Synthetic Strategies to Inherently Chiral Calix[4]arenes with Mixed Ligating Functionalities at the Lower Rim

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The syntheses of 19 atropisomeric inherently chiral calix[4]arenes derived from *syn-proximal* (1,2)-bis[(2-pyridylmethyl)oxy]calix[4]arene **2** and mixed *syn-distal* (1,3)-[(2-pyridylmethyl)oxy][(2-quinolylmethyl)oxy]calix[4]arene **6** are described. Treatment of **2** with 1 equiv of electrophile RX in DMF in the presence of Cs_2CO_3 afforded racemic tri-O-alkylated cone conformers **3a–k** ($A^\alpha A^\alpha B^\alpha C^\alpha$ type), while with an excess of alkylating agent under analogous conditions the chiral tetra-O-alkylated partial cone conformers **4a-d** ($A^\alpha A^\alpha B^\alpha B^\beta$ type) were formed. Similarly, exhaustive alkylation of **6** with either PicCl·HCl or QuinCl·HCl gave the chiral partial cone derivatives **7a,b** ($A^\alpha A^\alpha A^\beta B^\alpha$ type), respectively. Further alkylation of **3i** (R = benzyl) with PicCl·HCl and Cs_2CO_3 provided partial cone derivative **7c** ($A^\alpha A^\alpha A^\beta B^\alpha$ type), while with PrBr and NaH cone tetraether **8** ($A^\alpha A^\alpha B^\alpha C^\alpha$ type) was obtained. Proton and carbon NMR spectral features of these compounds are discussed. Atropisomerism in tri-O-alkylated calix[4]arenes was demonstrated by dynamic NMR studies on the less encumbered allyl derivative **3a**, which showed no hint for conformational inversion up to 375 K. 2D COSY spectra clearly show that in partial cone structures **4d** and **7a–c** the *N*-heteroaryl pendant group of the rotated aryl moiety lies in, and effectively fills, the calix cavity produced by the remaining three aryl rings. The structure of the trisubstituted racemic calix[4]arene **3i** has been determined by X-ray crystallography. The molecule adopts a distorted cone conformation with the two pendant pyridinyl groups in the *syn*-proximal arrangement on one side of the pendant benzyl moiety. There is an intramolecular O–H···O hydrogen bond between the phenolic oxygen OD and the proximal ethereal oxygen OA (to which is bonded the benzyl residue) with O···O 2.85 Å.

Introduction

Calixarenes are cavity-containing macrocyclic compounds, which are currently enjoying considerable interest in the field of supramolecular chemistry as useful building blocks for the design of selective cation receptors and carriers.[1] The architecture of calixarenes may also allow the buildup of totally synthetic enzyme mimics endowed with a chiral cavity (for the purpose of chiral recognition) as well as potential binding functionalities. Most of the synthetic efforts toward chiral calixarenes have been carried out on the smallest members of this family, i.e., calix[4]arenes, whose chemistry has been disclosed in recent years. General procedures have been developed for regio-[2] and stereoselective[3] functionalizations at the lower rim, and this basic knowledge is being skilfully applied for the production of chiral calix[4]arenes.

Although chiral derivatives can be obtained by simply attaching chiral residues at the upper[4] or lower[5] rim of the calixarene skeleton, recent interest has been focused on the possibility of synthesizing "inherently" chiral calix[4]arenes, which are built up of nonchiral subunits and consequently owe their chirality to the fact that the calixarene molecule is not planar.

Two strategies have been used for the preparation of inherently chiral calix[4]arenes: (i) the fragment condensation and (ii) lower-rim functionalization of a preformed calix[4]arene. The first one is based on the convergent stepwise synthesis of asymmetric calixarenes having three or four different phenolic units.[6,7] Although in principle versatile, the fragment condensation procedure

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(1) For comprehensive reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.

(2) For regioselective 1,2-functionalization of calix[4]arenes at the lower rim by direct substitution, or by protection–deprotection methods, see, for example: (a) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407. (b) van Loon, J.-D.; Kraft, D.; Ankoné, M. J. K.; Verboom, W.; Harkema, S.; Vogt, K.; Böhmer, V.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5176. (c) Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597. (d) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675. (e) See, K. A.; Fronczek, F. R.; Watson, W: H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256. (f) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325. (g) Brunink, J. A. J.; Verboom, W.; Engbersen, J. F. J.; Harkema, S.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 511.

(3) For the factors affecting the conformational outcome during the lower-rim functionalization of calix[4]arenes, see, for example: (a) Iqbal, M.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, *43*, 4917. (b) Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. *Tetrahedron Lett.* **1990**, *31*, 7169; **1991**, *32*, 830 (corrigendum). (c) Gutsche, C: D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783. (d) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (e) Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611. (f) Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, *57*, 7066.

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(6) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896. Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

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is plagued by serious synthetic problems (several steps with low overall yields). Furthermore, the resulting chiral calixarenes with free hydroxyl groups are incapable of resolution into their enantiomers because of cone-to-cone racemization ($\Delta G^{\ddagger}$ = 13–14 kcal/mol).[1] Therefore, it becomes necessary to further functionalize the phenolic OH groups by the introduction of bulky substituents (larger than ethyl groups)[3d,8] to suppress the oxygen-through-the-annulus conformational inversion. Very often asymmetry creates problems during the derivation step, leading to a mixture of conformational isomers difficult to separate.[9] Better results have been recently obtained from the lower rim derivatization of calix[4]arenes consisting of two different phenolic units in the order AABB[10] and of dissymmetric calix[4]arenes with C_2 or C_4 symmetry.[11]

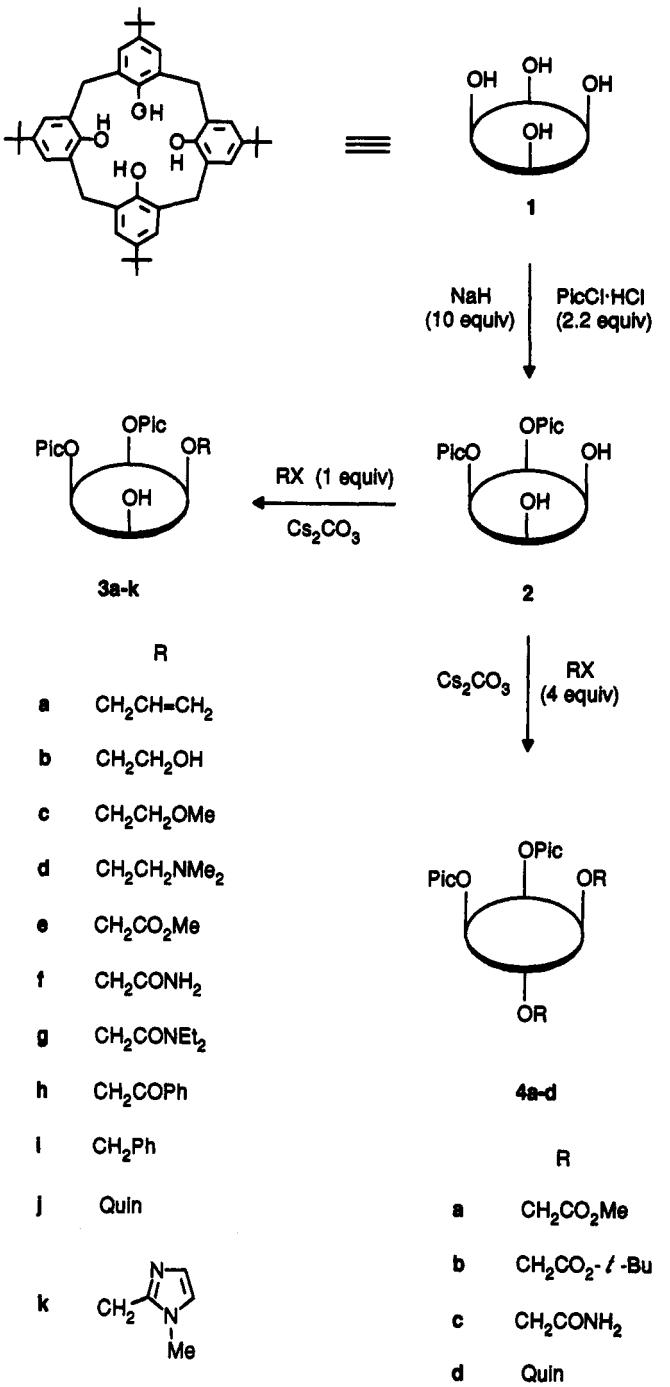
The second strategy is based on the regio- and stereoselective functionalization of conventional calixarenes at the lower rim; i.e., molecular asymmetry is introduced after the macrocyclization step. This methodology is more attractive for practical reasons: the parent *tert*-butylcalix[4]arene can be prepared in a large scale by a well-established procedure[12] and can be selectively functionalized in different ways to generate intrinsic chirality. This can arise from the substitution pattern at the lower rim and/or conformation. In this respect, Shinkai has recently reported a systematic classification of all possible chiral isomers derivable from calix[4]arene and delineated some basic concepts for the design and synthesis of chiral calix[4]arenes.[13]

