Syntheses and Optical Resolution of Calix[4]arenes with Molecular Asymmetry. Systematic Classification of All Possible Chiral Isomers Derivable from Calix[4]arene

Koji Iwamoto, Hiroyasu Shimizu, Koji Araki, and Seiji Shinkai*

Contribution from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan

Received December 21, 1992

Abstract: All possible chiral isomers that can be derived from calix[4]arene by modification of the OH groups were systematically classified. Molecular asymmetry can be generated not only by different substituents but also by conformational isomerism. The numbers of chiral isomers are 24 for tetra-O-substituted calix[4]arenes, 10 for tri-*O*-substituted calix[4]arenes, 3 for di-*O*-substituted calix[4]arenes, and 0 for mono-O-substituted calix[4]arenes. This implies that calix[4]arene is a useful building block for the design of novel asymmetric ring structures. In order to demonstrate asymmetry in these chiral calix[4]arenes, we synthesized several tetra-, tri-, and di-O-substituted calix[4]arenes by using the metal template method, the stepwise synthesis method, the protection–deprotection method, etc., which were developed in efforts directed toward regioselective O-alkylation and control of conformational isomerism in calix[4]arenes. Finally, we succeeded in complete optical resolution of chiral calix[4]arenes by an HPLC method using a chiral-packed column or by the formation of diastereomers with the (–)-menthoxyacetyl group. This article thus contains all of the molecular design concepts, syntheses, and optical resolutions of chiral calix[4]arenes.

Introduction

Calix[*n*]arenes are cyclic, cavity-shaped oligomers made up of phenol and formaldehyde building blocks.[1-3] Cyclodextrins have a similar cavity-shaped architecture and are known to serve as receptors with chiral recognition ability imparted by the chiral D-glucose subunits.[4-7] One may expect similar chiral recognition ability with calix[*n*]arenes if they are appropriately modified with chiral substituents. At the preliminary stages of this research, chiral substituents were introduced directly into the calix[*n*]arene framework,[8-10] and in some cases partially asymmetric molecular recognition was attained.[9,10] We considered, however, that if molecular asymmetry could be directly generated from calix[4]arene, it would be more interesting and more fruitful not only from a stereochemical viewpoint but also from the viewpoint of chiral recognition.

It was expected that if substituents are introduced into a calix[4]arene ring in an asymmetric manner, the product calix[4]arene would have no plane of symmetry. For example, calix[4]arenes with four different substituents should result in a pair of enantiomers. It is known, however, that in OH-unmodified calix[4]arenes ring inversion takes place at a speed comparable with the NMR time scale.[2,11,12] This implies that optical resolution can be effected only when the ring inversion which causes racemization is sufficiently suppressed. Recently, Böhmer et al.[13-15] and Vicens et al.[16] synthesized calix[4]arenes in which the substituents were arranged asymmetrically on the benzene rings. However, no further reports have appeared on their efforts toward the optical resolution of these racemates.

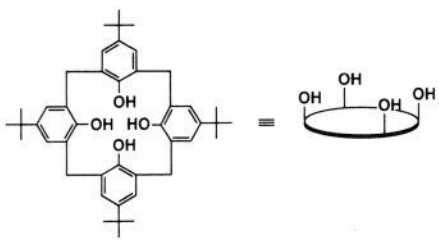
It is known that ring inversion can be readily inhibited by introducing substituents bulkier than an ethyl group onto the OH groups (e.g., by etherification).[17-20] We previously attempted O-propylation of a calix[4]arene asymmetrically substituted on the benzene ring to suppress the oxygen-through-the-annulus rotation and to obtain a pair of enantiomers for optical resolution.[21,22] However, suppression of the rotation by O-substitution resulted in a number of conformational isomers (because of the combination of cone, partial cone, 1,2-alternate, and 1,3-alternate conformations with inversion of four inequivalent phenol units).[21,22] This result taught us to selectively synthesize and isolate, prior to optical resolution, a pair of enantiomers from the many possible isomers. After much trial and error, we finally found that the metal template effect is very useful for selective synthesis of one

(1) Gutsche, C. D. *Prog. Macrocycl. Chem.* **1987**, *3*, 93.
(2) Gutsche, C. D. In *Calixarenes*; Royal Society of Chemistry: Cambridge, UK, 1989.
(3) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. chem.* **1989**, *60*, 483.
(4) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.
(5) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(6) Bender, M. L.; Komiyama, M. In *Cyclodextrim Chemistry*; Springer-Verlag: New York, 1977.
(7) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.
(8) Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962.
(9) (a) Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495. (b) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, M. *Chem. Lett.* **1987**, 2269.
(10) Arimura, T.; Kawabata, H.; Mutsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 301.
(11) Araki, K.; Shinkai, S.; Matuda, T. *Chem. Lett.* **1989**, 581.
(12) Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.
(13) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, *52*, 3200.
(14) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.
(15) Böhmer, V.; Wolff, A.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1990**, 968.
(16) Casabianca, H.; Royer, J.; Satrallah, A.; Taty-C, A.; Vicens, J. *Tetrahedron Lett.* **1987**, *28*, 6595.
(17) Araki, K.; Iwamoto, K.; Shinkai, S.; Matuda, T. *Chem. Lett.* **1989**, 1747.
(18) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.
(19) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.
(20) Conformational isomerism in calix[4]arenes and related compounds was also discussed by Reinhoudt et al., Ungaro et al., and Gutsche et al. (a) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385. (b) van Loon, J.-D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2378. (c) Casnati, A.; Pochini, A.; Ungaro, R.; Cacciapagli, R.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1991**, 2052. (d) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, *22*, 4763. (e) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.
(21) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Araki, K.; Iwamoto, K.; Matuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734.
(22) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429.

0002-7863/93/1515-3997$04.00/0

conformer (particularly the cone conformer).[17-19] This breakthrough enabled us for the first time to synthesize a conformationally fixed, asymmetrically substituted calix[4]arene and to optically resolve the racemate.[23,24]

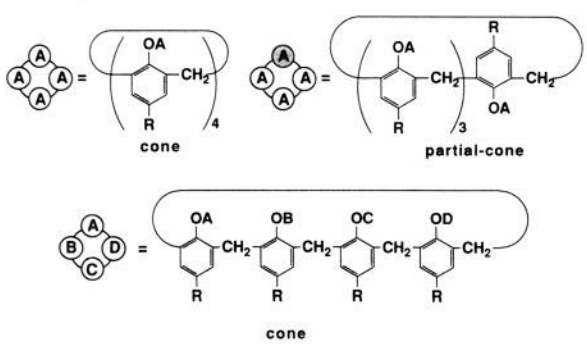
Throughout these studies, we were plagued by two difficult problems: (i) complicated conformational isomerism in calix[4]arenes and (ii) synthetic problems in calix[4]arenes asymmetrically substituted on the benzene moieties. It occurred to us that such complexity (i) might be rather useful in generating some new asymmetry on the calix[4]arene ring. For example, introduction of two different substituents may be enough to make the calix[4]arene ring chiral if one of them is inverted. The second difficulty may be resolved by introducing substituents onto the OH groups by a Williamson reaction instead of introducing them onto the benzene moieties. To further examine these ideas, introduction of different substituents onto the OH groups by a Williamson reaction was attempted, and the product calix[4]arenes were optically resolved by an HPLC method using a chiral-packed column or by the formation of diastereomers. On the basis of these studies, we can now systematically classify all possible "chiral" conformers derived from calix[4]arene.



$1(=H^{\alpha}H^{\alpha}H^{\alpha}H^{\alpha})$

Results and Discussion

Classification of All Possible Chiral Isomers. We now consider the O-alkylation products of calix[4]arene. All possible conformational isomers for tetra-O-alkylation of calix[4]arene are summarized in Table I. In this table, A, B, C, and D denote O-substituents, and shadowed circles denote inverted phenol units; for example,



It is seen from Table I that, basically, one can synthesize 43 different calix[4]arene derivatives by tetra-O-alkylation. Among the four possible conformations, the partial cone, which is classified as the conformation with the lowest symmetry, involves the largest number of O-alkylation products (19 products). Assuming that these O-substituents are bulky enough to inhibit oxygen-through-the-annulus rotation, one can count 24 chiral O-alkylation products, which are shown by an asterisk in Table I. Clearly, asymmetry in the calix[4]arene ring can be generated not only by different substituents but also by inversion of the same kind of substituent. To demonstrate the asymmetry in these isomers, we have synthesized $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ (Pr = *n*-propyl, Bzl = benzyl; α and β denote the direction of each phenol unit, that is, this compound has a partial-cone conformation with an inverted Pr^{β} group and is classified as $A^{\alpha}A^{\alpha}A^{\beta}B^{\alpha}$ in Table I).

In Table II, we summarize all possible O-alkylation products for tri-O-substituted calix[4]arenes (where H denotes the unsubstituted phenol unit). It is seen from Table II that 28 different calix[4]arene derivatives exist. In this table we can find 20 chiral compounds, which are shown by an asterisk. As we reported previously,[18] the unsubstituted phenol unit in tri-O-substituted calix[4]arenes can rotate at room temperature, and the direction of the OH group is determined by the relative thermodynamic stability. Thus, several conformers become equivalent after the oxygen-through-the-annulus rotation of the OH group. The compounds enclosed in the shadowed frame in Table II correspond to these conformers. For example, $A^{\alpha}A^{\beta}A^{\beta}H^{\alpha}$ in the shadowed frame becomes equivalent to $A^{\alpha}A^{\alpha}A^{\beta}H^{\alpha}$ after rotation of the OH group. Hence, the actual number of chiral compounds is 10. Eight of the 10 products have a partial-cone conformation, and the two remaining products have a cone conformation. Of the possible structures, we synthesized $Pr^{\alpha}Pr^{\alpha}Bzl^{\alpha}H^{\alpha}$ (cone $A^{\alpha}A^{\alpha}B^{\alpha}H^{\alpha}$), $Bzl^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ (cone $A^{\alpha}B^{\alpha}C^{\alpha}H^{\alpha}$; Pyl = 2-pyridylmethyl), $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}H^{\alpha}$ (partial cone $A^{\alpha}A^{\alpha}A^{\beta}H^{\alpha}$), and $Pr^{\alpha}Pr^{\beta}$-$Bzl^{\alpha}H^{\alpha}$ (partial cone $A^{\alpha}A^{\beta}B^{\alpha}H^{\alpha}$).

