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Chiral cage molecules generated by regioselective *O*-alkylation of a doubly-bridged calix[8]arene

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Abstract

A calix[8]arene doubly-bridged at the 1,5-phenol units and 3,7-phenol units has a cage structure with D_{2d} symmetry. Regioselective introduction of methyl groups into the residual 2,4,6,8-phenol units affords five different cage compounds: that is, three racemic compounds, one meso compound, and one achiral compound. This paper reports systematic studies on the preparation methods of these new cage compounds and spectroscopic classification of their molecular symmetries. The results indicate that these compounds have a latent potential as a platform for designing chiral cage molecules with an ionophoric inner cavity.

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1. Introduction

Calix[n]arenes are cyclic oligomers made up of a number of (n) phenol units.[1] This characteristic structure is very suitable to introduce regioselectively functional groups onto the OH groups, for example, by Williamson-type reactions. In fact, it is now possible to introduce the desired number of functional groups with the desired regioselectivity into calix[4]arenes.[1–3] The most exciting among such regioselective functionalizations is the molecular design of inherently chiral calix[4]arenes, the asymmetry of which is created by the asymmetric substitution of four OH groups.[4–8] In calix[4]arenes, one can now fully utilize the skeleton as a building-block to design various regioisomers. In comparison to calix[4]arenes, regioselective substitution of six OH groups in calix[6]arenes is more complicated and more difficult although a few attempts have so far been reported.[1,9–11] Judging from these results, it was believed that regioselective substitution of eight OH groups in calix[8]arenes is nearly impossible. More recently, however, we[12] and Neli et al.[13] unexpectedly found that when calix[8]arenes are treated with dibromides or ditosylates in the presence of an appropriate base, two OH groups are regioselectively bridged and in some cases four OH groups are regioselectively doubly-bridged. From the reaction of *p-tert*-butylcalix[8]arene and

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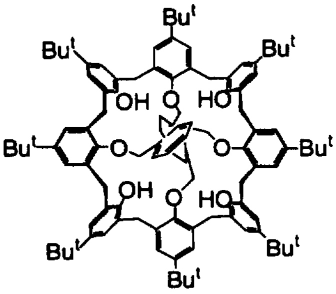
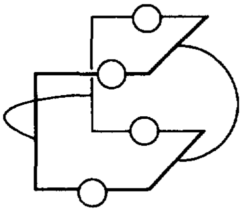
1,2-bis(bromomethyl)benzene, for example, a doubly-bridged compound **1** was isolated in 19% yield in addition to monobridged compounds.[12] The reason why such a large calix[8]arene ring can be bridged by a short *O*-xylylene strap is explained by its characteristic conformation called 'pinched cone'[1]: that is, the distance between two distal phenyl units is relatively short in this conformation. Here, we noticed that compound **1** has beautiful D_{2d} symmetry and therefore, substitution of residual OH groups demolishes the high symmetry and creates various stereoisomers (including optical isomers). In this paper, we report the optimized synthetic procedures for all possible compounds derived by *O*-alkylation of **1** and make intriguing comments on their stereochemical aspects.



Compound **1**



Simplified structure of **1**: ○ denotes unsubstituted phenol units.

2. Results and discussion

2.1. *Classification of partially* O*-methylated derivatives*

Molecular symmetry of partially *O*-methylated **1** is explained in Fig. 1 using a simplified structure of **1**. Compound **2** obtained by mono-*O*-methylation of **1** becomes racemic. Di-*O*-methylation results in two different molecules, $\mathbf{3}_{1,3}$ and $\mathbf{3}_{1,5}$. When two methyl groups are introduced into proximal OH groups in 1,3-phenol units, the product ($\mathbf{3}_{1,3}$) is a meso compound. When two methyl groups are introduced into distal OH groups in 1,5-phenyl units, the product ($\mathbf{3}_{1,5}$) is a racemic compound. When three methyl groups are introduced, the methyl groups are arranged in the same manner as OH groups in **2** and therefore, the product (**4**) is classified as a racemic compound. The tetra-*O*-methylated derivative (**5**), which has high D_{2d} symmetry (the same symmetry as **1**), becomes achiral. The foregoing classification indicates that one can generate three racemic compounds, one meso compound and one achiral compound from **1** by simple *O*-methylation. As already demonstrated in calix[4]arenes,[2–8] a variety of stereoisomers (mainly racemic compounds) can be derived if different substituents are introduced into **1** in a regioselective manner. In this paper, we concentrate our efforts on regioselective synthesis of *O*-methylated derivatives because the synthetic methods developed here should be readily applicable to the introduction of other substituents.