In a preliminary paper we have shown that *syn-proximal* disubstituted calix[4]arenes are a useful achiral source to inherently chiral derivatives.[14] As an extension of these studies, in this paper we wish to report the synthesis and structural characterization of a number of atropisomeric inherently chiral calix[4]arenes derived from readily available *syn-proximal* 5,11,17,23-tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-dihydroxycalix[4]-arene (**2**) and *syn-distal* 5,11,17,23-tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-27-[(2-quinolylmethyl)oxy]-26,28-dihydroxycalix[4]arene (**6**). The *N*-[(heteroaryl)methyl] pendant groups were chosen because of their well-known proclivity to form transition metal complexes. The enantiomeric resolution of most of the chiral derivatives here described has been reported elsewhere.[15]

Results and Discussion

Syntheses. (a) Chiral Tri-O-alkylated Calix[4]-arenes. We have described the first examples of regioselective *syn-proximal* difunctionalization of calix[4]-arenes,[2a] and Reinhoudt and his co-workers have demonstrated that 1,2-di-O-alkylated calix[4]arenes are general intermediates in the NaH/DMF tetra-O-alkylation of calix[4]arenes.[2d] By a slight modification of our original procedure, pivotal compound **2** can be now obtained in 85–90% yield by direct alkylation of **1** with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl, 2.2 equiv) in anhydrous DMF in the presence of NaH (10 equiv) (Scheme I). The NMR spectra of **2** are commensurate with a fixed cone conformation, which has been confirmed by a single crystal X-ray analysis.[16] Moreover, MM2 calculations on the monophenoxide anion generated from **2** have shown that the cone conformation is further

Scheme I



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(14) Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747.

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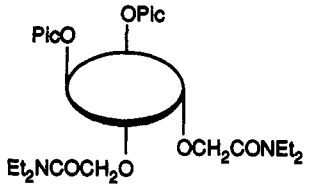
stabilized by a very favorable hydrogen bonding of the phenolate moiety with the adjacent OH group (OH···O distance ca. 2.3 Å).[3e] It turned out that (1,2)-di-O-alkykated calix[4]arenes are ideal precursors of tri-O-alkylated derivatives in a predetermined fixed cone conformation. If in particular the incoming substituent is different from those preexisting, *asymmetry can be introduced at the lower rim leading to inherently chiral structures of $A^{\alpha}A^{\alpha}B^{\alpha}C^{\alpha}$ type*[17] *in only two steps*, starting from the parent calix[4]arenes. Thus, when **2** was treated with an electrophile RX (1 equiv) in anhydrous DMF in the presence of Cs_2CO_3 (1 equiv) at 60 °C for a few hours, racemic calix[4]arenes **3a–k** were obtained in 42–93% yield (Scheme I) with excellent stereoselectivity.[18] In the case of the reaction with 2-bromoethanol, the yield of triether **3b** (8%) is considerably reduced owing to the consumption of the alkylating agent with formation of gaseous ethylene oxide, which escapes under the reaction conditions.

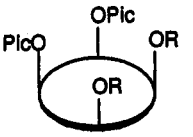
As previously observed,[3e] the conformational outcome of this reaction is not affected by metal template effects, but rather is determined by the strong hydrogen bonding stabilization of the phenolate intermediate in the cone conformation. The reaction appears to be general, as demonstrated by the wide variety of binding functionalities (including alkenic, alcoholic, ether, amino, ester, amide, *N,N*-dialkylamide, keto, aromatic, and *N*-heteroaromatic groups) which can be easily introduced at the lower rim *via* ether formation. The yields of tri-O-alkylated products with the quite reactive α-[(halomethyl)-carbonyl] reagents are curtailed by the concomitant formation (5–10%) of tetra-O-alkylated partial cone racemates, such as **4a** and **4c** (see below). In the reaction of **2** with 2-chloro-*N,N*-diethylacetamide, a trace amount (1–2%) of a byproduct was also isolated, which was identified as the achiral tetra-O-alkylated 1,2-alternate conformer **3ga** on the basis of distinctive ^1H and ^{13}C NMR spectral patterns (see Experimental Section).



3ga

The first chiral calix[4]arene possessing a sequence of substituents $A^{\alpha}A^{\alpha}B^{\alpha}C^{\alpha}$ at the lower rim, 5,11,17,23-tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-26,27-dipropoxy-28-hydroxycalix[4]arene, was obtained by Shinkai using a different strategy, i.e., a $BaO/Ba(OH)_2$-assisted bis-O-propylation of monopyridinocalix[4]arene **5**.[13,19]

(b) Chiral Tetra-O-alkylated Calix[4]arenes. Previous studies on the origin of stereoisomerism in [(2-pyridylmethyl)oxy]calix[4]arenes have shown that metal template effects play a major role in determining the conformational outcome of the product(s) of the base-catalyzed exhaustive alkylation of (1,2)-difunctionalized intermediates: Na^+ cation in the base employed induces only cone conformers, while the larger Cs^+ cation leads selectively to the partial cone conformers.[3e] Since these derivatizations proceed through the intermediacy of *syn*-tri-O-alkylated cone conformers, Cs^+ cation facilitates the inversion of the phenoxy group in the last alkylation step. These findings apply well for the production of calixarene derivatives with mixed ligating functional groups at the lower rim that are achiral if they assume the cone conformation (presence of a symmetry plane) but inherently chiral if in the partial cone conformation (absence of symmetry elements). Accordingly, treatment of **2** with the appropriate electrophile RX (4 equiv) in anhydrous DMF in the presence of Cs_2CO_3 at 60 °C for 20 h afforded racemic partial cone calix[4]arene derivatives **4a–d** in 25–60% yield, as shown in Scheme I. The reaction of **2** with methyl bromoacetate produced also the achiral cone conformer **4aa** (28%).



R = CH_2CO_2Me

4aa

When calix[4]arene adopts a cone conformation, the molecular asymmetry is realized with a minimum of three different substituents including the OH group. In the case of partial cone conformers, chirality can be generated with a minimum of two different substituents at the lower rim in the sequence $A^{\alpha}A^{\alpha}B^{\alpha}B^{\beta}$ (as in **4a–d**) or $A^{\alpha}A^{\alpha}A^{\beta}B^{\alpha}$. The syntheses of partial cone calix[4]arenes **7a–c** provide examples of chiral products of the latter type.

Treatment of [(2-pyridylmethyl)oxy]calix[4]arene **5**[2a,3e,13] with 2-(chloromethyl)quinoline hydrochloride (QuinCl·HCl, 2 equiv) in anhydrous DMF in the presence of K_2CO_3 (2 equiv) gave mixed *syn-distal* di-O-alkylated calix[4]arene **6** in 70% yield (Scheme II). The cone conformation of **6** is corroborated by a pair of AB systems for the bridging methylene protons and by two resonances for oxymethylene carbons at 78.14 and 78.79 ppm (resonances around 77 ppm for OCH_2-*N*-heteroaromatic groups are considered of diagnostic value for a cone conformation).[3e] Compound **6** was then reacted with either PicCl·HCl or QuinCl·HCl (15 equiv) in anhydrous DMF in the presence of Cs_2CO_3 (large excess) at 60 °C for 48 h to give **7a** (35%) and **7b** (28%), respectively (Scheme II). The lower reactivity of **6** as compared to **2** is suggestive of a flattened cone conformation for **6**, with the 1,3-dialkylated rings lying on parallel planes and the two free OH groups hidden into the calix[4]arene annulus.

Compound **7c** was obtained in 75% yield by treating **3i** with PicCl·HCl (4 equiv) in the presence of Cs_2CO_3 (8 equiv) as illustrated in Scheme III. The reaction produced also a small amount of the achiral cone conformer **7ca** (10%).

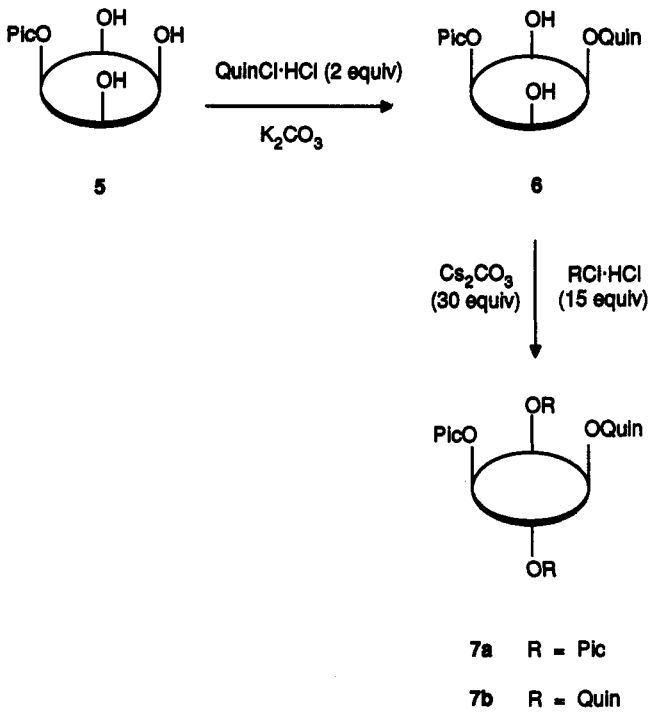
NMR Spectral Features. (a) Chiral Tri-O-alkylated Cone Conformers. The complete absence of symmetry elements in triethers **3a–k** is reflected by their

(17) Notations α and β, introduced by Shinkai[2f,3f,13] to define the stereochemistry of calix[4]arene atropisomers having mixed substituents at the lower rim, are used throughout the text.

