28-trihydroxy-p-t-butylcalix[4]arene (cone-$1H_3Bzl$). Compound $1H_4$ (10 g, 13.5 mmol) and BzlBr (3 78 ml, 30.8 mmol) were dissolved in toluene (400 ml), and the solution was heated in the presence of NaH (1 23 g, 30.8 mmol) at 70 °C for 4 h. Excess NaH was decomposed with methanol The solution was concentrated in vacuo. The residue was mixed with water-chloroform, the organic layer being separated and dried over $MgSO_4$ The solution was concentrated, the residue being recrystallized from chloroform-methanol mp

219-220 °C, yield 67%, IR (nujol) ν_{OH} 3320 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ 1.20 and 1 21 (t-Bu, s each, 18H each), 3.39, 3 40, 4 21, and 4 34 ($ArCH_2Ar$, d each, 2H each), 5 17 ($ArCH_2O$, s, 2H), 6 96, 7 02, 7 04, and 7.11 (ArH, d, s, d, and s, respectively, 2H each), 7 42-7 53 and 7 70-7 74 (ArH in Bzl, m each, 3H and 2H, respectively), 9.37 and 9 99 (OH, s each, 2H and 1H, respectively) Anal Calcd for $C_{51}H_{62}O_4$ 0 25CH_3OH C, 82 40, H, 8.50%. Found. C, 82 42; H, 8 31%.

25,27-Dipropoxy-26,28-dihydroxy-p-t-butylcalix[4]arene (distal-cone-1$H_2$$Pr_2$; 1H$^{\alpha}Pr^{\alpha}H^{\alpha}Pr^{\alpha}$). This compound was synthesized from 1H_4 and n-PrBr in DMF in the presence of K_2CO_3. mp 247-249 °C, yield 79%. The details of the method and the analytical data were described previously [17]

25,27-Dibenzyloxy-26,28-dihydroxy-p-t-butylcalix[4]arene (distal-cone-1$H_2$$Bzl_2$: 1H$^{\alpha}Bzl^{\alpha}H^{\alpha}Bzl^{\alpha}$). Compound 1$H_4$ (1 0 g, 1 35 mmol) and BzlBr (0 74 ml, 6 16 mmol) were dissolved in acetone (25 ml), and the solution was refluxed for 3 hr in the preference on K_2CO_3 (2 13 g, 15 4 mmol) The reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was separated and dried over $MgSO_4$ After filtration, the filtrate was concentrated to dryness The residue was recrystallized from chloroform-methanol mp 194-195 °C, yield 98%, IR (nujol) ν_{OH} 3400 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ 0 94 and 1 28 (t-Bu, s each, 18H each), 3 26 and 4 28 ($ArCH_2Ar$, d each, 4H each), 5 04 ($ArCH_2O$, s, 4H), 6.78 and 7 04 (ArH, s each, 4H each), 7 27 (OH, s, 2H), 7 34-7 36 and 7 62-7 65 (ArH in Bzl, m each, 3H and 2H, respectively) Anal Calcd for $C_{58}H_{68}O_4$ C, 84 02, H, 8 27% Found, C, 83.64; H, 8 05%

25,26,27,28-Tetrapropoxy-p-t-butylcalix[4]arene(cone- and partial-cone-1Pr_4). Cone-1Pr_4 and partial-cone-1Pr_4 were synthesized from 1H_4 and n-PrBr in THF-DMF in the presence of NaH These two isomers were isolated by a TLC method cone-1Pr_4, mp 246-247 °C, yield 38%; partial-cone-1Pr_4, mp 283-284 °C, yield 41% The details of the method and the analytical data were described previously.[17]