Judging from the molecular symmetry, one can predict the ^{1}H NMR spectral pattern of each compound. The *tert*-Bu protons which appear as sharp singlets are useful to count the number of inequivalent phenyl units. On the other hand, the ArCH$_2$O methylene protons become a pair of doublets only when the methylene bridge is asymmetrically affected by *O*-methyl substituents. By combination of the splitting patterns for these two groups one can easily distinguish five *O*-methyl derivatives (Table 1).

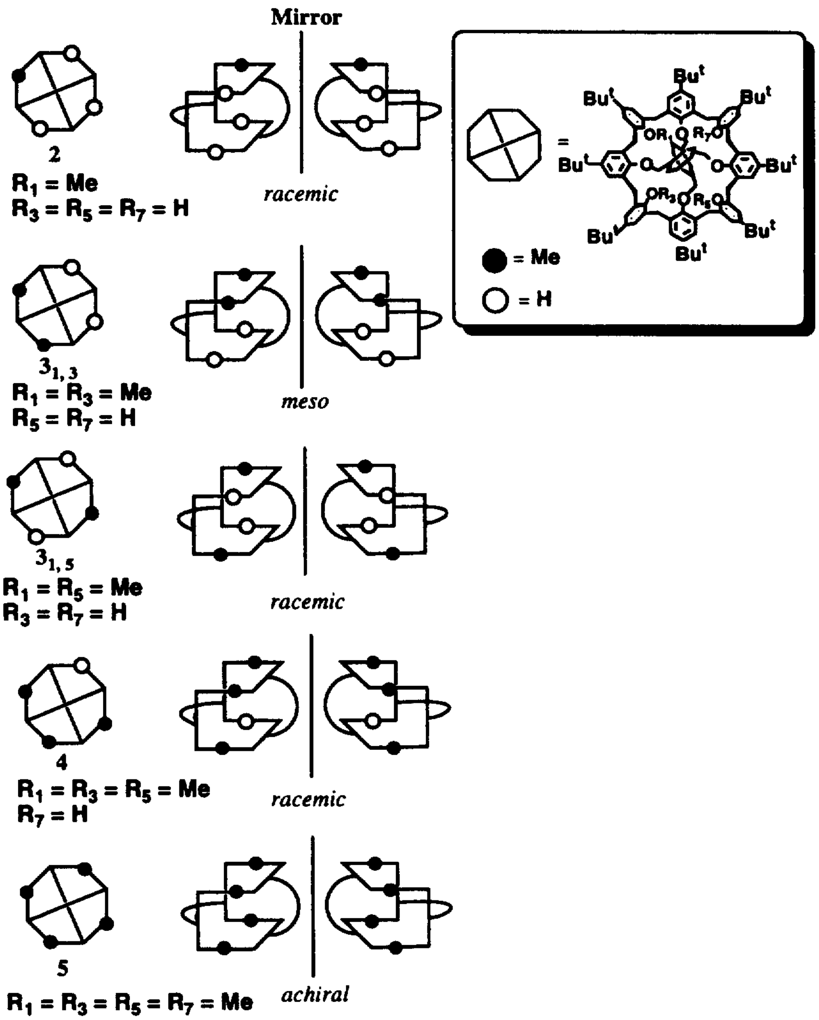


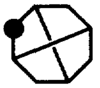
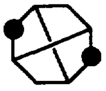
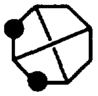
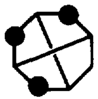
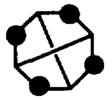
Fig. 1. Stereoisomers derived by *O*-alkylation of doubly-bridged calix[8]arene **1**: ● denotes *O*-alkylated phenol units

2.2. Synthetic procedures

Compound **1** (0.030 mmol) and MeI or MeOTs (0.30 mmol) was treated in an appropriate solvent (20 ml) in the presence of an appropriate base (0.24 mmol) under a nitrogen atmosphere. The reactions in acetone, acetonitrile, or THF were carried out at their reflux temperature for 3 h whereas those in DMF were carried out at 30°C, for 48 h. The products were isolated by a preparative TLC method (silica gel, hexane:ethyl acetate=20:1 v/v). The results are summarized in Table 2.