Similarly, we constructed Table III, which includes 25 different di-O-substituted calix[4]arenes. In this table we can count 14 chiral products, but after the rotation of the two OH groups, only three inequivalent chiral products remain. Among them, we have synthesized $Pr^{\alpha}Pr^{\beta}H^{\alpha}H^{\beta}$ (1,3 alternate-$A^{\alpha}A^{\beta}H^{\alpha}H^{\beta}$). Lastly, it is impossible to conceive of any chiral compound from mono-O-substituted calix[4]arenes.

Syntheses of Chiral Calix[4]arenes. In order to design asymmetrically substituted calix[4]arenes, Böhmer et al.[13-15] and Vicens et al.[16] modified the upper rim (i.e., benzene rings). To introduce substituents onto the upper rim, one has to employ troublesome synthetic methods such as the Friedel–Crafts reaction, the Claisen rearrangement reaction, etc.[25-33] We supposed that the same goal could be attained by simple O-alkylation of the OH groups. Following the guidelines summarized in Tables I–III, we decided to synthesize several calix[4]arenes (as in Schemes I–III) with no plane of symmetry by O-alkylation reactions and to demonstrate that these compounds actually behave as chiral compounds. Since the rotation is inhibited by substituents bulkier than the ethyl group,[18,19] we employed Pr, Bzl, and Pyl groups.

The starting material was 5,11,17,23-tetra-*tert*-butylcalix[4]-arene-25,26,27,28-tetrol (**1**). Treatment of **1** with benzyl bromide (1.25 equiv) in toluene in the presence of NaH (1.14 equiv) gave the mono-O-benzylated product (**2**) in 74% yield.[17,18,34] Treatment of **2** with propyl iodide (60 equiv) in THF/DMF (5:1, v/v) in the

(23) Iwamoto, K.; Yanagi, A.; Arimura, T.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 1901 (preliminary communication).

(24) Optical resolution of a tetra-O-substituted calix[4]arene using a similar method was recently reported: Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747.

(25) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633.

(26) Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.

(27) Iwamoto, K.; Araki, K.; Fujimoto, H.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1885.

(28) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

(29) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, *30*, 2681.

(30) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

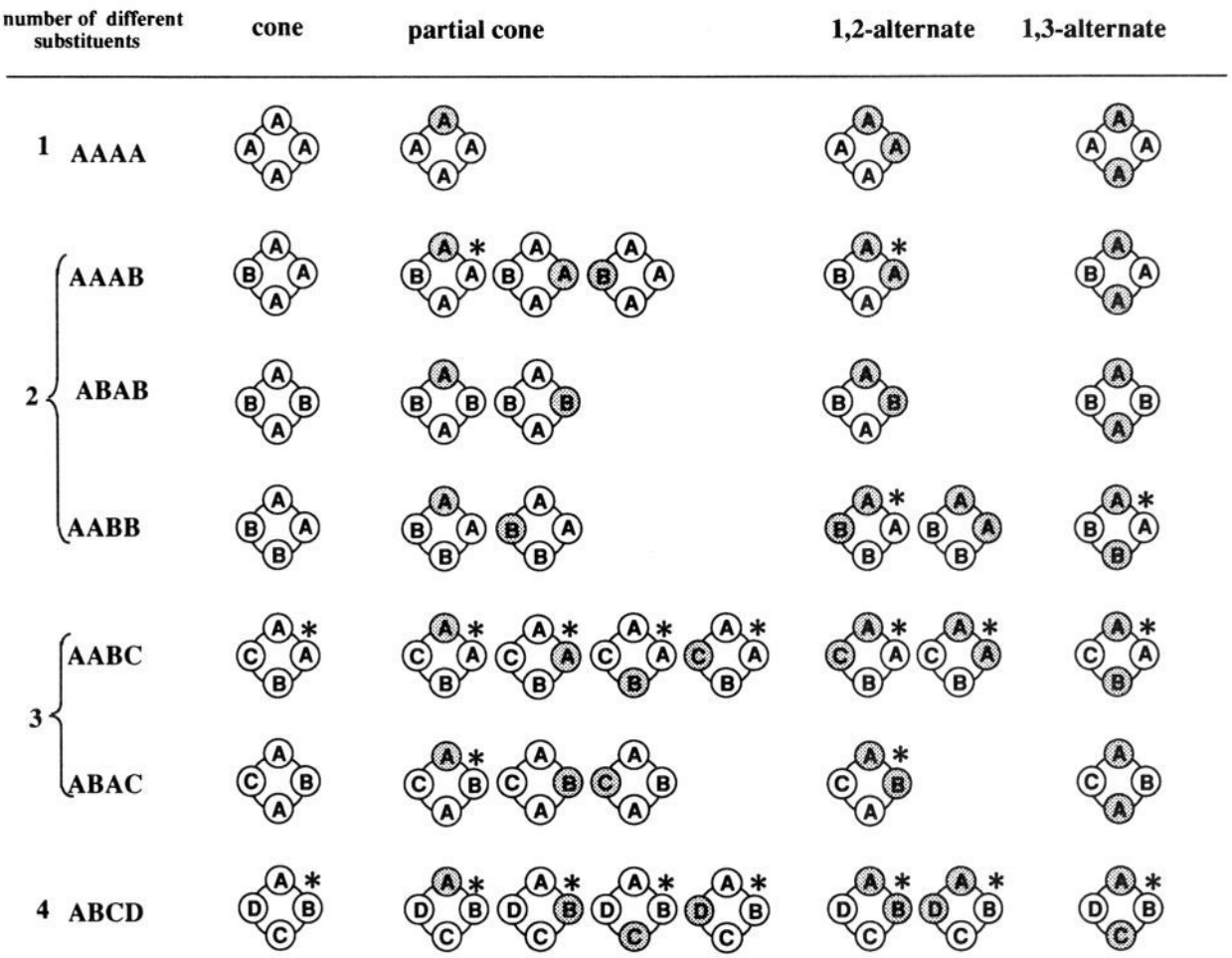
(31) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177.

(32) Shinkai, S.; Nagasaki, T.; Iwamoto, K.; Ikeda, A.; He, G.-X.; Matsuda, T.; Iwamoto, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 381.

(33) Arimura, T.; Nagasaki, T.; Shinkai, S.; Manabe, O. *J. Org. Chem.* **1989**, *54*, 3767.

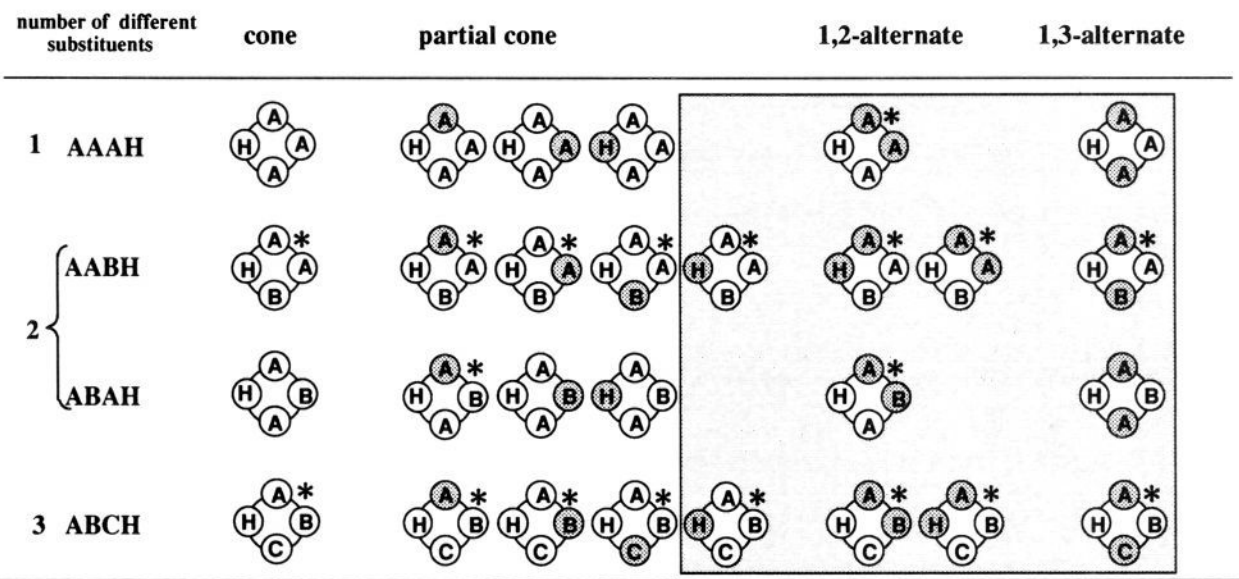
(34) The mono-O-alkylation method of **1** was also reported by Ungaro et al.: Groenen, L. C.; Ruel, B. H.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.

Table I. All Possible Tetra-O-alkylation Products Derived from Calix[4]arene[a]



[a] Asterisks indicate chiral calix[4]arenes.