25,26,27,28-Tetrapropoxy-p-t-butylcalix[4]arene(1,2- and 1,3-alternate-1Pr_4). Compound 1H_4 (500 mg, 0 77 mmol) and n-PrBr (3 79 g, 30 8 mmol) were dissolved in DMF (20 ml), and the solution was heated in the presence of Cs_2CO_3 (10 g, 30 8 mmol) at 70 °C for 3 h The HPLC analysis indicated that the product is a mixture of 34% partial-cone-1Pr_4, 9% 1,2-alternate-1Pr_4, and 57% 1,3-alternate-1Pr_4 From these three conformers 1,2-alternate-1Pr_4 and 1,3-alternate-1Pr_4 were isolated by a TLC method (silica gel, chloroform-hexane (1 4 v/v) 1,3-alternate-1Pr_4, R_f 0 38, mp 339-341 °C, isolated yield 49%, ^1H NMR ($CDCl_3$, 25 °C) δ 0 61 (CH_3, t, 12H), 0 94-1 03 ($CH_2(CH_3)$, m, 8H), 1 26 (t-Bu, s, 36H), 3 30 (CH_2O, t, 8H), 3 80 ($ArCH_2Ar$, s, 8H), 6.95 (ArH, s, 8H). Anal. Calcd for $(C_{14}H_{20}O)_4$ C, 82 30, H, 9 87% Found C, 82 12, H, 9 97% The analytical data for 1,2-alternate-1Pr_4 (mp 279-280 °C, isolated yield 6%) were described previously [17]

25,26,27-Tripropoxy-28-hydroxy-p-t-butylcalix[4]arene (cone-1HPr$_3$ and distal-OPr-inversed partial-cone-1HPr$_3$: 1H$^{\alpha}$Pr$^{\alpha}$Pr$^{\beta}$Pr$^{\alpha}$). Cone-1HPr$_3$ was synthesized from 1H$_4$ and n-PrBr in DMF in the presence of Ba(OH)$_2$ 8H$_2$O and BaO: mp 194-196 °C, yield 63% Distal-OPr-inversed partial-cone-1HPr$_3$ was synthesized from 1H$_4$ and n-PrBr in acetone in the presence of Cs$_2$CO$_3$ mp 169-171 °C, yield 48%. The details of the methods and the analytical data were described elsewhere.[17]