When CsF was used as the base and acetone or acetonitrile as the solvent, the reaction did not take place (entries 1–3). When more polar DMF was used as solvent, monomethylated **2** and dimethylated $\mathbf{3}_{1,3}$ were selectively obtained in moderate yields (entry 4). When the reaction temperature was raised to 60°C, the major products were shifted to more methylated compounds, $\mathbf{3}_{1,3}$ and **4** (entry 5). When K_2CO_3 or Cs_2CO_3 was used instead of CsF, the reaction took place in acetone, indicating that they are classified as stronger bases than CsF (entries 6–8). When MeOTs was used instead of MeI, the yields were generally decreased, indicating that MeI is a better alkylation reagent than MeOTs (entry 8). To

Table 1
Theoretical ^{1}H NMR splitting patterns

Derivative	***tert*-Bu protons**	**ArCH$_2$O protons**
 1	1 : 2 : 2 : 2 : 1	**two pairs of doublets**
 $2_{1,5}$	2 : 4 : 2	**a pair of doublets**
 $2_{1,3}$	1 : 2 : 2 : 2 : 1	**two singlets and a pair of doublets**
 3	1 : 2 : 2 : 2 : 1	**two pairs of doublets**
 4	4 : 4	**singlet**

find the optimal reaction conditions for MeOTs we used a stronger base, *tert*-BuOK: the reaction (entry 9) afforded **5** as the sole product although the yield is somewhat lower than entry 5.

As a summary of the foregoing results, one can offer the following optimal synthetic procedures for each isomer.

(i) Compound **2** can be obtained by entry 4 after isolation from $\mathbf{3_{1,3}}$.
(ii) Compound $\mathbf{3_{1,3}}$ can be prepared either by entry 4 or entry 5, but entry 4 is recommended because the isolation of $\mathbf{3_{1,3}}$ from **2** is easier than that from **4**.
(iii) Compound $\mathbf{3_{1,5}}$ is obtained only in low yield by entry 7 or entry 8 and must be collected by a preparative TLC method.
(iv) Compound **4** is obtained in moderate yield by entry 5 after isolation from $\mathbf{3_{1,3}}$.
(v) The highest yield for compound **5** is achieved by entry 7 (42% yield), but it is obtained more conveniently by entry 9 in which **5** becomes the sole product.

Among these synthetic guidelines, the $\mathbf{3_{1,3}}$ versus $\mathbf{3_{1,5}}$ selectivity is particularly worthy of mention. It is seen from Table 2 that the reaction in Cs_2CO_3/acetone at reflux yields both $\mathbf{3_{1,3}}$ and $\mathbf{3_{1,5}}$ whereas the reaction in CsF/DMF at room temperature selectively yields $\mathbf{3_{1,3}}$ in addition to **2**. To compare the product distribution under the identical reaction conditions we did an additional experiment in Cs_2CO_3/DMF at room temperature: the products isolated from this reaction are **2** (27%), $\mathbf{3_{1,3}}$ (25%), and $\mathbf{3_{1,5}}$ (48%). The result indicates that the difference in the product distribution is mainly due to the base. In the ^{1}H NMR spectrum of **2** (400 MHz, $CDCl_3$, 25°C), the δ_{OH} values for 3-OH (or 7-OH) and 5-OH appeared at 7.95 and 8.13 ppm, respectively, indicating that 5-OH is more strongly hydrogen bonded than 3-OH (or 7-OH).[14] It is likely, therefore, that the weaker base CsF dissociates only 3-OH (or 7-OH), selectively

Table 2
Reaction conditions and product distribution[a]