Table II. All Possible Tri-O-alkylation Products Derived from Calix[4]arene[a]

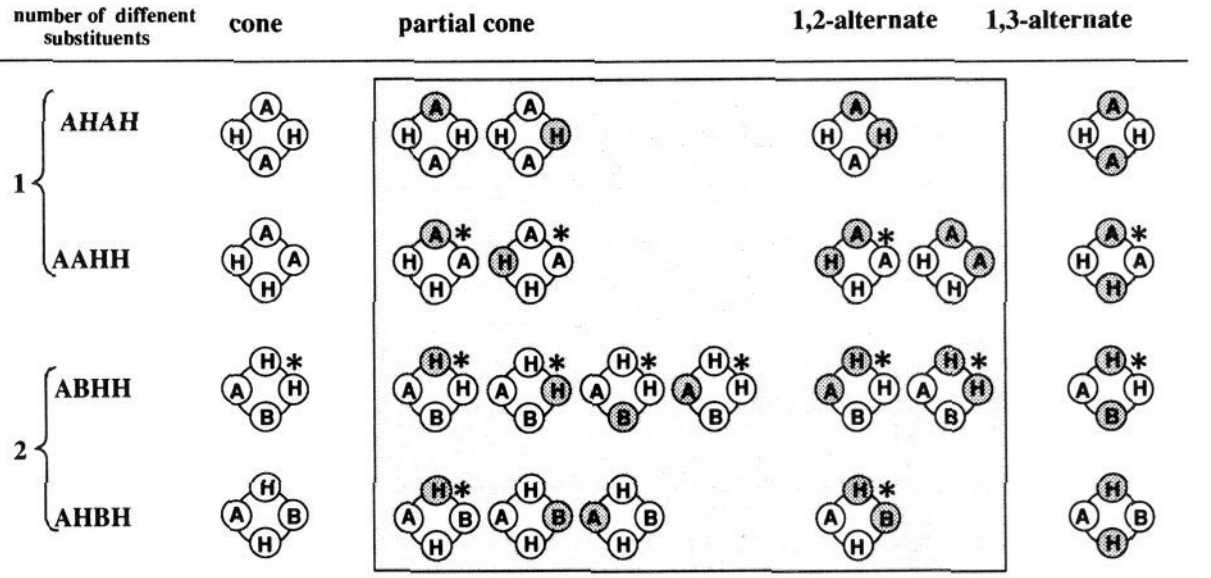


[a] Asterisks indicate chiral calix[4]arenes.

presence of NaH (12 equiv) gave $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ with a partial-cone conformation in 69% yield.

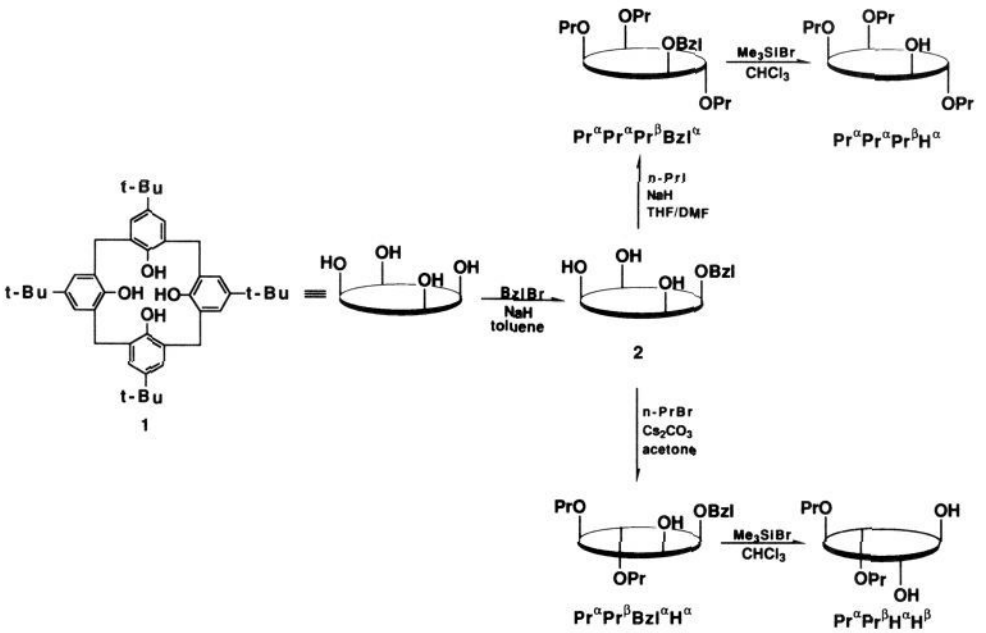
It has been established that the final conformer distribution is strongly affected by the metal template effect; a cone results when the metal cation can act as a template, but conformers other than the cone result when the metal cation cannot act as a template.[17-19] One-step tetra-O-propylation of **1** in the presence of NaH gives the cone and partial-cone conformers in approximately a 1:1 ratio.[17,19] This result suggests that the template effect of Na^+ in the present reaction is not so strong, and Pr^{α}-

Table III. All Possible Di-O-alkylation Products Derived from Calix[4]arene[a]



[a] Asterisks indicate chiral calix[4]arenes.

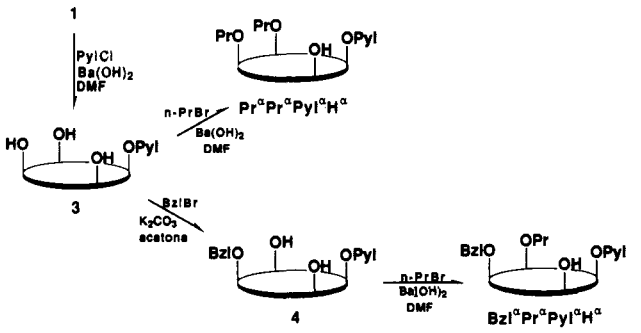
Scheme I



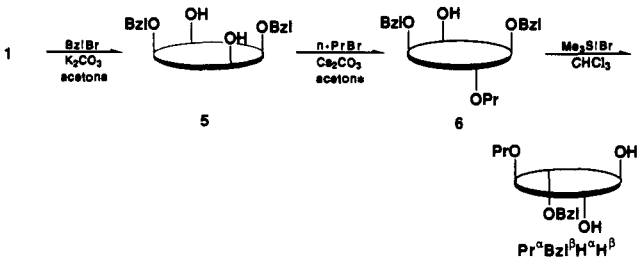
$Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ with a partial-cone conformation is the main product. $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ is an example of a tetra-O-substituted chiral product with two different substituents (i.e., $A^{\alpha}A^{\alpha}A^{\beta}B^{\alpha}$; see Table I). The presence of at least three different substituents is a prerequisite in the realization of asymmetry on the calix[4]arene ring. In $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$, this requirement is satisfied by two different substituents and one inverted phenol unit. The benzyl group in $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$ was then deprotected by Me_3SiBr to give $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}H^{\alpha}$ in 93% yield. This compound is an example of a tri-O-substituted chiral product with only one kind of substituent (i.e., $A^{\alpha}A^{\alpha}A^{\beta}H^{\alpha}$; see Table II). This result shows that the benzyl group can be used not only as a final substituent to generate asymmetry but also as a protecting group to synthesize less substituted chiral products.

Treatment of **2** with propyl bromide (30 equiv) in acetone in the presence of Cs_2CO_3 (3 equiv) gave di-O-propylated $Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}H^{\alpha}$ in 49% yield (Scheme I). We previously found that Cs^+ ion is weakly bound to calix[4]arene derivatives and therefore does not act as an effective template metal.[17-19] This nature of the Cs^+ ion facilitates inversion of one phenol unit and immobilizes the conformation in the partial cone. $Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}H^{\alpha}$ is a chiral product with two different substituents and one inverted phenol unit (i.e., $A^{\alpha}A^{\beta}B^{\alpha}H^{\alpha}$; Table II). Debenzylation of $Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}H^{\alpha}$ with Me_3SiBr gave $Pr^{\alpha}Pr^{\beta}H^{\alpha}H^{\beta}$ in 95% yield, which is classified as a di-O-substituted chiral product with only one kind of substituent (i.e., $A^{\alpha}A^{\beta}H^{\alpha}H^{\beta}$; Table III). Since inversion of the OH groups is allowed, this compound can adopt either the partial-cone, 1,2-alternate, or 1,3-alternate conformation. Examination of the literature reveals that mono-, di-, and tri-O-substituted calix[4]arenes tend to adopt the conformation in which the OH groups can form as many intramolecular hydrogen bonds as possible.[18,19] This rule predicts that this compound will favorably adopt a partial-cone conformation. However, the ^1H NMR spectrum in $CDCl_3$ indicates that this compound actually adopts a 1,3-alternate conformation. The reason for this observation is not well understood at present.

Scheme II



Scheme III



The mono-O-2-pyridylmethyl derivative **3** can be synthesized from **1** and 2-(chloromethyl)pyridine hydrochloride (1.7 equiv) in DMF in the presence of $Ba(OH)_2{\cdot}8H_2O$ (2.85 equiv.) and BaO (2.85 equiv) (Scheme II). The yield was 54%. We[19,21-23] and Gutsche et al.[35] have found that $Ba(OH)_2$ is a special base that stops the O-alkylation reaction at the tri-O-substituted stage. We also found that the product tri-*O*-substituted calix[4]arenes are only in the cone conformation.[19,21-23,26] The novel behavior of Ba^{2+} can be ascribed to suppression of the nucleophilicity of the phenoxide anion through the formation of ArO–Ba covalent bonds. This method is also useful for the stepwise introduction of substituents.

Treatment of compound **3** with propyl bromide (10 equiv) in DMF in the presence of $Ba(OH)_2{\cdot}8H_2O$ (4 equiv) and BaO (4 equiv) gave $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ with a cone conformation in 76% yield (Scheme II). Similarly, treatment of compound **3** with benzyl chloride (1.15 equiv) in acetone in the presence of K_2CO_3 (10 equiv) followed by treatment with propyl bromide (10 equiv) in DMF in the presence of $Ba(OH)_2{\cdot}8H_2O$ (4 equiv) and BaO (4 equiv) gave $Bzl^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ with a cone conformation. The yields for each step were 73% and 76%, respectively. When calix[4]-arene adopts a cone conformation, the molecular asymmetry is realized for a minimum of three different substituents. The unsubstituted OH group can be counted as one substituent, so that one has to introduce at least two different substituents. Thus, $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ satisfies the minimum requirement for asymmetry (i.e., $A^{\alpha}A^{\alpha}B^{\alpha}H^{\alpha}$; see Table II). $Bzl^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ also satisfies the requirement. These calix[4]arenes are classified as tri-O-substituted chiral products with two or three different substituents.