25,26,27-Tripropoxy-28-hydroxy-p-t-butylcalix[4]arene (proximal-OPr-inversed partial-cone-1HPr$_3$: 1H$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$Pr$^{\beta}$). This compound was synthesized by tri-O-propylation of cone-1H$_3$Bzl in the presence of NaH followed by deprotection of the benzyl group with Me$_3$SiBr Cone-1H$_3$Bzl (1 00 g, 1 35 mmol) was treated with oil-dispersed NaH (0.65 g, 16.2 mmol) in THF-DMF (2 ml) and then n-PrI (7 88 ml, 81 mmol) was added The reaction mixture was refluxed for 2 h. Excess NaH was decomposed with methanol. The mixture was diluted with water and extracted with chloroform. The chloroform layer was separated and dried over MgSO$_4$. After filtration, the filtrate was concentrated to dryness Recrystallization of the residue from chloroform and methanol yielded 1Pr$^{\alpha}$Pr$^{\alpha}$Pr$^{\beta}$Bzl$^{\alpha}$ white powder, mp 221-222 °C, yield 69%, ^{1}H NMR (CDCl$_3$, 25 °C) δ 0.50, 0 82, and 0 97 (CH$_3$, t each, 3H each), 1 03, 1 05, 1 21, and 1 34 (t-Bu, s each, 9H each), 1 30-1.38, 1 68-1 77, and 1 77-1 86 (CH$_2$(CH$_3$), m each, 2H each), 3 02, 3.40, 3 46, 3 63, 3 71, 4 07, and 4 11 (ArCH$_2$Ar, d each, 2H, 1H, 1H, 1H, 1H, 1H, and 1H, respectively), 3 34-3 48 and 3 60-3 74 (CH$_2$O, m each, 3H each), 4 60 and 4.74 (ArCH$_2$O, d each, 1H each), 6 58, 6 61, 6.84, 6 90, 7.05, 7 08, and 7 15 (ArH, d, d, d, d, d, s, and d, respectively, 1H, 1H, 1H, 1H, 1H, 2H, and 1H, respectively), 7 32-7 39 and 7.44-7 48 (ArH in Bzl, m each, 3H and 2H, respectively) Anal. Calcd for C$_{60}$H$_{80}$O$_4$ C, 83 29, H, 9 32% Found C, 83.10, H, 9 17% Compound 1Pr$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$Bzl$^{\beta}$ (0 50 g, 0 58 mmol) was dissolved in chloroform (20 ml), and Me$_3$SiBr (0.089 g, 0 58 mmol) was added dropwise The reaction mixture was refluxed for 2 h The reaction mixture was diluted with water and extracted with chloroform The chloroform layer was separated and dried over MgSO$_4$ After filtration, the filtrate was concentrated to dryness Recrystallization of the residue from chloroform-methanol yielded 1H$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$Pr$^{\beta}$. white powder, mp 122-124 °C, yield 69%, IR (nujol) ν_{OH} 3340 cm^{-1}, ^{1}H NMR (CDCl$_3$, 25 °C) δ 0 48, 0 50, and 0 61 (CH$_3$, t each, 3H each), 0 60-0 73 and 0 90-1 20 (CH$_2$(CH$_3$), m each, 2H and 4H, respectively), 1 27 and 1 32 (t-Bu, s each 27H and 9H, respectively), 3 15, 3 42, 3 87, 3 93, 3 94, 3 96, and 4 18 (ArCH$_2$Ar, d, d, d, d, s, d, and d, respectively, 1H, 1H, 1H, 1H, 2H, 1H, and 1H, respectively), 6 51 (OH, s, 1H), 6 99, 7.04, 7 05, 7 06, 7 07, and 7.10 (ArH, d, d, d, s, d, and d, respectively, 2H, 1H, 1H, 2H, 1H, and 1H, respectively). Anal. Calcd for C$_{53}$H$_{74}$O$_4$ C, 82 12, H, 9 62% Found C, 81 94; H, 9.48%