Entry	Base	Methylation reagent	Solvent	Yield (%)				
				2	$3_{1,3}$	$3_{1,5}$	4	5
1	CsF	MeI	Acetone	0	0	0	0	0
2	CsF	MeI	Acetonitrile	0	0	0	0	0
3	CsF	MeOTs	Acetonitrile	0	0	0	0	0
4[b]	CsF	MeI	DMF	0	48	0	52	0
5	CsF	MeI	DMF	54	46	0	0	0
6	K_2CO_3	MeI	Acetone	0	0	0	20	25
7	Cs_2CO_3	MeI	Acetone	0	9	7	33	42
8	Cs_2CO_3	MeOTs	Acetone	0	7	6	12	28
9	*t*-BuOK	MeOTs	THF	0	0	0	0	35

[a] The reactions in acetone or acetonitrile were carried out at their reflux temperature whereas those in DMF were carried out at 30 °C.

[b] At 60 °C.

yielding $3_{1,3}$ whereas the stronger base Cs_2CO_3 dissociates two to three OH groups, nonselectively yielding $3_{1,3}$ and $3_{1,5}$. It is not clear why 5-OH is more strongly hydrogen-bonded than 3-OH (or 7-OH). One possible rationale is the cage deformation induced by *O*-methylation against 1-OMe, 3-OH and 7-OH occupy the proximal position whereas 5-OH occupies the distal position. Accordingly, *O*-methylation may change the conformation around 3-OH and 7-OH and weaken the hydrogen-bonding interaction with neighboring phenyl ether units.

2.3. NMR measurements

The ^1H NMR spectra (400 MHz) of five compounds were measured in $CDCl_3$ at 25°C. The peaks for the *tert*-Bu protons split as expected from the molecular symmetry (except those for **2**): that is, five peaks in a 1:2:2:2:1 ratio for $3_{1,3}$ and **4**, three peaks in a 1:2:1 ratio for $3_{1,5}$, and two peaks in a 1:1 ratio for **5**. Judging from the molecular symmetry of **2**, it should give five peaks in a 1:2:2:2:1 ratio (Table 1). In fact, however, only three peaks with 18H:18H:36H (in the order from higher magnetic field) were observed because of the overlap. On the other hand, the spitting patterns of the $ArCH_2O$ methylene protons appeared as expected from the molecular symmetry (without exception).

In order to confirm that some of these five compounds consist of a pair of enantiomers, we measured their ^1H NMR spectra in the presence of chiral shift reagents. We found that, among several shift reagents tested, Pirkle's reagent, (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol is most effective. This result is the same as the results observed for other inherently chiral calix[n]arenes.[15] As a typical example, the ^1H NMR spectra for **2** are shown in Fig. 2. It is seen from Fig. 2 that most peaks split into pairs with a 1:1 intensity ratio. The similar peak splitting induced by Pirkle's reagent was also observed for $3_{1,5}$ and **4**, indicating that these compounds consist of a pair of enantiomers. In contrast, the peak splitting was not observed for achiral **5**. Very interestingly, the peak splitting upon addition of Pirkle's reagent was also observed for

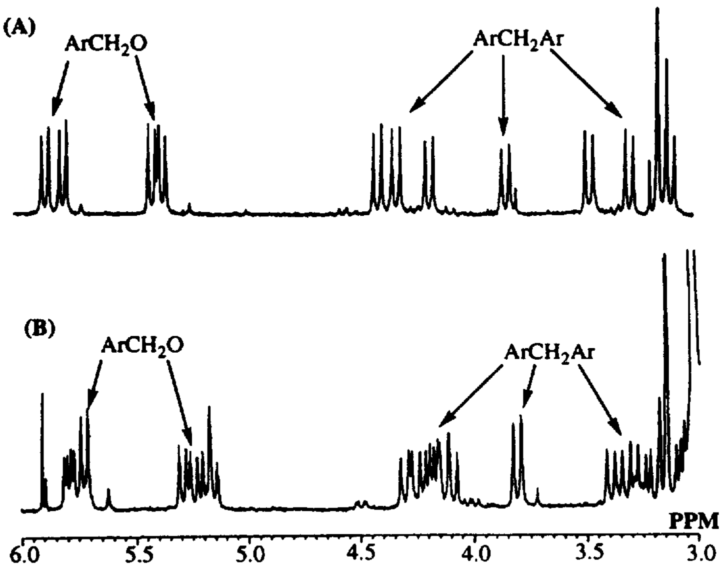


Fig. 2. Partial ^{1}H NMR spectra of **2** (1.0×10^{-2} mol dm^{-3}) in the absence (A) and the presence (B) of Pirkle's reagent (0.50 mol dm^{-3}): CDCl$_3$, 25°C, 400 MHz