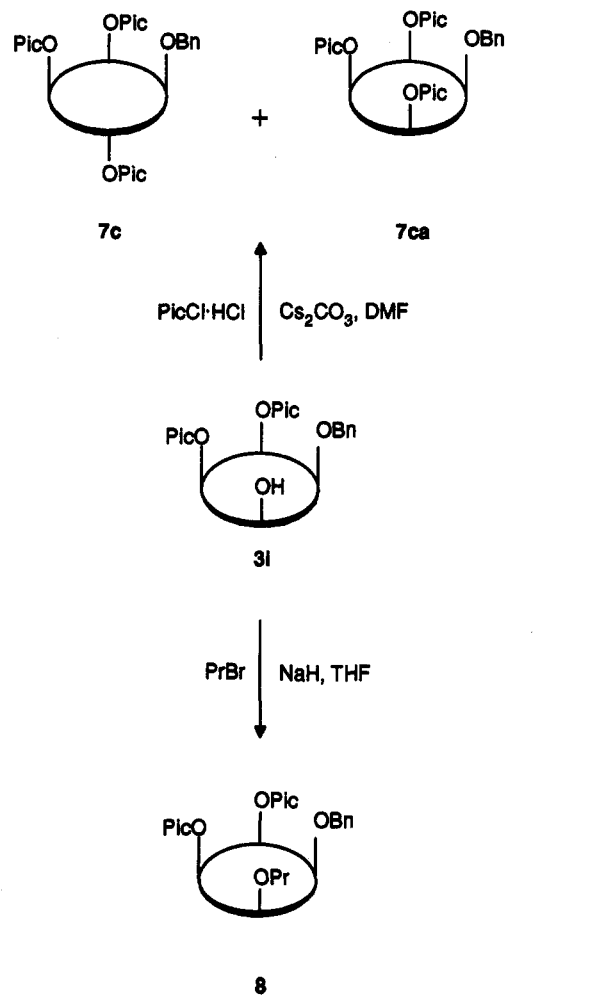
(18) No tri-O-alkylated partial cone conformers, notoriously less polar than the cone ones, could be detected by TLC analysis of the reaction mixture.

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

Scheme II



Scheme III



remarkably complex ^1H and ^{13}C NMR spectra, which display characteristic line patterns for the chiral calix[4]arene skeleton and the groups attached to it, spread out in the aromatic, methylene, and *tert*-butyl regions.

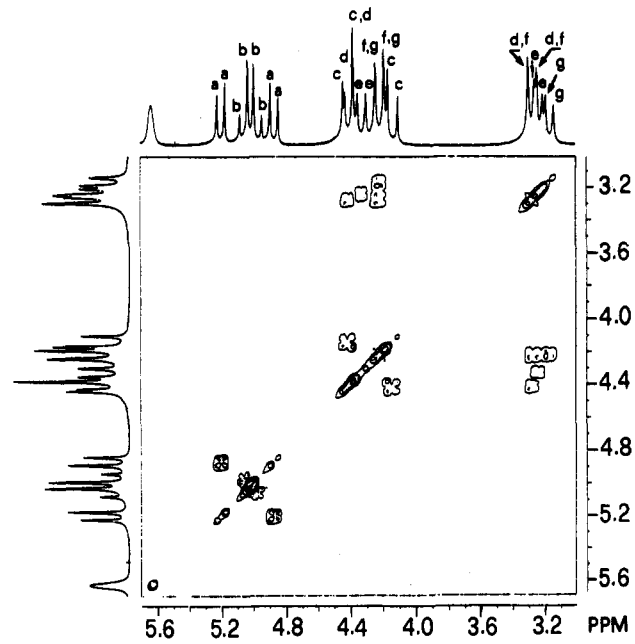


Figure 1. Methylene region of the COSY spectrum (250 MHz, $CDCl_3$, 295 K) of the trialkylated cone amide **3f**. Letters a–c refer to the three OCH_2 AB systems and letters d–g to those of the four $ArCH_2Ar$ groups.

The methylene and oxymethylene region is the more informative and diagnostic for conformational assignments, and a 28-line pattern arising from seven AB quartets is expected. This theoretical situation is always unsatisfied because overlapping of signals invariably occurred, giving less lines than those expected. To cope with the NMR analysis, in some cases we resorted to 2D COSY NMR spectra for attributions. For example, amide **3f** displays a 23-line pattern in this region, which is analyzed in terms of seven partly superimposed AB systems, as substantiated by appropriate cross-peak correlations in the COSY spectrum shown in Figure 1. The broad singlet at 5.53 ppm is correlated to another broad singlet at 8.25 ppm (not shown) and therefore assigned to amidic NH protons.

By analogy with the ^1H NMR spectra, the ^{13}C NMR spectra also show a high degree of complexity arising from the molecular asymmetry. However, due to the higher dispersion of the ^{13}C compared with the ^1H scale, the number of observed resonances is often very close to that expected. A typical example is reported in Figure 2, showing *inter alia* the characteristic eight-line pattern for bridgehead C_{sp2} carbons in the range 127–136 ppm.

The cone conformation of **3a–k** is corroborated by a chemical shift difference ($\Delta\delta$) of 1.10 ± 0.15 ppm between the four CH_{exo} and CH_{endo} pairs of resonances (J = 12.8 ± 0.8 Hz) arising from the bridging methylene protons.[20] Further confirmation was provided by a pattern of four resonances for the pertinent carbon atoms in the range 31.1 ± 0.8 ppm, in fairly good agreement with the single rule proposed by de Mendoza for the determination of calix[4]arene conformations.[21] Only in a few cases was one of the $ArCH_2Ar$ signals obscured by one of the *tert*-butyl peaks.

Chiral triethers **3a–k** in principle may undergo conformational inversion by rotation of the residual unalky-

(20) See ref 1a, p 111.
(21) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

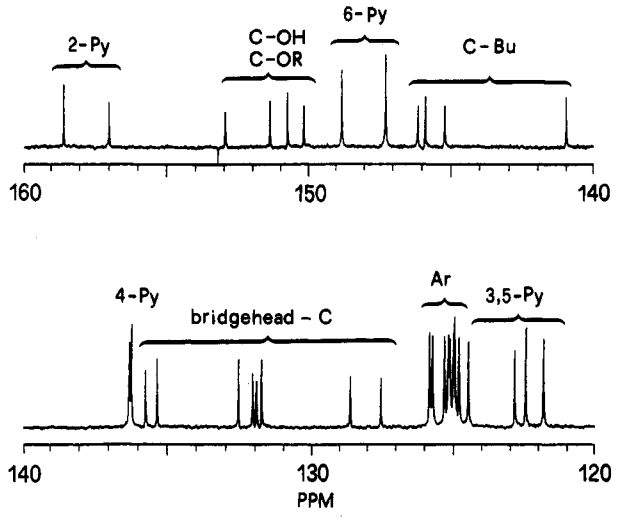


Figure 2. Aromatic region and relative assignments of the broad-band decoupled ^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, 295 K) of compound **3c**, showing the expected 34-line pattern.

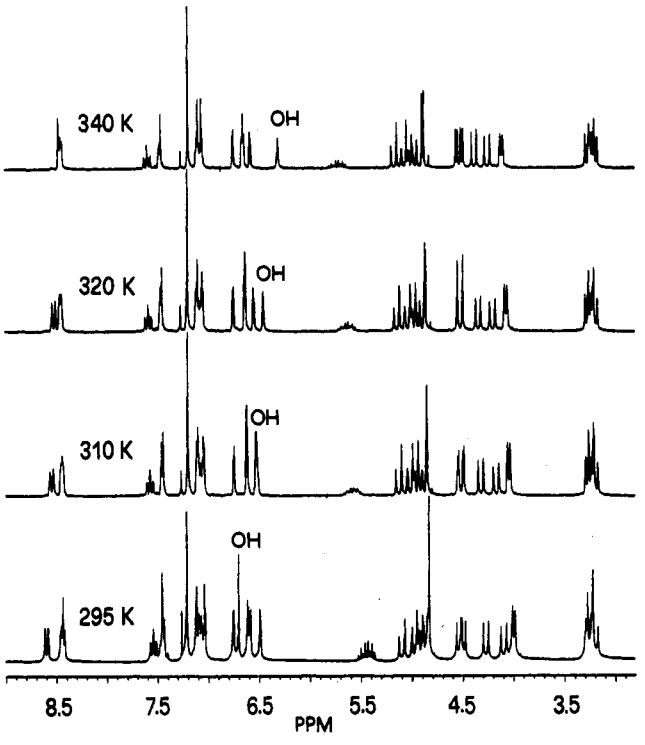


Figure 3. ^1H NMR spectra (250 MHz, $CDCl_3$) of cone allyl derivative **3a** at relevant temperatures.