25,26-Dipropoxy-27,28-dihydroxy-p-t-butylcalix[4]arene (proximal-cone-1H$_2$Pr$_2$: 1H$^\alpha$H$^\alpha$Pr$^\alpha$Pr$^\alpha$). This compound was synthesized by di-O-propylation of cone-1H$_3$Bzl in the presence of Ba(OH)$_2$ 8H$_2$O and BaO followed by deprotection of the benzyl group with Me$_3$SiCl because Me$_3$SiBr cleaved nonselectively not only the benzyl group but also the propyl group. Me$_3$SiCl selectively cleaved only the benzyl group Cone-1H$_3$Bzl (1 0 g, 1.35 mmol) and n-PrBr (1.00 ml, 10 83 mmol) were dissolved in DMF (50 ml), and the solution was stirred at 60 °C for 23 h in the presence of Ba(OH)$_2$ 8H$_2$O (1.76 g, 5.42 mmol) and BaO (0.832 g, 5.42 mmol) The reaction mixture was diluted with water and extracted with chloroform The chloroform layer was separated and dried over MgSO$_4$ After filtration, the filtrate was concentrated to dryness. Recrystallization of the residue from chloroform-methanol yielded 25,26-dipropoxy-27-benzyloxy-28-hydroxy-p-t-butylcalix[4]arene (cone-1HPr$_2$Bzl: 1H$^\alpha$Pr$^\alpha$Pr$^\alpha$Bzl$^\alpha$) mp 192-194 °C, yield 71.3%, IR (nujol) ν_{OH} 3550 cm^{-1}, ^{1}H NMR (CDCl$_3$, 25 °C) δ 0 59 and 1 07 (CH$_3$, t each, 3H each), 0 82, 0 83, 1 33, and 1.34 (t-Bu, s each, 9H each), 1 81-2 09 (CH$_2$(CH$_3$), m, 4H), 3 11, 3 14, 3.24, 4 29, 4 32, 4.34, and 4 44 (ArCH$_2$Ar, d each, 1H, 1H, 2H, 1H, 1H, 1H, and 1H, respectively), 3.66-3 77 (CH$_2$O, m, 4H), 4 73 and 4 88 (ArCH$_2$O, d each, 1H each), 5.51 (OH, s, 1H), 6.51, 7 05-7 07, and 7 13 (ArH, s, m, and s, respectively, 4H, 2H, and 2H, respectively), Anal Calcd for C$_{57}$H$_{74}$O$_4$ C, 83 17, H, 9 06% Found: C, 83 23, H, 9 04%. Treatment of 1H$^\alpha$Pr$^\alpha$Pr$^\alpha$Bzl$^\alpha$ with Me$_3$SiCl in chloroform, as described above, yielded proximal-cone-1H$_2$Pr$_2$ (1H$^\alpha$H$^\alpha$Pr$^\alpha$Pr$^\alpha$): mp 119-121 °C, yield 78%; IR (nujol) ν_{OH} 3170 and 3340 cm^{-1}, ^{1}H NMR (CDCl$_3$, 25 °C) δ 1 10 and 1 20 (t-Bu, s each, 18H each), 1 12 (CH$_3$, t, 6H), 2 04-2 13 (CH$_2$(CH$_3$), m, 4H), 3 32, 3 33, 3 34, 4 29, 4.32, and 4 49 (ArCH$_2$Ar, d each, 1H, 1H, 2H, 1H, 2H, and 1H, respectively), 3.82-3 90 and 4 00-4 08 (CH$_2$O, m each, 2H each), 6 90, 6 96, 6.97, and 7 00 (ArH, d each, 2H each), 8 85 (OH, s, 2H). Anal Calcd for C$_{50}$H$_{68}$O$_4$ CH$_3$OH· C, 80 06; H, 9 48% Found C, 80 02, H, 9.43%

25,27-Dipropoxy-26,28-dihydroxy-p-t-butylcalix[4]arene (distal-partial-cone-1H$_2$Pr$_2$: 1H$^\alpha$Pr$^\alpha$H$^\alpha$Pr$^\beta$). This compound was synthesized by di-O-propylation of distal-cone-1H$_2$Bzl$_2$ in the presence of NaH followed by deprotection of the benzyl groups with Me$_3$SiBr The method is basically similar to that described for proximal-OPr-inversed partial-cone-1HPr$_3$ (1H$^\alpha$Pr$^\alpha$Pr$^\alpha$Pr$^\beta$) OPr-Inversed partial-cone-1Pr$_2$Bzl$_2$ (1Pr$^\alpha$Bzl$^\alpha$Pr$^\beta$Bzl$^\alpha$) mp 228-230 °C, yield 67%, ^{1}H NMR (CDCl$_3$, 25 °C) δ 0 33 and 0 85 (CH$_3$, t each, 3H each), 1 04, 1 05, and 1 34 (t-Bu, s each, 9H, 18H, and 9H, respectively), 1 15-1 25 and 1 72-1 82 (CH$_2$(CH$_3$), m each, 2H each), 2 99, 3 63, 3 68, and 4 08 (ArCH$_2$Ar, d each, 2H each), 3 26-3 31 and 3 45-3 49 (CH$_2$O, m each, 2H each), 4 57 and 4 71 (ArCH$_2$O, d each, 2H each), 6 78, 6.88, 7 00, and 7 08 (ArH, d, d, s, and s, respectively, 2H each), 7 30-7 44 (ArH in Bzl, m, 10H) Anal Calcd for C$_{64}$H$_{80}$O$_4$ 0.5CH$_3$OH· C, 83.36, H, 8 89% Found C, 83 56, H, 8 63% Distal-partial-cone-1H$_2$Pr$_2$ (1H$^\alpha$Pr$^\alpha$H$^\alpha$Pr$^\beta$) mp 286-287 °C, yield 90%, IR