The last example is $Pr^{\alpha}Bzl^{\alpha}H^{\alpha}H^{\beta}$ (Scheme III), which is classified as a di-O-substituted chiral product with two different substituents (Table III). Treatment of **1** with benzyl bromide (4.5 equiv) in acetone in the presence of K_2CO_3 (11.4 equiv) gave di-O-benzylated **5** in 98% yield. It is known that to stop the O-alkylation reaction at the mono-O-substituted stage is quite difficult.[11,21] As mentioned above for the synthesis of **2**, the molar ratio of benzyl bromide:**1** is adjusted to 1.25 and that of NaH:**1** to 1.14. In contrast, when the combination of K_2CO_3 as base and acetone as solvent is used, most O-alkylation reactions "automatically" stop at the di-O-substituted stage, even in the presence of excess alkyl halide and excess base. The low reactivity is attributed to the conformational characteristics of di-O-substituted calix[4]arenes in which two unreacted OH groups are flattened into the annulus and to the formation of relatively tight ion pairs.[37]

Compound **5** was treated with propyl bromide (30 equiv) in acetone in the presence of Cs_2CO_3 (3 equiv). Cs_2CO_3, the nontemplate metal ion, was used to facilitate the rotation of the phenol unit. Compound **6** was then treated with Me_3SiBr (2 equiv) to give $Pr^{\alpha}Bzl^{\beta}H^{\alpha}H^{\beta}$ in 88% yield. This compound is classified as a di-O-substituted, optically active calix[4]arene with two different substituents (Table III). Interestingly, the ^1H NMR spectrum indicated that $Pr^{\alpha}Bzl^{\beta}H^{\alpha}H^{\beta}$ also adopts a 1,3-alternate conformation, although this conformation possesses a smaller number of intramolecular hydrogen bonds than a cone conformation.

The foregoing synthetic studies indicate that a variety of new chiral O-alkylation products from **1** can be designed, taking appropriate consideration of these synthetic strategies: (i) mono-O-alkylation is achieved either by the adjustment of molar ratios of alkyl halide:**1** and base:**1** or by the use of $Ba(OH)_2$; (ii) K_2CO_3 in acetone can halt the reaction at the di-O-substituted stage; (iii) Na^+ ion tends to suppress inversion of the phenol unit, whereas the Cs^+ ion tends to facilitate it; (iv) $Ba(OH)_2$ is also useful for selective synthesis of tri-O-substituted calix[4]arenes with a cone conformation; and (v) a benzyl group is very useful not only as a substituent but also as a protecting group.

Synthesis of Calix[4]arene-Based Diastereomers. Chiral calix-[4]arenes may be optically resolved by an HPLC method using a chiral-packed column, but a more expeditious method is to convert them to diastereomers. Fortunately, some of the chiral calix[4]arenes listed in Tables II and III contain unsubstituted OH group(s) useful for further modifications. We thus synthesized a diastereomer **10** according to Scheme IV. Here we used calix[4]arene-25,26,27,28-tetrol (**7**) as the starting material instead of **1** because we later found that the reaction of alkyl halides with **7** can be stopped at each O-alkylation stage more easily than the reaction with **1**.[38]

First, compound **7** was mono-O-propylated to yield **8**. This compound was treated with benzyl bromide in the presence of K_2CO_3 to give di-O-substituted **9**. This compound was treated with propyl bromide again in the presence of NaH to yield **10**. Finally, the OH group in **10** was allowed to react with (–)-menthoxyacetyl chloride to yield diastereomer **11**. We also used (*S*)-(+)-2-methylbutyryl chloride and *N*-(*p*-tolylsulfonyl)-L-phenylalanyl chloride to modify the residual OH group, but they did not yield ester derivatives probably because of steric hindrance. Compound **11** was subjected to HPLC separation using a conventional ODS column.

Optical Resolution. In order to confirm that seven asymmetrically substituted compounds shown in Schemes I–III consist of a pair of enantiomers, we measured their ^1H NMR spectra in the presence of chiral shift reagents. We found that, among the several shift reagents tested,[39] Pirkle's reagent ((*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) is most effective. In seven compounds the peaks split into pairs with a 1:1 intensity ratio even at 25 °C. The cleanest split was observed for Pyl-containing calix[4]arenes. The finding suggests that Pirkle's reagent interacts via hydrogen bonding with the pyridine nitrogen of these calix[4]arenes. The

(35) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; Hyun, K.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

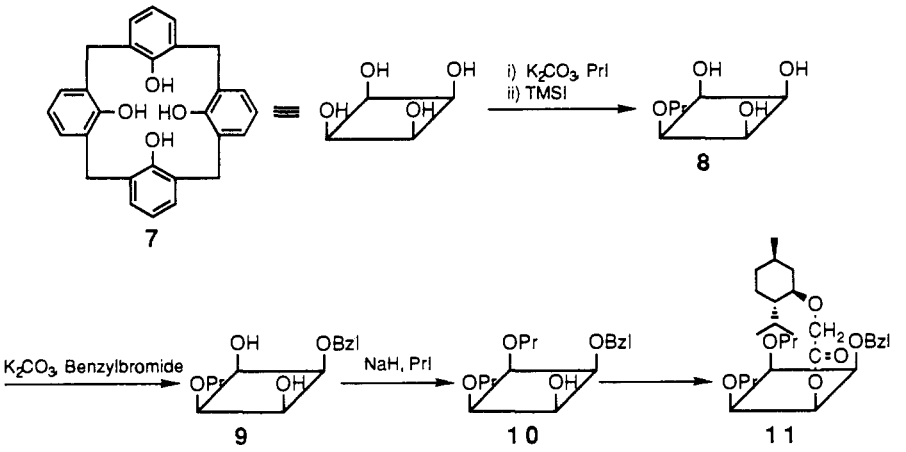
(36) We later found that CaH shows a similar property in the reaction of calix[4]arene-25,26,27,28-tetrol and ethyl bromoacetate: Shimizu, H.; Iwamoto, K.; Fujimoto, K.; Shinkai, S. *Chem. Lett.* **1991**, 2147.

(37) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Himmel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

(38) Shimizu, H.; Iwamoto, K.; Shinkai, S. Unpublished results.

(39) 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.

Scheme IV



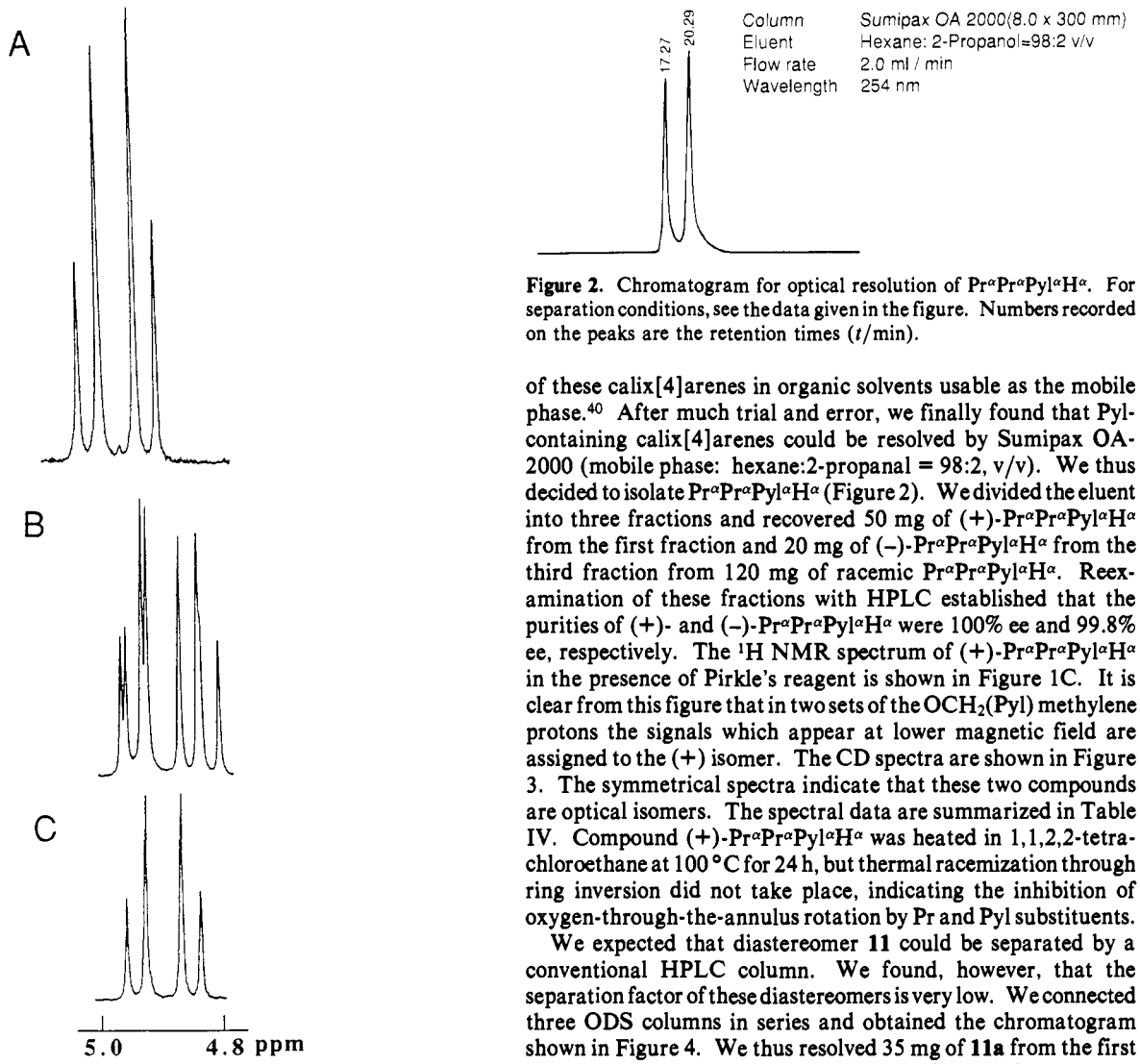


Figure 1. Partial ^1H NMR spectra for the $PylCH_2$ protons in $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ (1.22×10^{-2} M) at 30 °C in $CDCl_3$: (A) racemic $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$; (B) racemic $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ plus Pirkle's reagent (1.2 equiv); (C) (+)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ plus Pirkle's reagent (1.2 equiv).

typical ^1H NMR spectra observed for $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ in the absence and the presence of Pirkle's reagent are shown in Figure 1.