lated ring around the C_2–C_6 axis. A VT-NMR study of the less encumbered allyl derivative **3a**, conducted in three different solvents ($CDCl_3$, DMSO-d_6, and $C_6D_5NO_2$) in the temperature range 295–375 K, allowed us to exclude for compounds **3a–k** the oxygen-through-the-annulus rotation of the free OH group. As a matter of fact, a ^{13}C NMR spectrum of **3a** in $C_6D_5NO_2$ at 370 K confirmed the absence of resonances around 38 ppm for the bridging methylene carbons, considered of diagnostic value for an inverted phenyl ring.[21] However, the ^1H NMR spectra of **3a** on heating show some spectral changes in the aromatic and methylene region as shown in Figure 3. These are believed to be associated with the weakening of the hydrogen bond between the OH group and the adjacent oxymethylene group(s) (with a pseudocoalescence tem-

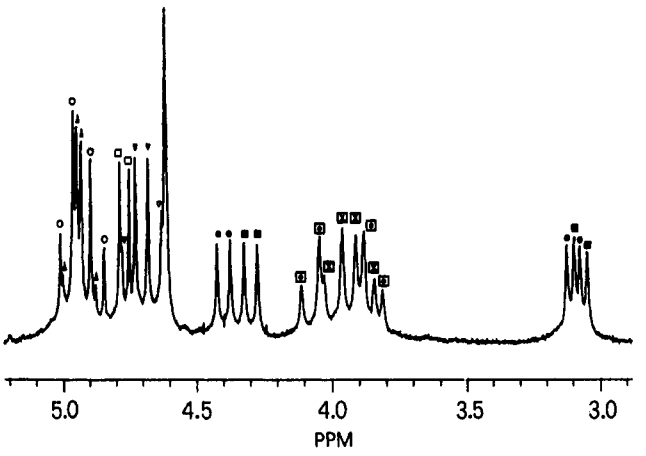


Figure 4. ^1H NMR spectral patterns (250 MHz) of OCH_2 and $ArCH_2Ar$ groups in the methylene region of tetraalkylated partial cone **7b**.

perature around 315 K) as suggested by the significant upfield shift experienced by the OH resonance over 320 K.

(b) Chiral Tetra-O-alkylated Partial Cone Conformers. Compounds **4a–d** and **7a–c** present distinctive ^1H NMR spectral patterns for methylene and oxymethylene protons. Usually the $ArCH_2Ar$ groups show up as four different AB systems, whereas the OCH_2 groups appear as three AB systems and a singlet attributed (on the basis of chemical shift considerations and COSY correlations) to the oxymethylene protons of the inverted aryloxy moiety, as shown in Figure 4. As in the case of trialkylated derivatives, in some instances the superimposition of signals reduced the number of the resonance lines. In compounds **4b** and **7a** the number of lines is further reduced by the accidental isochrony of two *exo*-C*H* protons.

The partial cone conformation of these derivatives can be easily inferred from the chemical shift difference between the four pairs of pertinent geminal protons. In other words, for methylene groups linking alkylated phenol rings in a *syn* orientation the $\Delta\delta$ is around 1 ppm (with geminal couplings in the range 12.1 to 12.8 Hz), while in the *anti* disposition this value decreases dramatically to 0.1–0.2 ppm,[20] with geminal couplings ranging from 14.1 to 17.5 Hz. The partial cone conformation for these compounds was confirmed by the ^{13}C NMR spectra, which showed appropriate resonance values for methylene and oxymethylene carbons.

A scrutiny of the COSY spectra (typified in Figure 5 by the spectrum of **4d**), while confirming the assignments made, revealed for **4d** and **7a–c** the presence in the oxymethylene region of an additional doublet which correlates with 4-QuinH (compounds **4d** and **7b**) or 4-PyH (compounds **7a** and **7c**), and therefore assigned to the 3-positioned *N*-heteroaryl protons of the substituents attached to the inverted phenol unit. The remarkable upfield shift experienced by the H-3 proton of the inverted *N*-heteroaromatic residue strongly suggests for these compounds a particular conformation in solution, as shown in Figure 6. As confirmed by MM2 calculations, the inverted pyridine or quinoline unit is tightly accommodated inside the hydrophobic cavity generated by the remaining three aryl moieties, in a sort of self-inclusion complex. The ring nitrogen is oriented outward to the cavity, whereas the H-3 is subjected to the ring current

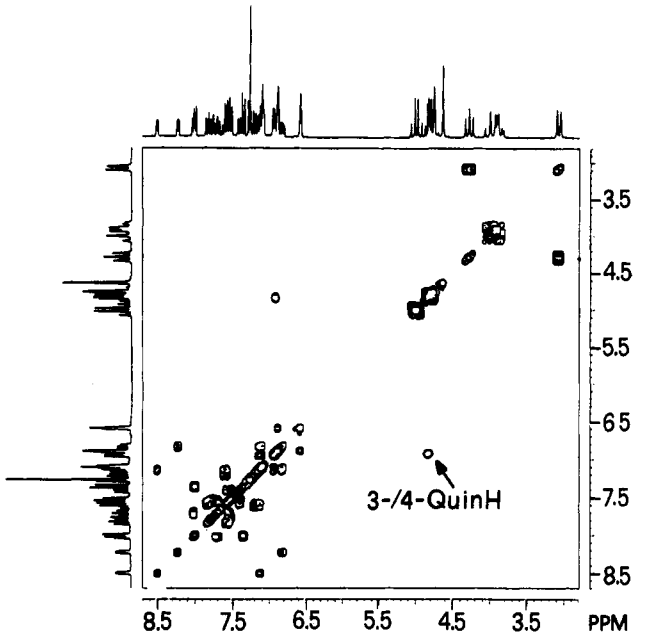


Figure 5. The 3.0–8.5 ppm region in the COSY spectrum (250 MHz) of partial cone **4d** showing the correlation between H-4 and the strongly shielded H-3 of the inverted quinoline moiety.

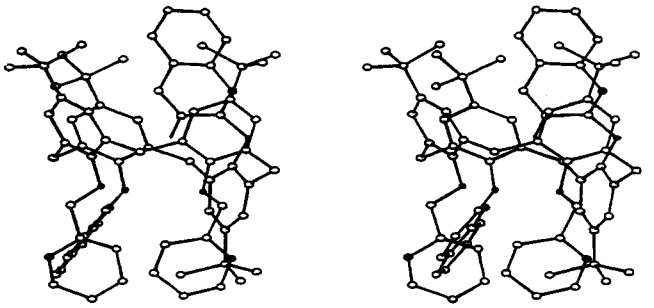


Figure 6. Stereopairs of the MM2 minimum energy conformation of partial cone **4d**. With the exception of the shielded 3-QuinH, H atoms are omitted for clarity. The filled spheres refer to heteroatoms.

shielding effect from the two flanking aryl units. MM2 results indicate that the inward orientation of the N atom is quite less stable (ca. 4 kcal/mol). This self-inclusion phenomenon has been previously observed in both the solid state and solution for the achiral partial cone *p-tert*-butyltetrakis[(2-pyridylmethyl)oxy]calix[4]arene.[3e]

Enantiomeric Resolution. Apart from NMR spectral patterns showing molecular asymmetry, evidence of chirality for cone **3a–k** and partial cone **4a–d** and **7a–c** was provided by the addition of Pirkle's reagent (*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol to a $CDCl_3$ solution of each calixarene, which caused doubling of (in principle) all signals. However, the complexity of such spectra in most cases may not allow the observation of all different signals separately. The split pattern for the "clean" *tert*-butyl region of compounds **4a** and **4d** is shown in Figure 7. No splitting was observed if the chiral Eu(dcm)$_3$ shift reagent was used.

The direct HPLC separation of most chiral tri-O-alkylated calix[4]arenes here described has been achieved using Chiralcel OD phase,[15] while it was ineffective for partial cone tetra-O-alkylated products. Nevertheless, compound **4d** could be separated into its enantiomers by using a Chiralpak OP(+) HPLC column.[14] Sufficient amounts of each pair of enantiomers from racemic **3i** and

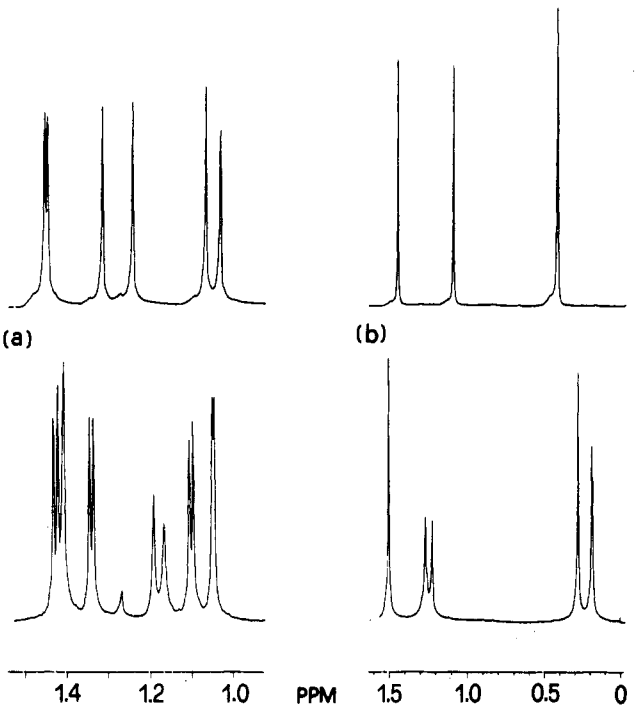


Figure 7. Section of the ^{1}H NMR spectra (250 MHz) of (a) **4a** and (b) **4d** in the absence (top) or in the presence (bottom) of (*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol.