(nujol) ν_{OH} 3310 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ 0.29 (CH_3, t, 6H), 1.03-1 12 ($CH_2(CH_3)$, m, 4H), 1 29 and 1 30 (t-Bu, s each, 18H each), 3.51 (CH_2O, t, 4H), 3 74 and 3.96 ($ArCH_2Ar$, d each, 4H each), 7.05 (OH, s, 2H), 7.06 and 7.15 (ArH, s each, 4H each) Anal Calcd for $C_{50}H_{68}O_4$ 0.5CH_3OH. C, 80.97; H, 9.42%. Found: C, 80 99; H, 9 13%

25,26-Dipropoxy-27,28-dihydroxy-p-t-butylcalix[4]arene (proximal-1,3-alternate-1H_2Pr_2; 1$H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$). This compound was synthesized by di-O-propylation of cone-1H_3Bzl in the presence of Cs_2CO_3 followed by deprotection of the benzyl group with Me_3SiBr Recrystallization of the residue from chloroform-methanol yielded distal-OPr-inversed partial-cone-1HPr_2Bzl (1$H^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$)· mp 104-105 °C, yield 49%, IR (nujol) ν_{OH} 3320 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ -0 35 and 1.02 (CH_3, t each, 3H each), 0.71-0.80 and 1 81-1 94 ($CH_2(CH_3)$, m each, 2H each), 1.07, 1 15, 1.18, and 1 25 (t-Bu, s each, 9H each), 1 61-1 71, 1 72-1 80, 3 54-3 61, and 3 96-4.01 (CH_2O, m each, 1H each), 3.12, 3 32, 3 83, 3 84, 3 89, 3 90, 4.04, and 4 27 ($ArCH_2Ar$, d each, 1H each), 4 70 and 5.06 ($ArCH_2O$, d each, 1H each), 6 98, 7 00, 7.03, 7 04, 7 05, and 7.11 (ArH, d each, 2H, 2H, 1H, 1H, 1H, and 1H, respectively), 7 23-7.30 and 7 47-7 49 (ArH in Bzl, m each, 3H and 2H, respectively), 7 31 (OH, s, 1H) Anal Calcd for $C_{57}H_{74}O_4$ 0 5CH_3OH. C, 82 29; H, 9 13% Found C, 82 34, H, 8 90% Treatment of 1$H^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ with Me_3SiBr in chloroform yielded proximal-1,3-alternate-1H_2Pr_2 (1$H^{\alpha}H^{\beta}Pr^{\alpha}Pr^{\beta}$) mp 203-204 °C, yield 95%, IR (nujol) ν_{OH} 3380 cm^{-1}, ^1H NMR ($CDCl_3$, 25 °C) δ 0 14 (CH_3, t, 6H), 0 80-0 91 and 0.91-1 10 ($CH_2(CH_3)$, m each, 2H each), 1 21 and 1 30 (t-Bu, s each, 18H each), 2 84-2 92 and 3.06-3.14 (CH_2O, m each, 2H each), 3 73, 3 77, 3 91, and 3 98 ($ArCH_2Ar$, d, s, d, and s, respectively, 2H each), 6 97, 7 04, 7 06, and 7 22 (ArH, d each, 2H each), 7 99 (OH, s, 2H) Anal. Calcd for $C_{50}H_{68}O_4$ CH_3OH: C, 80 06, H, 9 48% Found C, 79 82, H, 9 12%

Miscellaneous

In O-alkylation of 1H_4, the progress of the reaction was followed by an HPLC method column, Zorbax-ODS 46 x 250 mm, mobile phase, methanol chloroform = 4 1 v/v. For the TLC separation, silica gel and chloroform-hexane (1 4 v/v) were used unless otherwise stated ^1H NMR spectra were measured with a JEOL GX-400 NMR apparatus

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