We attempted the optical resolution of these racemic compounds by an HPLC method. We tested several chiral-packed columns (see the Experimental Section), but the optical resolution was very difficult. The difficulty arose from the poor solubility of these calix[4]arenes in organic solvents usable as the mobile phase.[40] After much trial and error, we finally found that Pyl-containing calix[4]arenes could be resolved by Sumipax OA-2000 (mobile phase: hexane:2-propanal = 98:2, v/v). We thus decided to isolate $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ (Figure 2). We divided the eluent into three fractions and recovered 50 mg of (+)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ from the first fraction and 20 mg of (−)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ from the third fraction from 120 mg of racemic $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$. Reexamination of these fractions with HPLC established that the purities of (+)- and (−)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ were 100% ee and 99.8% ee, respectively. The ^1H NMR spectrum of (+)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ in the presence of Pirkle's reagent is shown in Figure 1C. It is clear from this figure that in two sets of the $OCH_2(Pyl)$ methylene protons the signals which appear at lower magnetic field are assigned to the (+) isomer. The CD spectra are shown in Figure 3. The symmetrical spectra indicate that these two compounds are optical isomers. The spectral data are summarized in Table IV. Compound (+)-$Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ was heated in 1,1,2,2-tetrachloroethane at 100 °C for 24 h, but thermal racemization through ring inversion did not take place, indicating the inhibition of oxygen-through-the-annulus rotation by Pr and Pyl substituents.

Figure 2. Chromatogram for optical resolution of $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$. For separation conditions, see the data given in the figure. Numbers recorded on the peaks are the retention times (t/min).

We expected that diastereomer **11** could be separated by a conventional HPLC column. We found, however, that the separation factor of these diastereomers is very low. We connected three ODS columns in series and obtained the chromatogram shown in Figure 4. We thus resolved 35 mg of **11a** from the first fraction and 25 mg of **11b** from the third fraction from 100 mg of diastereomeric **11**. Reexamination of these isolated diastereomers with HPLC established that the purities of **11a** and **11b** were 99.8% and 99.0%, respectively. The CD spectra are shown in Figure 5. Since **11a** and **11b** are diastereomeric compounds, they may not give symmetrical CD spectra. As shown in Figure 5, however, the CD spectra are nearly symmetrical. Compound **12** corresponds to a phenyl unit bearing a (−)-menthoxyacetyl

(40) Calix[4]arenes are soluble in halogen-containing solvents such as $CHCl_3$ and CH_2Cl_2, but these solvents are not usable as a mobile phase for most of the above-mentioned chiral-packing columns.

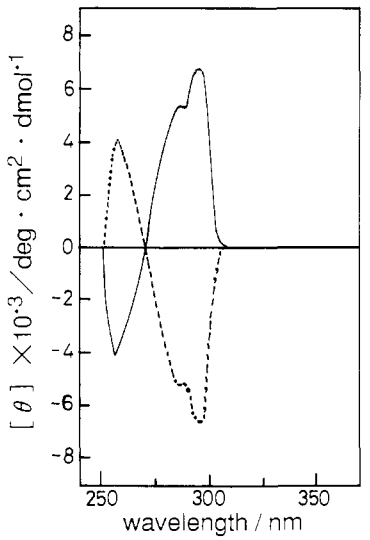


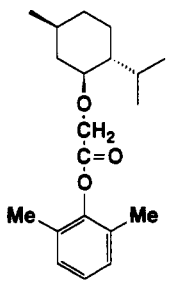
Figure 3. CD spectra of (+)- and (–)-Pr$^{\alpha}$Pr$^{\alpha}$Pyl$^{\alpha}$H$^{\alpha}$ (solid and dotted lines, respectively) at 25 °C in hexane.

Table IV. Spectral Parameters for Chiral Calix[4]arenes (25 °C)

calix[4]arene	$[\alpha]^{25}$/deg	λ_{max}/nm	$[\theta]_{max}$/deg·cm² dmol⁻¹
(+)-Pr$^{\alpha}$Pr$^{\alpha}$Pyl$^{\alpha}$H$^{\alpha}$	+12.5[a]	254[b]	–4100[b]
		286[b]	+6720[b]
(–)-**10**	–7.35[c]	240[d]	+5100[d]
		282[d]	–6500[d]
11a	–27.7[c]	240[d]	+7800[d]
		278[d]	+900[d]
11b	–44.2[c]	240[d]	–7800[d]
		278[d]	–900[d]
12	–73.0[c]	231[d]	–150[d]

[a] c = 0.004, hexane. [b] [(+)-Pr$^{\alpha}$Pr$^{\alpha}$Pyl$^{\alpha}$H$^{\alpha}$] = 1.22 × 10⁻³ M, hexane. [c] c = 1.00, chloroform. [d] [**11a** or **11b**] = 5.00 × 10⁻³ M, [(+)-**10** or (–)-**10**] = 1.00 × 10⁻¹ M, [**12**] = 5.00 × 10⁻³ M, acetonitrile.

group in **11**. It only shows a weak, negative CD band at 231 nm (θ –150). Thus, the CD spectra of **11** are not related to the (–)-menthoxyacetyl-bearing phenyl unit but arise from the asymmetric deformation of the calix[4]arene ring. The nearly symmetrical CD spectra imply that **11a** and **11b** possess a nearly mirror-image structure.



12

The ^{1}H NMR spectra of diastereomeric **11**, **11a**, and **11b** are shown in Figure 6. It is seen from Figure 6A that the ^{1}H NMR spectrum of diastereomeric **11** is very complex. On the other hand, the ^{1}H NMR spectra of **11a** and **11b** are reasonably assigned to these compounds. The signals for the ArCH$_2$Ar methylene protons appear as four pairs of doublets at 3.0–3.4 and 4.0–4.5 ppm, indicating that **11a** and **11b** adopt cone conformations and have no planes of symmetry. Also, the multiplet resonance at 3.3–3.4 ppm in diastereomeric **11** changes to double triplets in **11a** and **11b**, indicating that this signal is assignable to the OCH methine proton in the (–)-menthoxy group. The most significant difference between **11a** and **11b** is seen for the signals of the OCH$_2$CO methylene protons: **11a** gives a pair of doublets with

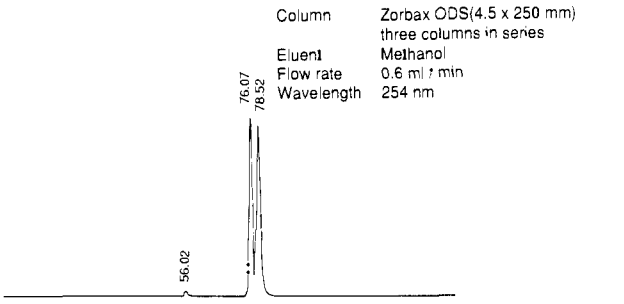


Figure 4. Chromatogram for resolution of diastereomeric **11**. For separation conditions, see the data given in the figure. Numbers recorded on the peaks are the retention times (t/min). The peak at 56.02 min is assigned to unreacted **10** (ca. 1%).

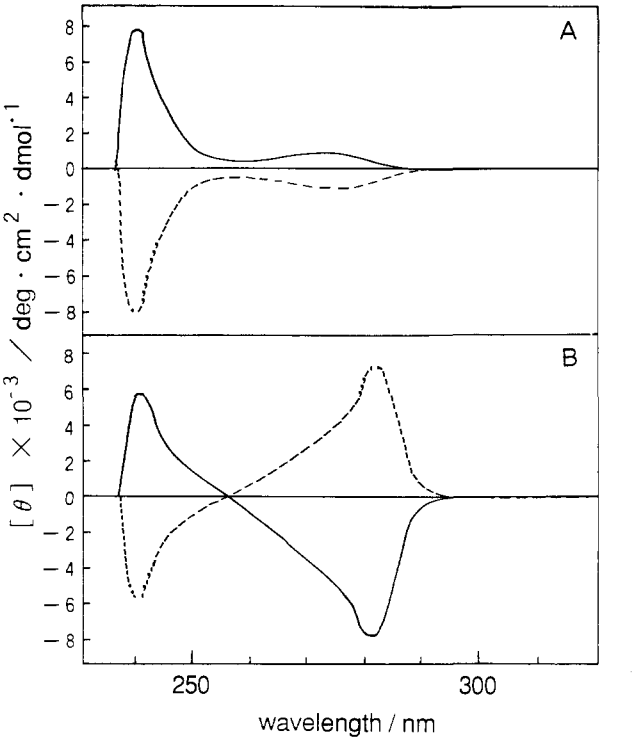


Figure 5. (A) CD spectra of **11a** (first fraction) and **11b** (third fraction) (solid and dotted lines, respectively) at 25 °C in acetonitrile. (B) CD spectra of (–)-**10** and (+)-**10** (solid and dotted lines, respectively) at 25 °C in acetonitrile.

a large chemical shift difference whereas **11b** gave a doublet resonance. (Basically, the OCH$_2$CO methylene should appear as a pair of doublets in both **11a** and **11b**. As seen Figure 6, those in **11b** appear apparently as a doublet reasonance. We consider that the chemical shifts of these two protons are very close.) This suggests that the rotation of the (–)-menthoxy group in **11a** is more restricted than that in **11b**.