4d could be obtained to qualitatively measure their CD spectra. These are almost mirror images of each other, indicating that the eluates from the two chromatographic peaks are optical isomers.

Among the various factors influencing enantioselection, hydrogen bonding between the residual hydroxyl group of tri-O-alkylated compounds and the Chiralcel OD phase seems to play an important part. As a matter of fact, the separation factor of compound **3i** ($\alpha = 3.45$ under optimum conditions) dramatically drops to 1.24 when the OH group is replaced by a propoxy group, as in **8**. Calix[4]arene **8** was obtained in 80% yield by subjecting **3i** to propyl bromide in THF in the presence of NaH, as shown in Scheme III.

X-ray Structural Analysis. Although the crystal of **3i** diffracted relatively poorly (see Experimental Section), we were able to obtain sufficient data to allow us to determine the details of its conformation unequivocally. The calixarene **3i** adopts a distorted cone conformation in the solid state (Figure 8), and the major conformation determining feature in this molecule is the presence of an intramolecular O–H···O hydrogen bond between the phenolic OH group and the proximal ethereal oxygen to which is bonded the benzyl group; the hydroxyl H atom could not be located but the O1D···O1A distance [2.85(1) Å] is clearly consistent with an O–H···O hydrogen bond. The other proximal ethereal oxygen O1C is 3.32(1) Å from O1D. The conformation of **3i** is defined by the angles which the aromatic rings make with the plane of the four methylene carbon atoms which link them, viz. 98.5(4)° (A), 131.0(4)° (B), 85.5(4)° (C), and 152.1(4)° (D) (interplanar angles >90° indicate that the aromatic ring system is tilted so that its *tert*-butyl group is directed *away from* the ring cavity; angles <90° indicate that these groups are directed *in toward* the cavity). Two opposite rings (A and C) are almost parallel to one another [interplanar angle 4.1(5)°], ring A tilted so that its *tert*-butyl group is pitched slightly away from the calix cavity, ring C tilted so that its *tert*-

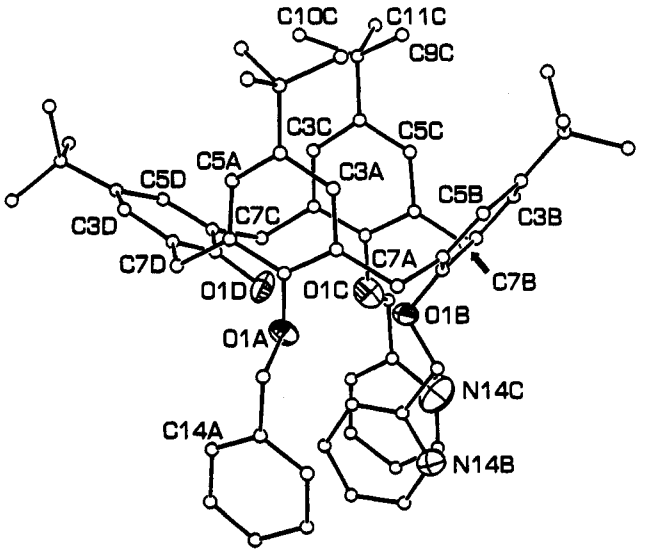


Figure 8. View of the calix[4]arene **3i** with our labeling scheme. For clarity, only the major orientation of the disordered pyridinyl ring C is shown, the carbon atoms are drawn as small spheres of an arbitrary size, and the hydrogen atoms are omitted. The oxygen and nitrogen atoms are depicted with their thermal ellipsoids at the 35% level.

butyl group is pitched slightly toward the cavity. The pyridinyl-substituted ring B and phenolic ring D are almost normal to one another [interplanar angle 103.2(5)°], both rings B and D being tilted so that their *tert*-butyl groups are pitched well away from the calix cavity. This conformation leads to O···O separations between O1A and O1C across the calixarene cavity of 5.31(1) and 3.44(1) Å between O1B and O1D. The other O···O separations between the ethereal oxygen O1B and the adjacent oxygens O1A, O1C are 3.17(1) and 3.40(1) Å. The conformation thus adopted by **3i** effectively precludes a solvent molecule being enclathrated in the cavity, due to the close approach of the *tert*-butyl groups on the aromatic rings A and C.

The benzyl and two pyridinyl ring systems attached to the ethereal oxygen atoms O1A, O1B, and O1C are at angles of 102.7(5) (A*), 99.3(4) (B*), and 92.6(6) (C*) to the plane defined by the four methylene carbon atoms (C7A, C7B, C7C, C7D); i.e., these aromatic groups are almost normal to this plane; the interplanar angles between A*, B* and C* are less than 11° indicating that they are also almost parallel to one another (Figure 8).

The conformation adopted by **3i** is broadly similar to that reported for the tetra-*tert*-butyltetrakis[(2-pyridylmethyl)oxy]calix[4]arene (cone conformer),[3e] where three of the pendant pyridinyl groups are oriented in a fashion similar to that found in **3i**. The two pendant pyridinyl groups of **2** in the solid state[16] are also oriented in a fashion similar to those in **3i**; the two pendant $-CH_2$-Py groups are oriented at an interplanar angle of 21.3(3)° to one another and at angles of 66.0(3)° and 87.3(3)° to the plane through the calixarene methylene carbon atoms.

In the crystal lattice of molecule **3i**, the molecules pack in double layers which have the phenyl and pyridinyl rings adjacent; this results in sheets of *tert*-butyl carbon atoms being on the face of each double layer. This can be viewed in Figure 9 and corresponds to a molecular "zipper". This has been previously observed in the structure of the *N,N'*-dimethylenediamine derivative of a 1,3-distally substituted calix[4]arene.[22]

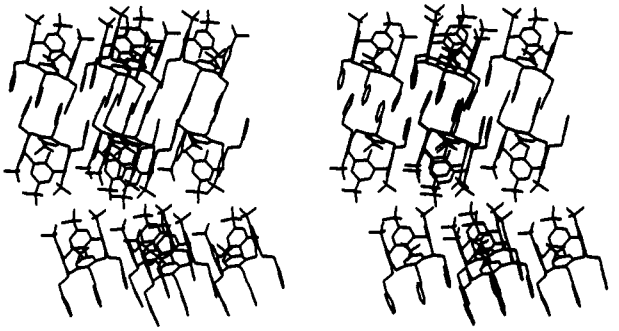


Figure 9. Stereoview of the molecular stacking showing the double layers which have the phenyl and pyridinyl rings adjacent.

Conclusions

This paper demonstrates the utility of readily available *syn-proximal* **2** and mixed *syn-distal* **6** for the production of atropisomeric inherently chiral calix[4]arenes endowed with mixed ligating functionalities at the lower rim in one step. The synthetic strategies applied take advantage of hydrogen bonding stabilization of the involved phenolate anion intermediates (trialkylated cone conformers) and of the control by the base used on the conformational outcome of the exhaustive alkylation process (tetraalkylated partial cone structures). Most racemates may be optically resolved by enantioselective HPLC, but in order to pursue further studies larger quantities of the pure enantiomers are desirable. Therefore, future studies will be directed toward the chemical resolution of tri-O-alkylated racemates by converting them into diastereomers upon further alkylation with suitable optically active derivatizing agents.

Experimental Section

General Comments. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were taken on a Bruker AC-250 or Varian Gemini spectrometers for $CDCl_3$ solutions using Me_4Si as an internal standard. Multiplicities in ^{13}C NMR spectra were obtained by DEPT experiments. EIMS were recorded on a Kratos MS 50 double-focusing mass spectrometer, operating at 18 eV. All chemicals were reagent grade and were used without further purification. (Anhydrous DMF and THF were purchased from Fluka). *p-tert*-Butylcalix[4]arene-toluene 1:1 complex (**1**)[12] and 2-(chloromethyl)-*N*-methylimidazole hydrochloride[23] were prepared by literature procedures. All reactions were carried out under N_2. MM2 molecular mechanics calculations were performed using the MacroModel V2.5 program as previously described.[3e]

***Syn-Proximal* 5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-dihydroxycalix[4]arene (2).** A mixture of **1** (0.74 g, 1 mmol) and NaH (0.24 g, 10 mmol) in anhydrous DMF (20 mL) was allowed to stir at rt for 5 h. Solid PicCl·HCl (0.36 g, 2.2 mmol) was then added, and the mixture was heated at 60 °C for 2 h. Addition of MeOH (2 mL) followed by dilution with water gave a precipitate, which was collected by filtration and dried. The solid was dissolved in $CHCl_3$ and passed through a short SiO_2 column (eluent cyclohexane–AcOEt (3:1)). Evaporation of the solvent, followed by recrystallization from MeOH, gave colorless crystals (0.7 g, 85%), identical in all respects with an authentic sample of **2**.[3e]

Chiral Tri-O-alkylated Calix[4]arenes, Cone Conformers. General Procedure. A stirred mixture of **2** (0.25 g, 0.3 mmol),

(22) Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Phillips, J.; Williams, G. J. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1521.