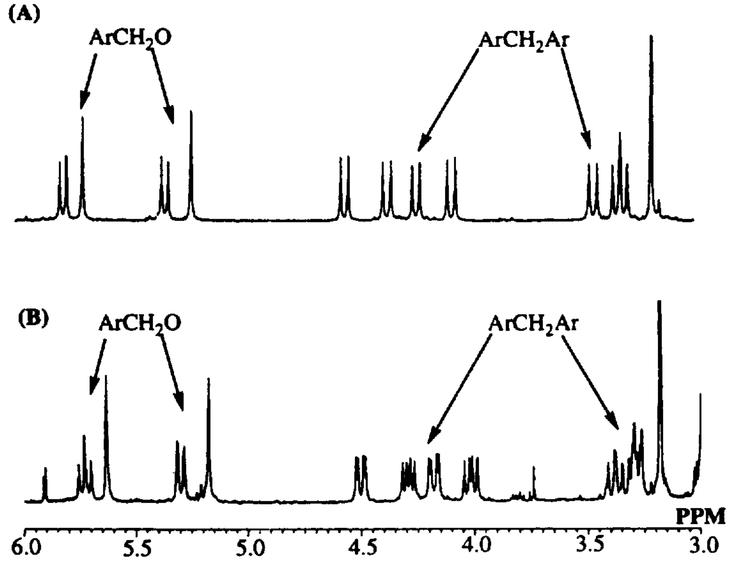


Fig. 3. Partial ^{1}H NMR spectra of $\mathbf{3}_{1,3}$ (1.0×10^{-2} mol dm^{-3}) in the absence (A) and the presence (B) of Pirkle's reagent (0.50 mol dm^{-3}): CDCl$_3$, 25°C, 400 MHz

meso compound $\mathbf{3}_{1,3}$ (Fig. 3). This molecule has a plane of symmetry and therefore, should be achiral. Conceivably, Pirkle's reagent interacts with one of these two intramolecular stereogenic centers and the meso isomer can apparently become asymmetric as an optically-active complex.[16]

To confirm that **2**, $\mathbf{3}_{1,5}$, and **4** consist of a pair of enantiomers, we attempted a resolution by an HPLC method with chiral-packed columns. We tested four different columns (Chiralpak OP(+), Chiralpak AD, TMC-Pak KO3, and Sumichiral OA-3100), but none of them were useful for the resolution although some of them are known to be effective in the resolution of inherently chiral calix[n]arenes. We previously applied this method to the resolution of inherently chiral calix[4]arenes with different *O*-substituents.[2–5] Through this study, we learned that calix[4]arenes resolved by this method all have some heteroatoms (N or O) in the *O*-substituent. Presumably, these heteroatoms effectively interact with the surface of the chiral solid phase, which would result in the sufficient peak separation. Unfortunately, compounds **2**, $\mathbf{3}_{\mathbf{1,5}}$, and **4** do not have not such heteroatoms outside the cavity, which make the resolution difficult.

3. Conclusion

The present study has demonstrated that a variety of new chiral and achiral cage compounds can be readily derived by simple *O*-alkylation of a doubly-bridged calix[8]arene **1**. It is interesting that the molecular symmetry changes from one to another by an increase in the number of *O*-substituents. As has been demonstrated for calix[4]arenes,[1d2,3,5] introduction of different *O*-substituents in a stepwise manner into **1** will further increase the number of stereoisomers and create new stereogenic centers based on the arrangement of different *O*-substituents. Meanwhile, it is known that compound **5** shows high affinity to Cs^+ and RNH_3^+ ions.[12] Undoubtedly, these cage compounds serve as a new building-block library for designing new functionalized cage molecules.