We hydrolyzed **11a** and **11b** with tetramethylammonium hydroxide in THF. We recovered (–)-**10** with the negative α value from **11a** and (+)-**10** with the positive α value from **11b**. The ^{1}H NMR spectra of (–)- and (+)-**10** in the presence of Pirkle's reagent (30 °C, CDCl$_3$) show that these compounds are optical isomers with a purity higher than 99%. The CD spectra are shown in Figure 5. The symmetrical spectra again support the idea that these two compounds are optical isomers. It is not yet clear why (–)-**10** and (+)-**10** give exciton coupling-type CD spectra and **11a** and **11b** do not.

Conclusions

In the present article, we systematically classified all chiral calix[4]arenes which can be obtained by O-substitution and/or conformational isomerism. Of the 37 possible chiral calix[4]-arenes, we have synthesized six chiral calix[4]arenes and optically

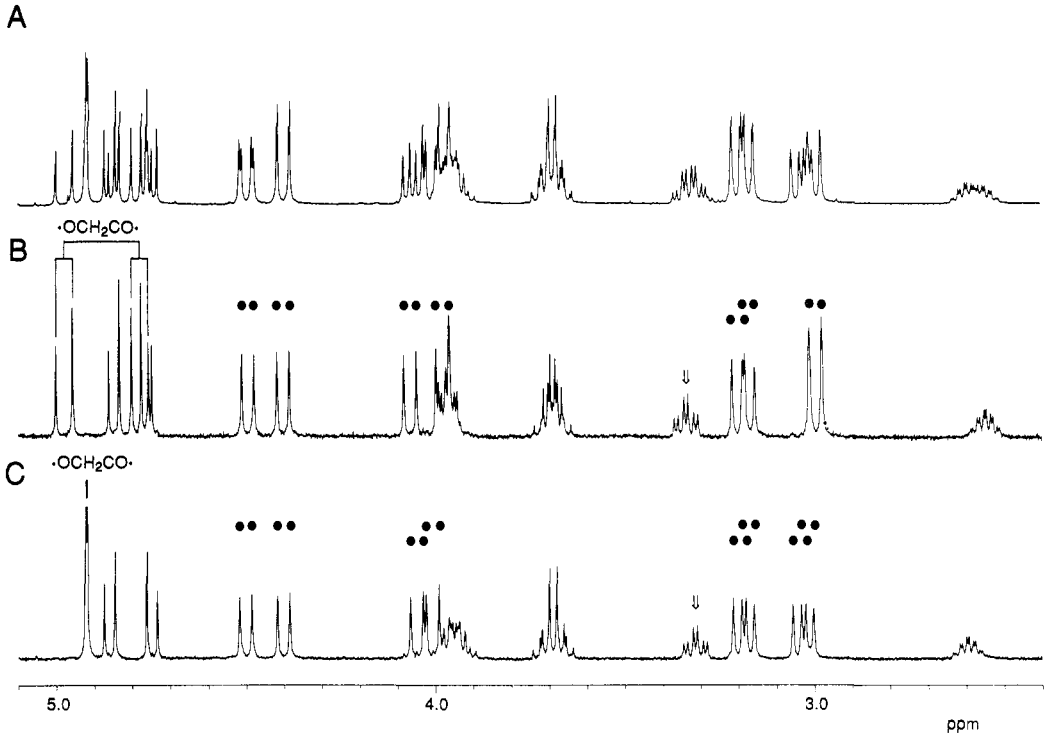


Figure 6. Partial ^{1}H NMR spectra for diastereomeric **11** (A), **11a** (B), and **11b** (C) at 30 °C in $CDCl_3$ (concentration, 2.0×10^{-3} M). The filled circles indicate the $ArCH_2Ar$ methylene protons, and the arrow indicates the OCH methine proton in the (–)-menthoxy group.

resolved two chiral calix[4]arenes, one by an HPLC method using a chiral-packed column and the other by the preparation of diastereomers. With such diversity of conformational isomerism and chirality in calix[4]arenes, we are reminded of carbohydrate chemistry. We therefore believe that the basic skeleton of chiral calix[4]arenes will provide the impetus for design of chiral host molecules, chiral synthons, chiral metal complexes, etc.

Experimental Section

Materials. Preparations of the following compounds have been described: 5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-(benzyloxy)-calix[4]arene (**2**),[11] $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}$,[11] $Pr^{\alpha}Pr^{\alpha}Pr^{\beta}H^{\alpha}$,[11] $Pr^{\alpha}Pr^{\beta}Bzl^{\alpha}H^{\alpha}$,[11] $Pr^{\alpha}Pr^{\beta}H^{\alpha}H^{\beta}$,[11] and 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-(dibenzyloxy)calix[4]arene (**5**).[11] (To represent the stereoisomerism in calix[4]arene, we introduce here $R_1R_2R_3R_4$ for O-substituents and α and β for phenyl inversion. For example, $Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}$ is a tetra-*O*-propylcalix-[4]arene with a cone conformation and $H^{\alpha}H^{\alpha}R_1{}^{\beta}R_2{}^{\beta}$ is a proximal R_1,R_2-substituted 1,2-alternate calix[4]arene.)

5,11,17,23-Tetra-*tert*-butyl-25,26,27-trihydroxy-28-(2-pyridylmethoxy)-calix[4]arene (3). 5,11,17,23-Tetra-*tert*-butylcalix[4]arene-25,26,27,-28-tetrol (**1**) (the crystal contains 1 mol of toluene, 1.0 g; 1.35 mmol), $Ba(OH)_2{\cdot}8H_2O$ (1.22 g, 3.85 mmol), and 2-(chloromethyl)pyridine hydrochloride (0.38 g, 2.31 mmol) were mixed in DMF (20 mL), and the reaction mixture was stirred for 22 h at room temperture under a nitrogen stream. The mixture was diluted with chloroform/water. The organic layer was separated, washed with water, and dried over $MgSO_4$. HPLC analysis (Zorbax ODS column, chloroform:methanol = 1:5, v/v) at this stage indicated that the solution contained **3** in 70% yield. The chloroform solution was evaporated to dryness, and the residue was recrystallized from chloroform/methanol: yield 54%, mp 274–276 °C; IR (Nujol) ν_{OH} 3120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 1.20, 1.21, and 1.22 (*t*-Bu, s each, 9 H, 18 H, and 9 H), 3.42, 3.44, 4.24, and 4.49 ($ArCH_2Ar$, d each, J = 13.7 Hz for 3.42 and 4.24, J = 13.1 Hz for 3.44 and 4.49), 5.29 (OCH_2, s, 2 H), 6.98, 7.04, 7.08, and 7.12 (ArH, s, d, J = 2.4 Hz, s, d, J = 2.4 Hz, 2 H each), 7.31–8.69 (pyridine protons, m, 4 H), 9.53 and 10.10 (OH, broad s, 2 H and 1 H). Anal. Calcd for $C_{50}H_{61}NO_4$: C, 81.15; H, 8.31; N, 1.89. Found: C, 80.98; H, 8.23; N, 2.10.

5,11,17,23-Tetra-*tert*-butyl-25-hydroxy-26,27-dipropoxy-28-(2-pyridylmethoxy)calix[4]arene ($Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$). Compound **3** (1.0 g, 1.35 mmol), $Ba(OH)_2{\cdot}8H_2O$ (1.68 g, 5.40 mmol), BaO (0.84 g, 5.40 mmol), and propyl bromide (0.49 mL, 5.40 mmol) were mixed in DMF (20 mL). The reaction mixture was heated at 70 °C for 7 h under a nitrogen stream. The mixture was diluted with chloroform/water. The organic layer was separated, washed with water, and dried over $MgSO_4$. The chloroform solution was evaporated to dryness, the residue being recrystallized from methanol: yield 89%, mp 170–172 °C; IR (Nujol) ν_{OH} 3155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 0.81, 0.86, 1.33, and 1.34 (*t*-Bu, s each, 9 H each), 0.61 and 1.10 (CH_3, t each, 3 H each), 1.81–2.12 (CCH_2C, m, 4 H), 3.16, 3.20, 3.23, 3.28, 4.22, 4.34, 4.43, and 4.47 ($ArCH_2Ar$, d each, J = 12.8 Hz for 3.16 and 4.47, J = 12.5 Hz for 3.20, 3.23, 4.34, and 4.43, and J = 13.3 Hz for 3.28 and 4.22, 1 H each), 3.70–3.84 (OCH_2, m, 4 H), 4.93 and 5.01 (OCH_2(Pyl) methylene protons, d each, J = 12.4 Hz, 1 H each), 5.59 (OH, s, 1 H), 6.51, 6.56, 6.58, 7.05, 7.08, 7.13, and 7.15 (ArH, d each, J = 2.4–2.7 Hz, 2 H for 6.51 and 1 H for other ArH), 7.21–8.60 (pyridine protons, m, 4 H). Anal. Calcd for $C_{56}H_{69}NO_4{\cdot}0.5CH_3OH$: C, 81.16; H, 8.56; N, 1.67. Found: C, 81.29; H, 8.39; N, 1.61. The appearance of four inequivalent *tert*-butyl groups and $ArCH_2Ar$ groups supports the view that this calix[4]arene has no plane of symmetry.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26-(benzyloxy)-28-(2-pyridylmethoxy)calix[4]arene (4). Compound **3** (1.0 g, 1.35 mmol) was treated with benzyl chloride (1.55 mL, 13.5 mmol) in acetone in the presence of K_2CO_3 (1.87 g, 13.5 mmol). The reaction was continued for 24 h at reflux temperature under a nitrogen stream. The mixture was diluted with chloroform/water. The organic layer was separated, washed with water, and dried over $MgSO_4$. HPLC analysis (Zorbax ODS column, chloroform:methanol = 1:5, v/v) at this stage indicated that the solution contained **4** in 100% yield. The solution was evaporated to dryness, the residue being recrystallized from chloroform/methanol: yield 73%, mp 217–219 °C; IR (Nujol) ν_{OH} 3270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 0.93, 0.94, and 1.30 (*t*-Bu, s each, 9 H, 9 H, and 18 H), 3.31, 3.32, 4.27, and 4.33 ($ArCH_2Ar$, d each, J = 13.1 Hz for all signals, 2 H each), 5.04 (OCH_2Ar, s, 2 H), 5.16 (OCH_2(Pyl) methylene protons, s, 2 H), 6.78, 6.80, and 7.07 (ArH, s, 2 H, 2 H, and 4 H), 7.21–8.58 (pyridine protons, m, 4 H), 7.36–7.74 (ArH in Bzl, m, 5 H). Anal. Calcd for $C_{57}H_{68}NO_4$: C, 82.34; H, 8.25; N, 1.68. Found: C, 82.33; H, 8.09; N, 1.68.