(23) Jocelyn, P. C. *J. Chem. Soc.* **1957**,3305.

the alkylating agent (0.3 mmol), and Cs_2CO_3 (0.98 g, 0.3 mmol) in dry DMF (10 mL) was heated at 60 °C for 2.5–4 h. Progress of the reaction was followed by monitoring the disappearance of 2 on TLC (SiO_2, cyclohexane–AcOEt (2:1)). The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2 (DCM). The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed (column, SiO_2) by eluting with a gradient of AcOEt in *n*-hexane to afford the desired triether. For the polar derivatives **3d**, **3f**, and **3g** chromatographic purification was performed on neutral alumina, while compds **3a**, **3i**, and **3j** were obtained in a pure form by direct recrystallization of the crude reaction product from the appropriate solvent.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-(allyloxy)-28-hydroxycalix[4]arene (3a). Reaction of 2 with allyl bromide (1 equiv) according to the general procedure gave racemic triether **3a** in 67% yield: mp 199–200 °C (MeOH); ^{1}H NMR δ 0.78, 0.91, 1.33, 1.36 [s, C(CH_3)$_3$, 9 H each], 3.19 (d, *J* = 12.9 Hz, ArCH_2Ar, 1 H), 3.24 (d, *J* = 13.1 Hz, ArCH_2Ar, 2 H), 3.26 (d, *J* = 13.6 Hz, ArCH_2Ar, 1 H), 3.99 (d, *J* = 5.5 Hz, OCH_2CH=CH_2, 2 H), 4.09 (d, *J* = 13.6 Hz, ArCH_2Ar, 1 H), 4.27 (d, *J* = 12.4 Hz, ArCH_2Ar, 1 H), 4.51 (t, *J* = 11.9 Hz, ArCH_2Ar, 2 H), 4.8–5.1 (m, OCH_2Py and OCH_2CH=CH_2, 6 H), 5.44 (m, OCH_2C*H*=CH_2, 1H), 6.49, 6.58, 6.61 (d, *J* = 2.3 Hz, ArH, 1 H each), 6.70 (s, OH, 1H), 6,75, 7.03 (d, *J* = 2.3 Hz, ArH, 1 H each), 7.07 (m, 5-PyH + 5-Py′H, 2 H), 7.11 (d, *J* = 2.1 Hz, ArH, 1 H), 7.20 (s, ArH, 2 H), 7.43 (m, 3-PyH + 4-Py′H, 2 H), 7.54 (td, *J* = 7.6, 1.6Hz, 4-PyH, 1 H), 8.42, 8.44 (d, *J* = 4.5 Hz, 6-PyH + 6-Py′H, 1 H each), and 8.60 (d, *J* = 8.1 Hz, 3-PyH, 1 H); ^{13}C NMR δ 30.62, 31.09, 31.77, 31.97 (t, ArCH_2Ar), 31.01, 31.68, 31.73 [q, C(*C*H_3)$_3$], 33.64, 33.80, 34.16 (s, *C*(CH_3)$_3$], 76.98, 77.25, 78.57 (t, OCH_2), 117.98 (t, OCH_2CH=*C*H_2), 121.86, 122.47, 122.83, 124.56, 124.68, 124.91, 125.22, 125.45, 125.70, 125.85 (d), 127.12, 128.99, 131.60, 131.95, 132.22, 132.80, 135.22, 135.76 (s, bridgehead-C), 133.38 (d, OCH_2C*H*=CH_2), 136.25, 136.50 (4-Py and 4-Py′), 141.12, 145.17, 146.08, 146.16 (s), 147.15, 148.81 (d, 6-Py and 6-Py′), 149.93, 150.74, 151.54, 152.95 (s), 157.14 and 158.23 (s, 2-Py and 2-Py′); MS *m/z* 870 (M^+, 100). Anal. Calcd for $C_{59}H_{70}N_2O_4$: C, 81.34; H, 8.10; N, 3.22. Found: C, 81.21; H, 8.46; N, 3.37.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[(2-hydroxy ethyl)oxy]-28-hydroxycalix[4]arene (3b). Reaction of 2 with 2-bromoethanol (1 equiv) under standard conditions afforded triether **3b** in 8% yield: mp 240–243 °C; ^{1}H NMR δ 0.89, 0.93, 1.25, 1.27 [s, C(CH_3)$_3$, 9 H each], 3.06–3.28 (m, *exo*-ArCH_2Ar, 4 H), 3.48–3.88 (m, OCH_2CH_2OH), 4.24 (d, *J* = 13.4 Hz, *endo*-ArCH_2Ar, 1 H), 4.32 (d, *J* = 12.6 Hz, endo-ArCH_2-Ar, 1 H), 4.37 (d, *J* = 13.1 Hz, *endo*-ArCH_2Ar, 1 H), 4.50 (d, *J* = 12.8 Hz, *endo*-ArCH_2Ar, 1 H), 4.85, 5.03 (ABq, *J* = 12.2 Hz, OCH_2Py, 2 H), 5.08, 5.22 (ABq, *J* = 12.8 Hz, OCH_2Py′, 2 H), 6.60 (d, *J* = 2.4 Hz, ArH, 1 H), 6.62 (s, OH, 1 H), 6.66, 6.68, 6.70 (d, *J* = 2.4 Hz, ArH, 1 H each), 7.02 (m, ArH, 3 H), 7.08 (d, *J* = 2.4 Hz, ArH, 1 H), 7.16 (m, 5-PyH and 5-Py′H, 2 H), 7.55 (d, *J* = 7.7 Hz, 3-PyH, 1 H), 7.62 (td, *J* = 7.6, 1.7 Hz, 4-PyH and 4-Py′H, 2 H), 7.92 (d, *J* = 7.7 Hz, 3-Py′H, 1 H), and 8.50 (d, *J* = 4.9 Hz, 6-PyH and 6-Py′H, 2 H); ^{13}C NMR δ 29.68, 30.77, 31.27, 31.38 (t, ArCH_2Ar), 31.08, 31.54, 31.65 [q, C(*C*H_3)$_3$], 33.75, 33.80, 34.08 [s, *C*(CH_3)$_3$], 61.59 (t, OCH_2CH_2OH), 77.20, 77.87, 78.52 (t, OCH_2), 122.77, 122.85, 124.72, 124.92, 125.15, 125.22, 125.68, 125.76 (d), 128.25, 128.90, 132.10, 132.34, 132.42, 132.94, 134.96, 135.40 (s, bridgehead-C), 136.72 (d, 4-PyH), 141.68, 145.72, 146.00, 146.22 (s), 149.01 (d, 6-Py), 150.10, 150.84, 151.62, 151.95 (s), and 157.02 (s, 2-Py); MS *m/z* 874 (M^+, 100). Anal. Calcd for $C_{59}H_{70}N_2O_5$·0.5H_2O: C, 78.78; H, 8.09; N, 3.17. Found: C, 78.70; H, 8.30; N, 3.05.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[(2-methoxyethyl)oxy]-28-hydroxycalix[4]arene (3c). Reaction of 2 with 2-chloroethyl methyl ether (1 equiv) and a trace amount of NaI produced triether **3c** in 53% yield: mp 227–228 °C (*n*-hexane); ^{1}H NMR δ 0.80, 0.89, 1.33, 1.37 [s, C(CH_3)$_3$, 9 H each], 3.03 (m, OCH_2CH_2OCH_3, 2 H), 3.08 (s, OCH_3, 3 H), 3.19–3.27 (m, *exo*-ArCH_2Ar, 4 H), 3.68 (t, *J* = 5.1 Hz, OCH_2CH_2-OCH_3, 2 H), 4.30 (t, *J* = 13.9 Hz, *endo*-ArCH_2Ar, 2 H), 4.45 (d, *J* = 12.5 Hz, *endo*-ArCH_2Ar, 1 H), 4.48 (d, *J* = 13.1 Hz, *endo*-ArCH_2Ar, 1 H), 4.78 (s, OCH_2Py, 2 H), 4.99, 5.05 (ABq, *J* = 13.8 Hz, OCH_2Py′, 2 H), 6.50 (d, *J* = 2.3 Hz, ArH, 1 H), 6.59, 6.60 (d, *J* = 2.3 Hz, ArH, 1 H each), 6.64 (s, OH, 1 H), 6.72 (d, *J* = 2.3 Hz, ArH, 1H), 7.05–7.10 (m, 5-PyH + 5-Py′H + ArH, 4 H), 7.21 (s, ArH, 2 H), 7.33 (d, *J* = 7.3 Hz, 3-PyH, 1 H), 7.43, 7.58 (td, *J* = 7.7, 1.6 Hz, 4-PyH and 4-Py′H, 1 H each), 8.41, 8.45 (d, *J* = 4.9 Hz, 6-PyH and 6-Py′H, 1 H each), and 8.67 (d, *J* = 7.8 Hz, 3-Py′H, 1 H); ^{13}C NMR δ 30.28, 30.56, 31.12, 31.25 (t, ArCH_2Ar), 31.02, 31.70, 31.76 [q, C(*C*H_3)$_3$] 33.66, 33.76, 33.82, 34.17 [s, *C*(CH_3)$_3$], 58.50 (q, OCH_3), 70.64 (t, OCH_2CH_2OCH_3), 74.55 (t, OCH_2CH_2OCH_3), 77.04, 78.63 (t, OCH_2Py and OCH_2Py′), 121.82, 122.45, 122.85, 124.49, 124.82, 124.97, 125.13, 125.18, 125.32, 125.73, 125.84 (d), 127.52, 128.62, 131.78, 131.96, 132.08, 135.35, 135.76 (s, bridgehead-C), 136.23, 136.30 (d, 4-Py and 4-Py′), 141.01, 145.23, 145.90, 146.15 (s), 147.28, 148.81 (d, 6-Py and 6-Py′), 150.18, 150.77, 151.39, 152.98 (s), and 157.02, 158.57 (s, 2-Py and 2-Py′); MS *m/z* 888 (M^+, 100). Anal. Calcd for $C_{59}H_{72}N_2O_5$: C, 79.69; H, 8.16; N, 3.15. Found: C, 79.50; H, 8.51; N, 3.30.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[[2-(dimethylamino)ethyl]oxy]-28-hydroxycalix[4]arene (3d). Reaction of 2 with 2-(dimethylamino)ethyl chloride hydrochloride (1 equiv) and Cs_2CO_3 (2 equiv) in the presence of catalytic amounts of NaI under standard conditions gave triether **3d** in 53% yield: mp 220–223 °C (*n*-hexane); ^{1}H NMR δ 0.79, 0.90, 1.33, 1.37 [s, C(CH_3)$_3$, 9 H each], 1.85–2.15 [m, OCH$_2$-CH_2N(CH_3)$_2$, 2 H], 2.02 [s, OCH_2CH_2N(CH_3)$_2$, 6 H], 3.21, 4.29 (ABq, *J* = 12.5 Hz, ArCH_2Ar, 2 H), 3.24, 4.48 (ABq, *J* = 12.2 Hz, ArCH_2Ar, 2 H), 3.26, 4.14 (ABq, *J* = 13.6 Hz, ArCH_2Ar, 2 H), 3.27, 4.52 (ABq, *J* = 13.6 Hz, ArCH_2Ar, 2 H), 3.63 [t, *J* = 7.3 Hz, OCH_2CH_2N(CH_3)$_2$, 2 H], 4.81 (s, OCH_2Py, 2 H), 4.97, 5.06 (ABq, *J* = 13.8 Hz, OCH_2Py′, 2 H), 6.49 (d, *J* = 2.3 Hz, 1 H), 6.59 (d, *J* = 2.3 Hz, ArH, 2 H), 6.63 (s, OH, 1 H), 6.73, 7.04, 7.11 (d, *J* = 2.3 Hz, ArH, 1 H each), 7.08 (m, 5-PyH + 5-Py′H, 2 H), 7.36 (d, *J* = 7.7 Hz, 3-PyH, 1 H), 7.42 (td, *J* = 7.6, 1.7 Hz, 4-PyH, 1 H), 7.54 (td, *J* = 7.7, 1.7 Hz, 4-Py′H, 1 H), 8.41, 8.46 (d, *J* = 4.9 Hz, 6-PyH and 6-Py′H, 1 H each), and 8.62 (d, *J* = 7.7 Hz, 3-Py′H, 1 H); ^{13}C NMR δ 30.28, 30.53, 31.1, 31.52 (t, ArCH_2Ar), 31.01, 31.68, 31.74 [q, C(*C*H_3)$_3$], 33.64, 33.76, 33.83, 34.16 [s, *C*(CH_3)$_3$], 45.70 [q, OCH_2CH_2N(*C*H_3)$_2$], 57.72 [t, OCH_2*C*H_2N(CH_3)$_2$], 73.74 [t, O*C*H_2CH_2N(CH_3)$_2$], 77.02, 78.65 (t, OCH_2Py and OCH_2Py′), 121.84, 122.48, 122.87, 124.41, 124.77, 124.94, 125.18, 125.43, 125.75, 125.86 (d), 127.27, 128.80, 131.57, 131.92, 132.14, 132.56, 135.30, 135.73 (s, bridgehead-C), 136.20, 136.28 (d, 4-Py and 4-Py′), 141.13, 145.23, 145.96, 146.19 (s), 147.37, 148.82 (d, 6-Py and 6-Py′), 150.23, 150.71, 151.45, 152.89 (s), and 156.99, 158.46 (s, 2-Py and 2-Py′); MS *m/z* 901 (M^+, 100). Anal. Calcd for $C_{60}H_{75}N_3O_4$: C, 79.87; H, 8.38; N, 4.66. Found: C, 79.83; H, 8.68; N, 4.73.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[[(methoxycarbonyl)methyl]oxy]-28-hydroxycalix[4]arene (3e). Reaction of 2 with methyl bromoacetate (1 equiv) under standard conditions produced triether **3e** in 62% yield: mp 183–186 °C (*n*-hexane); ^{1}H NMR δ 0.82, 0.87, 1.32, 1.35 [s, C(CH_3)$_3$, 9 H each], 3.18–3.27 (m, *exo*-ArCH_2Ar, 4 H), 3.57 (s, OCH_2CO$_2$CH_3, 3 H), 4.20 (s, OCH_2CO$_2$CH_3, 2 H), 4.33, (d, *J* = 13.3 Hz, *endo*-ArCH_2Ar, 1 H), 4.34 (d, *J* = 12.6 Hz, *endo*-ArCH_2-Ar, 1 H), 4.40 (d, *J* = 12.6 Hz, *endo*-ArCH_2Ar, 1 H), 4.46 (d, *J* = 13.4 Hz, *endo*-ArCH_2Ar, 1 H), 4.76, 4.83 (ABq, *J* = 11.9 Hz, OCH_2Py, 2 H), 4.97, 5.12 (ABq, *J* = 13.3 Hz, OCH_2Py′, 2 H), 6.51 (s, OH, 1 H), 6.53, 6.59, 6.62, 6.70 (d, *J* = 2.4 Hz, ArH, 1 H each), 7.05–7.12 (m, 5-PyH, 5-Py′H and ArH, 4 H), 7.17, 7.20 (ABq, *J* = 2.4 Hz, ArH, 2 H), 7.39 (d, *J* = 7.7 Hz, 4-Py′H, 1 H), 7.48 (td, *J* = 7.5, 1.7 Hz, 4-PyH, 1 H), 7.60 (td, *J* = 7.7, 1.6 Hz, 4-Py′H, 1 H), and 8.43 (m, 6-PyH, 6-Py′H and 3-Py′H, 3 H); ^{13}C NMR δ 30.62, 31.03, 31.29, 31.46 (t, ArCH_2Ar), 30.96, 31.01, 31.66, 31.73 [q, C(*C*H_3)$_3$], 33.68, 33.75, 33.81, 34.15 [s, *C*(CH_3)$_3$], 51.64 (q, OCH_2CO$_2$CH_3), 71.75 (t, OCH_2CO$_2$CH_3), 77.05, 78.78 (t, OCH_2-Py and OCH_2Py′), 121.87, 122.60, 122.85, 124.24, 124.97, 125.16, 125.21, 125.80 (d), 128.03, 128.19, 131.74, 131.82, 132.01, 132.45, 135,39 (s, bridgehead-C), 136.47 (4-Py and 4-Py′), 141.18, 145.82, 145.86, 146.15 (s), 147.34, 148.89 (d, 6-Py and 6-Py′), 150.66, 150.75, 151.30, 153.03 (s), 156.67, 158.26 (s, 2-Py and 2-Py′), and 169.58 (s, OCH_2*C*O$_2$CH$_3$); MS *m/z* 902 (M^+, 23). Anal. Calcd for $C_{59}H_{70}N_2O_6$: C, 78.46; H, 7.81; N, 3.10. Found: C,78.17; H, 8.26; N, 3.23.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[[(aminocarbonyl)methyl]oxy]-28-hydroxycalix[4]arene (3f). Reaction of 2 with 2-iodoacetamide (1 equiv) under standard conditions gave triether **3f** in 42% yield: mp 225–227