4. Experimental

4.1. General procedure

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,54,52,56-bis(*O*-xylenyldioxy)-calix[8]arene[12] (0.05 g, 0.030 mmol) and MeI or MeOTs (0.04 g, 0.30 mmol) were treated in dry solvent (20 ml) in the presence of base (0.24 mmol) at room temperature, 60°C, or reflux temperature under a nitrogen atmosphere. The progress of the reaction was followed by a TLC method (silica gel, hexane:ethyl acetate=20:1 v/v) and the reaction was continued until compound **1** was no longer detected in the reaction mixture. After 12 h, the reaction was stopped by the addition of aqueous 0.1 mol dm^{-3} HCl solution (5 ml). The resultant mixture was extracted with dichloromethane. The dichloromethane layer was separated, washed three times with water, and dried over $MgSO_4$. The solution was concentrated to dryness and the residual solid was purified by a preparative TLC method (silica gel, hexane:ethyl acetate=20:1 v/v or hexane:dichloromethane=5:3 v/v).

4.2. Materials

Preparations and spectroscopic data of compound **1** and **5** have been described.[12]

4.2.1. 5,11,17,23,29,35,41,47-Octa-tert-butyl-49-monomethoxy-50,54,52,56-bis(O-xylenyl dioxy)calix[8]arene 2

This compound was prepared according to the conditions in entry 5 (Table 2) and purified by a preparative TLC method (silica gel, hexane:ethyl acetate=20:1 v/v): white powder, mp (dec) >341°C; R_f=0.10 (hexane:ethyl acetate=20:1 v/v); ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS, δ ppm) 1.02 (18H, s, *t*-Bu), 1.13 (18H, s, *t*-Bu), 1.29 (36H, s, *t*-Bu), 3.09 and 3.82 (8H, d, $ArCH_2Ar$), 3.12 and 4.31 (8H, d, $ArCH_2Ar$), 3.28 and 4.16 (8H, d, $ArCH_2Ar$), 3.45 and 4.40 (8H, d, $ArCH_2Ar$), 5.33 and 5.78 (4H, d, $ArCH_2O$), 5.38 and 5.86 (4H, d, $ArCH_2O$), 6.68 (2H, s, ArH), 6.84 (2H, s, ArH), 6.98 (2H, s, ArH), 7.08 (2H, s, ArH), 7.10 (2H, s, ArH), 7.12 (4H, s, ArH), 7.21 (4H, s, ArH), 7.26 (4H, s, ArH), 7.32–7.36 (2H, m, ArH), 7.41–7.46 (2H, m, ArH), 7.95 (2H, s, OH), 8.13 (1H, s, OH). Anal. Calcd for $C_{105}H_{126}O_8 \cdot H_2O \cdot CHCl_3$: C, 76.99; H, 7.81. Found: C, 76.83; H, 7.95. SIMS(+) $[M+Cs]^+$=1648.

*4.2.2. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51-dimethoxy-50,54,52,56-bis(*O*-xylenyl dioxy)calix[8]arene* $3_{1,3}$

This compound was prepared according to the conditions in entry 5 (Table 2): a preparative TLC method (silica gel, hexane:ethyl acetate=20:1 v/v), white powder, mp (dec) >330°C; R_f=0.21 (hexane:ethyl acetate=20:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS, δ ppm) 1.02 (18H, s, *t*-Bu), 1.09 (18H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu), 1.35 (18H, s, *t*-Bu), 1.36 (9H, s, *t*-Bu), 2.92 and 4.06 (4H, d, $ArCH_2Ar$), 3.12 and 4.22 (4H, d, $ArCH_2Ar$), 3.19 (6H, s, OMe), 3.35 and 4.28 (4H, d, $ArCH_2Ar$), 3.48 and 4.36 (4H, d, $ArCH_2Ar$), 5.30 and 5.77 (4H, d, $ArCH_2O$), 5.40 and 5.85 (4H, d, $ArCH_2O$), 6.72 (2H, s, ArH), 6.83 (2H, s, ArH), 6.98 (2H, s, ArH), 7.08 (2H, s, ArH), 7.10 (2H, s, ArH), 7.12 (4H, s, ArH), 7.21 (4H, s, ArH), 7.26 (4H, s, ArH), 7.32–7.36 (2H, m, ArH), 7.41–7.46 (2H, m, ArH), 7.84 (2H, s, OH). Anal. Calcd for $C_{106}H_{128}O_8 \cdot 2H_2O \cdot 2CHCl_3$: C, 71.86; H, 7.48. Found: C, 71.80; H, 7.37. SIMS(+) $[M+Cs+H]^+$=1663.