5,11,17,23-Tetra-*tert*-butyl-25-hydroxy-26-(benzyloxy)-27-propoxy-28-(2-pyridylmethoxy)calix[4]arene ($Bzl^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$). This compound was synthesized from **4** (0.3 g, 0.36 mmol), $Ba(OH)_2{\cdot}8H_2O$ (0.454 g, 1.44 mmol), BaO (0.221 mg, 1.44 mmol), and propyl bromide (0.74 mL, 3.60 mmol) in DMF (20 mL). The reaction was continued for 1.5 h at 70 °C under a nitrogen stream. The workup was similar to that described for **3**: yield 76%, mp 210–213 °C; IR (Nujol) ν_{OH} 3375 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 0.81, 0.87, 1.33, and 1.34 (*t*-Bu, s each, 9

H each), 0.26 (CH_3, t, 3 H), 1.68–1.80 (CCH_2C, m, 2 H), 3.11, 3.17, 3.24, 3.29, 4.32, 4.38, 4.39, and 4.43 ($ArCH_2Ar$, d each, J = 12.8 Hz for 3.17 and 4.38, J = 12.5 Hz for 3.11 and 4.32, J = 13.1 Hz for 3.24 and 4.43, and J = 13.4 Hz for 3.29 and 4.39, 1 H each), 3.60 (OCH_2C, t, 2 H), 4.76 and 4.90 (OCH_2Ar, d each, J = 11.0 Hz, 1 H each), 4.91 and 4.98 (OCH_2(Pyl) methylene protons, d each, J = 12.5 Hz, 1 H each), 5.50 (OH, s, 1 H), 6.52, 6.59, 7.07, 7.08, 7.12, and 7.13 (ArH, m, 2 H, 2 H, 1 H, 1 H, 1 H, and 1 H), 7.20–8.58 (pyridine protons, m, 4 H), 7.33–7.54 (ArH in Bzl, m, 5 H). Anal. Calcd for $C_{60}H_{73}NO_4$: C, 82.62; H, 8.44; N, 1.61. Found: C, 82.12; H, 8.28; N, 1.51.

5,11,17,23-Tetra-*tert*-butyl-25-hydroxy-26,28-(dibenzyloxy)-27-propoxycalix[4]arene (6). Compound **5** (1.0 g, 1.21 mmol) was treated with propyl bromide (3.68 mL, 40.5 mmol) in acetone (25 mL) in the presence of Cs_2CO_3 (1.32 g, 4.05 mmol). The reaction mixture was refluxed under a nitrogen stream for 22 h. The mixture was diluted with chloroform/water. The organic layer was washed with water, dried over $MgSO_4$, and concentrated to dryness. The residue was recrystallized from chloroform/methanol: yield 76%, mp 209–211 °C; IR (Nujol) ν_{OH} 3310 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 0.99, 1.18, and 1.29 (*t*-Bu, s each, 9 H, 18 H, and 9 H), 0.04 (CH_3, t, 3 H), 1.11–1.25 (CCH_2C, m, 2 H), 2.34 (OCH_2C, t, 2 H), 3.11 and 4.01 ($ArCH_2Ar$, d each, J = 12.8 Hz, 2 H each), 3.90 ($ArCH_2Ar$, s, 4 H), 4.74 and 5.17 (OCH_2Ar, d, J = 11.9 Hz, 2 H each), 6.80 (OH, s, 1 H), 6.95 and 7.04 (ArH, d, J = 2.6 Hz, 2 H each), 7.01 and 7.12 (ArH, s, 2 H each), 7.34–7.48 (ArH in Bzl, m, 10 H). Anal. Calcd for $C_{61}H_{74}O_4$: C, 84.09; H, 8.56. Found: C, 83.91; H, 8.14. The splitting pattern of the $ArCH_2Ar$ methylene protons and the upfield shift of the signals for the propyl protons indicate that **6** adopts a partial-cone conformation and the propyl group is inverted.

5,11,17,23-Tetra-*tert*-butyl-25,26-dihydroxy-27-propoxy-28-(benzyloxy)-calix[4]arene ($Pr^{\alpha}Bzl^{\beta}H^{\alpha}H^{\beta}$). One of the two benzyl groups was deprotected by treatment of **6** (0.50 g, 0.57 mmol) with Me_3SiBr (0.151 mL, 1.14 mmol) in chloroform (25 mL) for 2 h at room temperature. The workup method was reported previously:[11] yield 88%, mp 173–174 °C; IR (Nujol) ν_{OH} 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 400 MHz) δ 0.81, 0.85, 1.41, and 1.43 (*t*-Bu, s each, 9 H each), 0.71 (CH_3, t, 3 H), 1.44–1.58 (CCH_2C, m, 2 H), 3.52, 3.61, 3.87, 4.02, 4.09, and 4.15 ($ArCH_2Ar$, d each, J = 13.1 Hz for 3.52 and 4.15, J = 14.0 Hz for 3.61 and 4.02, and J = 16.0 Hz for 3.87 and 4.09, 1 H each), 4.05 ($ArCH_2Ar$, broad s, 2 H), 3.50–3.74 (OCH_2, m, 2 H), 4.27 and 4.34 (OCH_2Ar, d each, J = 12.4 Hz, 1 H each), 5.78–6.76 (ArH in benzyl, m, 5 H), 6.70, 6.72, 6.86, 7.00, 7.15, 7.16, 7.24, and 7.32 (ArH, d each, J = 2.4 Hz, 1 H each), 8.00 and 9.09 (OH, s each, 1 H each). Anal. Calcd for $C_{54}H_{68}O_4$: C, 83.03; H, 8.56. Found: C, 82.91; H, 8.22.

25,26,27-Trihydroxy-28-propoxycalix[4]arene (8). Calix[4]arene-25,26,27,28-tetrol (**7**) (10.0 g, 23.6 mmol) was treated with propyl bromide (18.2 mL, 200 mmol) in anhydrated DMF (300 mL) at room temperature under the anaerobic conditions in the presence of $Ba(OH)_2{\cdot}8H_2O$ (14.2 g, 45.0 mmol) and BaO (13.8 g, 90.0 mmol). The reaction was stopped after 24 h by addition of aqueous 1.0 M HCl (100 mL). The solution was extracted with chloroform (300 mL). The organic layer was separated and washed with aqueous 1.0 M HCl, aqueous sodium thiosulfate solution, and saturated NaCl solution (three times). The solution was dried over $MgSO_4$. Concentration under reduced pressure yielded a white powder containing 25,27-dihydroxy-26,28-dipropoxycalix[4]arene (95% purity) in quantitative yield. We recrystallized the small amount from chloroform/methanol for analysis: mp 262–264 °C; IR (KBr) ν_{OH} 3250, ν_{COC} 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 60 MHz) δ 1.28 (CH_3, t, 6 H), 2.04 (CCH_2C, m, 4 H), 3.36 and 4.34 ($ArCH_2Ar$, d each, 4 H each), 3.96 (OCH_2, t, 4 H), 6.56–7.20 (ArH, m, 12 H), 8.29 (OH, s, 2 H). Anal. Calcd for $C_{37}H_{42}O_4$: C, 80.36; H, 7.14. Found: C, 80.28; H, 7.13. The result indicates that the reaction in the presence of $Ba(OH)_2$ at the reflux temperature yields tri-O-substituted calix[4]arenes[19,21–23,35] whereas at room temperature it yields di-O-substituted calix[4]arenes.

The white powder was dissolved in anhydrated chloroform (200 mL) and treated with Me_3SiI (3.4 mL, 24.9 mmol) at reflux temperature. After 18 h, the reaction was stopped by addition of an aqueous 3.0 M HCl solution. The organic layer was separated and washed with aqueous sodium thiosulfate solution and saturated NaCl solution (three times). The solution was dried over $MgSO_4$. The solution was evaporated to dryness, the solid residue being recrystallized from chloroform/methanol: yield (from **7**) 78%, mp 264–266 °C; IR (Nujol) ν_{OH} 3190 and 3320, ν_{COC} 1090 and 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 30 °C, 60 MHz) δ 1.24 (CH_3, t, 3 H), 2.11 (CCH_2C, m, 2 H), 3.43, 4.28, and 4.38 ($ArCH_2Ar$, d each, 4 H, 2 H, and 2 H), 4.11 (OCH_2, t, 2 H), 6.25–7.10 (ArH, m, 12 H), 9.38 and 9.69 (OH, s each, 2 H and 1 H). Anal. Calcd for $C_{31}H_{30}O_4{\cdot}CH_3OH$: C, 77.33; H, 6.64. Found: C, 77.65; H, 6.32.