°C (*n*-hexane); ^{1}H NMR δ 0.99, 1.07, 1.17, 1.23 [s, C(CH$_3$)$_3$, 9 H each], 3.13–3.29 (m, *exo*-ArCH$_2$Ar, 4 H), 4.14, 4.40 (ABq, *J* = 15.3 Hz, OCH$_2$CONH$_2$, 2 H), 4.20 (d, *J* = 12.5 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.21 (d, *J* = 13.6 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.32 (d, *J* = 13.0 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.39 (d, *J* = 12.7 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.86, 5.19 (ABq, *J* = 12.2 Hz, OCH$_2$Py, 2 H), 4.97, 5.05 (ABq, *J* = 12.4 Hz, OCH$_2$Py′, 2 H), 5.53 (bs, OCH$_2$CONH$_2$, 1 H), 6.74, 6.79, 6.82, 6.94, 6.97, 6.98, 7.00, 7.02 (d, *J* = 2.4 Hz, ArH, 1H each), 7.18, 7.24 (m, 5-PyH and 5-Py′H, 1 H each), 7.34 (s, OH, 1 H), 7.40 (d, *J* = 7.7 Hz, 3-PyH, 1 H), 7.60 (td, *J* = 7.6, 1.8 Hz 4-PyH, 1 H), 7.63 (td, *J* = 7.7, 1.8 Hz, 4-Py′H, 1 H), 7.69 (d, *J* = 7.7 Hz, 3-Py′H, 1 H), 8.25 (bs, OCH$_2$CONH$_2$, 1 H), 8.53, 8.58 (dd, *J* = 4.9, 1.1 Hz, 6-PyH and 6-Py′H, 1 H each); ^{13}C NMR δ 30.84, 30.94, 31.62, 32.32 (t, ArCH$_2$Ar), 31.17, 31.41, 31.54 [q, C(CH$_3$)$_3$], 33.79, 33.82, 33.98, 34.01 [s, C(CH$_3$)$_3$], 73.67 (t, OCH$_2$CONH$_2$), 77.89, 78.81 (t, OCH$_2$Py and OCH$_2$Py′), 122.73, 122.78, 123.13, 123.29 (d, 3,5-Py and 3,5-Py′), 124.88, 125.20, 125.48, 125.63, 125.74, 126.09 (d, Ar), 127.65, 129.11, 132.28, 132.35, 133.21, 133.71, 133.79, 134.56 (s, bridgehead-C), 136.52, 136.74 (d, 4-Py and 4-Py′), 142.10, 146.02, 146.06, 146.88 (s), 148.95, 149.74 (d, 6-Py and 6-Py′), 150.98, 151.35, 152.06 (s), 156.40, 157.40 (s, 2-Py and 2-Py′), and 172.52 (s, OCH$_2$CONH$_2$); MS *m/z* 887 (M$^+$, 100). Anal. Calcd for C$_{58}$H$_{69}$N$_3$O$_5$: C, 78.43; H, 7.83; N, 4.73. Found: C, 78.29; H, 8.30; N, 4.79.