*4.2.3. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,53-dimethoxy-50,54,52,56-bis(*O*-xylenyl dioxy)calix[8]arene* $3_{1,5}$

This compound was prepared according to the conditions in entry 7 (Table 2): a preparative TLC method (silica gel, hexane:dichloromethane=5:3 v/v), white powder, mp (dec) >330°C; R_f=0.23 (hexane:dichloromethane=5:3 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS, δ ppm) 1.08 (36H, s, *t*-Bu), 1.30 (18H, s, *t*-Bu), 1.31 (18H, s, *t*-Bu), 3.07 and 4.30 (8H, d, $ArCH_2Ar$), 3.43 and 4.30 (8H, d, $ArCH_2Ar$), 3.45 (6H, s, OMe), 5.39 and 5.62 (8H, d, $ArCH_2O$), 6.85 (4H, s, ArH), 6.94 (4H, s, ArH), 7.09 (4H, s, ArH), 7.17 (4H, s, ArH), 7.25 (4H, ArH), 7.38–7.41 (4H, m, ArH), 7.83 (2H, s, OH). Anal. Calcd for $C_{106}H_{128}O_8 \cdot CHCl_3$: C, 77.91; H, 7.88. Found: C, 77.84; H, 7.91. SIMS(+) $[M+Cs]^+$=1662.

*4.2.4. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53-trimethoxy-50,54,52,56-bis(*O*-xylenyl dioxy)calix[8]arene 4*

This compound was prepared according to the conditions in entry 4 (Table 2): a preparative TLC method (silica gel, hexane:ethyl acetate=20:1 v/v), white powder, mp (dec) >341°C; R_f=0.29 (hexane:ethyl acetate=20:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS, δ ppm) 1.03 (18H, s, *t*-Bu), 1.08 (18H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu), 1.33 (18H, s, *t*-Bu), 1.36 (9H, s, *t*-Bu), 3.13 and 4.28 (4H, $ArCH_2Ar$), 3.26 and 4.35 (4H, $ArCH_2Ar$), 3.27 (3H, s, OMe), 3.29 and 4.51 (4H, $ArCH_2Ar$), 3.36 and 4.55 (4H, $ArCH_2Ar$), 3.45 (6H, s, OMe), 5.15 and 5.45 (4H, d, $ArCH_2O$), 5.51 and 5.60 (4H, d, $ArCH_2O$), 6.82 (2H, s, ArH), 6.86 (2H, s, ArH), 6.91 (2H, s, ArH), 7.04 (2H, s, ArH), 7.06 (2H, s, ArH), 7.18 (4H, s, ArH), 7.21 (4H, s, ArH), 7.26 (4H, s, ArH), 7.38–7.41 (2H, m, ArH), 7.46 (2H, m, ArH), 7.62 (1H, s, OH). Anal. Calcd for $C_{107}H_{130}O_8 \cdot H_2O \cdot CHCl_3$: C, 77.14; H, 7.97. Found: C, 77.08; H, 7.93. SIMS(+) $[M+H]^+$=1544.

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15. Chiral shift reagents tested herein are (*S*)-(−)-1,1′-bi-2-naphthol, (+)-tris[3-[(heptafluoropropyl)hydroxymethylene]camphorato]praseodymium(III), and Pirkle's reagent. Among them, Pirkle's reagent was the most effective.
16. The similar peak splitting induced by a chiral shift reagent was observed for a meso calix[4]arene derivative: Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S. *J. Chem Soc., Perkin Trans. 1*, **1996**, 1945.