25,27-Dihydroxy-26-propoxy-28-(benzyloxy)calix[4]arene (9). 25,26,27-Trihydroxy-28-propoxycalix[4]arene (2.35 g, 5.0 mmol) was treated with benzyl bromide (0.7 mL, 5.8 mmol) in DMF at 70 °C under a nitrogen stream in the presence of K_2CO_3 (1.38 g, 10.0 mmol). The progress of the reaction was monitored by an HPLC method (Zorbax ODS, chloroform:methanol = 1:5, v/v). The reaction was stopped after 8 h by the addition of an aqueous 1 M HCl solution (50 mL). After cooling, the aqueous solution was extracted with chloroform (200 mL). The organic layer was separated, washed with an aqueous 1 M HCl solution, an aqueous sodium thiosulfate solution, and aqueous NaCl-saturated solution, and dried over $MgSO_4$. After filtration the solution was concentrated to dryness. The residue (white powder) was recrystallized from chloroform/methanol: yield 72%, mp 231–233 °C; IR (Nujol) ν_{OH} 3380, ν_{COC} 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 60 MHz) δ 1.22 (CH_3, t, 3 H), 2.04 (CCH_2C, m, 2 H), 3.35, 4.30, and 4.36 ($ArCH_2Ar$, d each, J = 12.9 Hz for all peaks, 4 H, 2 H, and 2 H), 3.45 (OCH_2 in Pr, t, 2 H), 5.06 (OCH_2 in benzyl, s, 2 H), 6.62–7.80 (ArH, m, 17 H), 8.07 (OH, s, 2 H). Anal. Calcd for $C_{38}H_{36}O_4$: C, 81.98; H, 6.51. Found: C, 81.60; H, 6.42.

25-Hydroxy-26,27-dipropoxy-28-(benzyloxy)calix[4]arene (10). Compound **9** (1.20 g, 2.15 mmol) was treated with oil-dispersed NaH (90 mg, 2.25 mmol) in DMF (100 mL) at 0 °C under a nitrogen stream. After 15 min propyl bromine (0.22 mL, 2.25 mmol) was added, and the progress of the reaction was monitored by an HPLC method (Zorbax ODS, chloroform:methanol = 1:5, v/v). The HPLC peak for **10** became the maximum after 24 h. Unreacted NaH was decomposed by a few drops of methanol, and the reaction was stopped here by the addition of an aqueous 1 M HCl solution (25 mL). The solution was extracted with chloroform (100 mL). The organic layer was separated, washed with an aqueous 1 M HCl solution, an aqueous sodium thiosulfate solution, and an aqueous NaCl-saturated solution, and dried over $MgSO_4$. After filtration the solution was concentrated to dryness. The residue (yellow oil) was subjected to preparative thin-layer chromatography (silica gel, hexane:chloroform = 1:1, v/v). We collected the fraction with R_f = 0.58. The recovered product (white powder) was recrystallized from chloroform/methanol: yield 72%, mp 138–140 °C; IR (Nujol) ν_{OH} 3400, ν_{COC} 1090, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 30 °C, 400 MHz) δ 0.67 and 1.08 (CH_3, t each, 3 H each), 1.87 and 2.05 (CCH_2C, m each, 2 H each), 3.14, 3.19, 3.27, 3.30, 4.35, 4.38, 4.41, and 4.47 ($ArCH_2Ar$, d each, J = 13.4 Hz for 3.14, 3.19, 3.27, 4.35, 4.38, and 4.41 and J = 13.7 Hz for 3.30 and 4.47, 1 H each), 3.72 (OCH_2 in propyl, m, 4 H), 4.68 (OH, s, 1 H), 4.81 (OCH_2 in benzyl, dd, 2 H), 6.3–7.5 (ArH, m, 17 H). Anal. Calcd for $C_{41}H_{42}O_4$: C, 82.20; H, 7.07. Found: C, 82.25; H, 7.30. The appearance of four inequivalent $ArCH_2Ar$ methylene groups in a pair of doublets supports the view that **9** adopts a cone conformation and has no plane of symmetry.

25-[(–)-Menthoxyacetoxy]-26,27-dipropoxy-28-(benzyloxy)calix[4]-arene (11). Compound **10** (0.60 g, 1.0 mmol) was treated with oil-dispersed NaH (80 mg, 2.0 mmol) in DMF (2 mL)/THF (20 mL) at 0 °C under a nitrogen stream. After 30 min (–)-menthoxyacetyl chloride (0.35 g, 1.5 mmol) was added. After 3 h, **10** was no longer detected by HPLC (Zorbax ODS, chloroform:methanol = 1:5, v/v). Unreacted NaH was decomposed by a few drops of methanol, and the reaction was stopped by addition of an aqueous 1 M HCl solution (20 mL). The solution was extracted with chloroform (100 mL). The organic layer was separated, washed three times with water, and dried over $MgSO_4$. After filtration the solution was concentrated to dryness. The residue (yellow oil) was crystallized from chloroform/ethanol: yield 80%, mp 141–143 °C; IR (Nujol) ν_{OH} 1760, ν_{COC} 1120, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 30 °C, 400 MHz) δ 0.81–2.58 (menthyl protons and CH_3CH_2 in propyl, m, 56 H), 3.00, 3.02, 3.12, 3.17, 3.20, 3.98, 4.01, 4.05, 4.07, 4.40, 4.49, and 4.50 ($ArCH_2Ar$, d each, J = 13.1 Hz for 3.00, 3.02, 3.12, 4.40, 4.49, and 4.50, J = 13.4 Hz for 3.17 and 4.05, and J = 14.7 Hz for 3.20, 3.98, and 4.01, 2 H, 1 H, 1 H, 2 H, 2 H, 1 H, 1 H, 1 H, 1 H, 2 H, 1 H, and 1 H), 3.33 (OCH in menthyl, m, 2 H), 3.69 and 3.95 (OCH_2 in propyl, m each, 4 H each), 4.80 and 4.81 (OCH_2Ar, dd, 2 H each), 4.88 and 4.92 (OCH_2CO, dd, 2 H each), 6.35–7.35 (ArH, m, 34 H) (the ^1H NMR spectrum of diastereomeric **11** was very complex but could be assigned basically as duplicate signals of each diastereomer). Anal. Calcd for $C_{53}H_{62}O_6$: C, 80.06; H, 7.86. Found: C, 79.93; H, 7.88.

2,6-Dimethylphenyl (–)-Menthoxyacetate (12). To a THF solution (25 mL) containing 2,6-dimethylphenol (0.47 g, 3.84 mmol) and triethylamine (2.0 mL, 9.88 mmol) was added (–)-menthoxyacetyl chloride dropwise from a microsyringe. The reaction was continued at 0 °C for 12 h. The reaction was stopped by the addition of an aqueous 1 M HCl solution (20 mL). The solution was extracted with chloroform (100 mL).

The organic layer was separated, washed three times with an aqueous NaCl-saturated solution, and dried over $MgSO_4$. After filtration the solution was concentrated to dryness. The residue (yellow oil) was subjected to column chromatography (silica gel, hexane:ethyl acetate = 8:1, v/v): slightly yellow oil, yield 72%; IR (Nujol) ν_{OH} 1750, ν_{COC} 1100, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 250 MHz) δ 0.81–2.3 (methyl protons, m, 18 H), 2.15 ($ArCH_3$, s, 6 H), 3.28 (OCH, 2t, 1 H), 4.42 (OCH_2, 2d, 2 H), 7.05 (ArH, s, 3 H). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.48; H, 9.35.

Optical Resolution. In order to optically resolve racemates, we tested six chiral-packed HPLC columns: Daicel chiralpak OP and AD, Sumitomo Sumipax OA 2000 and OA 3100, Merck Chiraspher, and YMC-Pac KO_3. Among several asymmetrically substituted calix[4]-arenes, we found that Sumipax OA 2000 is useful for optical resolution of $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ (mobile phase, hexane:2-propanol = 98:2, v/v). On the other hand, we could not find any chiral-packed HPLC column suitable for the optical resolution of **10**. We thus converted **10** to the ester derivative with (–)-menthylacetyl chloride, and the resultant diastereomers **11** were isolated by a conventional HPLC method (Zorbax ODS column, 4.5 × 250 mm, three columns in series; mobile phase, methanol).

We divided the eluent into three fractions and recovered one optical isomer from the first fraction and another optical isomer from the third fraction. Optically resolved $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$: from the first fraction, mp 136–137 °C (note that this mp is lower than that for racemic $Pr^{\alpha}Pr^{\alpha}Pyl^{\alpha}H^{\alpha}$ (mp 170–172 °C)), recovery 42%, 100% ee (from HPLC analysis); from the third fraction, mp 130–134 °C, recovery 17%, 99.8% ee (from HPLC analysis). Optically resolved **11**: from the first fraction, mp 138–139 °C, recovery 35%, diastereomeric purity 99.8% (from HPLC analysis); from the third fraction, mp 161–163 °C, recovery 25%, diastereomeric purity 99.0% (from HPLC analysis).

Hydrolysis of Optically Resolved 11 to 10. Optically resolved **11** (30 mg, 0.04 mmol) in THF (25 mL) was treated with aqueous 10% tetramethylammonium hydroxide solution (10 mL) at reflux temperature. The reaction was followed by an HPLC method (Zorbax ODS, chloroform: methanol = 1:5, v/v): the HPLC peak for **11** disappeared after 24 h. After cooling, the solution was neutralized with an aqueous 3 M HCl solution (25 mL). The aqueous solution was extracted with chloroform (50 mL). The organic layer was separated, washed with an aqueous NaCl-saturated solution, and dried over $MgSO_4$. After filtration, the filtrate was evaporated to dryness. Crystallization of the slightly yellow, oily residue from chloroform/methanol gave white crystals: mp 97–99 °C (note that this melting point is lower than that for racemic **10** (mp 138–140 °C)), yield 80%, higher than 99% ee (from ^1H NMR spectroscopy with Pirkle's reagent).

Acknowledgment. This research was supported in part by a grant from the Ministry of Education of Japan. We thank Dr. T. James (JRDC, Chemirecognics Project) for helpful discussions.