The reaction produced also the chiral partial cone diamide **4d** (10%) (see below for analytical and spectral data).

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[[[(*N*,*N*-diethylamino)carbonyl]methyl]oxy]-28-hydroxycalix[4]arene (3g). Reaction of **2** with 2-chloro-*N*,*N*-diethylacetamide (1 equiv) under standard conditions afforded triether **3g** in 62% yield: mp 185–188 °C (*n*-hexane-DCM); ^{1}H NMR δ 0.85, 0.86, 1.31, 1.34 [s, C(CH$_3$)$_3$, 9 H each], 0.97, 1.04 [t, *J* = 7.1 Hz, N(CH$_2$CH$_3$)$_2$, 3 H each], 3.21 (d, *J* = 12.6 Hz, *exo*-ArCH$_2$Ar, 2 H), 3.23 (d, *J* = 12.8 Hz, *exo*-ArCH$_2$Ar, 2 H), 3.05–3.4 [m, N(CH$_2$CH$_3$)$_2$, 4 H], 4.17, 4.31 [ABq, *J* = 13.1 Hz, OCH$_2$CON(CH$_2$CH$_3$)$_2$, 2 H], 4.27 (d, *J* = 13.1 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.39 (d, *J* = 12.6 Hz, *endo*-ArCH$_2$Ar, 2 H), 4.53 (d, *J* = 13.3 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.75, 4.82 (ABq, *J* = 12.1 Hz, OCH$_2$Py, 2 H), 4.96, 5.09 (ABq, *J* = 13.4 Hz, OCH$_2$Py′, 2 H), 6.54, 6.64 (ABq, *J* = 2.4 Hz, ArH, 2 H), 6.59, 6.68 (ABq, *J* = 2.3 Hz, ArH, 2 H), 6.91 (s, OH, 1 H), 7.04 (s, ArH, 2 H), 7.07 (m, 5-PyH and 5-Py′H, 2 H), 7.16, 7.18 (ABq, *J* = 2.3 Hz, ArH, 2 H), 7.43 (d, *J* = 8.0 Hz, 3-PyH, 1 H). 7.47 (m, 4-PyH, 1 H), 7.59 (td, *J* = 7.7, 1.7 Hz, 4-Py′H, 1 H), 8.41 (d, *J* = 4.4 Hz, 6-PyH and 6-Py′H, 2 H), and 8.45 (d, *J* = 7.8 Hz, 3-Py′H, 1 H); ^{13}C NMR δ 12.88, 14.19 [q, N(CH$_2$CH$_3$)$_2$], 30.60, 30.91, 31.30, 31.53 (t, ArCH$_2$Ar), 31.01, 31.65, 31.73 [q, C(CH$_3$)$_3$], 33.67, 33.76, 34.12 [s, C(CH$_3$)$_3$], 39.95, 40.92 [t, N(CH$_2$CH$_3$)$_2$], 73.16 [t, OCH$_2$CON(CH$_2$CH$_3$)$_2$], 77.04, 78.62 (t, OCH$_2$Py and OCH$_2$Py′), 121.80, 122.42, 122.76, 124.06, 124.94, 125.05, 125.26, 125.70, 125.77 (d), 127.98, 128.07, 131.97, 132.04, 132.10, 132.33, 135.13, 135.44 (s, bridgehead-C), 136.37, 136.61 (d, 4-Py and 4-Py′), 140.86, 145.58, 145.70, 146.04 (s), 147.44, 148.77 (d, 6-Py and 6-Py′), 150.76, 150.98, 151.57, 152.92 (s), 156.96, 158.36 (s, 2-Py and 2-Py′), and 166.92 [s, OCH$_2$CON(CH$_2$CH$_3$)$_2$]; MS *m/z* 943 (M$^+$, 33). Anal. Calcd for C$_{62}$H$_{77}$N$_3$O$_5$: C, 78.86; H, 8.22; N, 4.45. Found: C, 78.74; H, 8.74; N, 4.61.

From this reaction a very small amount of a byproduct was also isolated, which was identified as the achiral tetra-O-alkylated 1,2-alternate conformer **3ga** on the basis of the following NMR spectral data: ^{1}H NMR δ 0.61, 1.01 [t, *J* = 7.0 Hz, N(CH$_2$CH$_3$)$_2$, 6 H each], 1.10, 1.31 [s, C(CH$_3$)$_3$, 18 H each], 2.83, 3.07, 3.37 [m, ratio 1:2:1, N(CH$_2$CH$_3$)$_2$, 8 H], 2.91, 3.37, 3.81, 5.00 (d, *J* = 12.6 Hz, ArCH$_2$Ar, 4 H), 3.83, 4.08 (ABq, *J* = 16.3 Hz, ArCH$_2$Ar, 4 H), 3.98, 4.44 (ABq, *J* = 13.5 Hz, OCH$_2$, 4 H), 4.34, 4.41 (ABq, *J* = 13.3 Hz, OCH$_2$, 4 H), 6.01 (d, *J* = 7.7 Hz, 3-PyH, 2 H), 6.86, 7.12, 7.18, 7.26 (d, *J* = 2.3 Hz, ArH, 2 H each), 6.94 (m, 5-PyH, 2 H), 7.09 (m, 4-PyH, 2 H), and 8.28 (d, *J* = 4.7 Hz, 6-PyH, 2 H); ^{13}C NMR δ 12.80, 14.14 [q, N(CH$_2$CH$_3$)$_2$], 29.31, 30.65, 39.15 (t, ArCH$_2$Ar), 31.32, 31.60 [q, C(CH$_3$)$_3$], 33.89, 34.08 [s, C(CH$_3$)$_3$], 39.87, 41.21 (t, N(CH$_2$CH$_3$)$_2$), 71.44 (t, OCH$_2$CO), 74.45 (t, OCH$_2$Py), 121.47, 122.31 (3,5-Py), 125.42, 125.77, 125.91, 126.23 (d, ArH), 132.34, 132.40, 134.07, 134.10 (s, bridgehead-C), 136.38 (d, 4-Py), 144.56, 144.75 [s, C$_{Ar}$C(CH$_3$)$_3$], 153.03, 154.52 (s, C$_{Ar}$O) and 157.59 (s, 2-Py).

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[(benzoylmethyl)oxy]-28-hydroxycalix[4]arene (3h). Reaction of **2** with 2-bromoacetophenone (1 equiv) under standard conditions gave triether **3h** in 53% yield: mp 173–176 °C (MeOH); ^{1}H NMR δ 0.86, 0.87, 1.31, 1.34 [s, C(CH$_3$)$_3$, 9 H each], 3.18–3.26 (m, *exo*-ArCH$_2$Ar, 4 H), 4.26 (d, *J* = 12.4 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.43 (d, *J* = 12.7 Hz, *endo*-ArCH$_2$Ar, 2 H), 4.50 (d, *J* = 13.4 Hz, *endo*-ArCH$_2$Ar, 1 H), 4.77, 4.98 (ABq, *J* = 16.1 Hz, OCH$_2$, 2 H), 4.79, 4.87 (ABq, *J* = 12.1 Hz, OCH$_2$, 2 H), 4.89, 5.12 (ABq, *J* = 13.0 Hz, OCH$_2$, 2 H), 6.59, 6.68 (bt, *J* = 2.6 Hz, ArH, 2 H each), 6.91 (m, 5-PyH, 1 H), 6.93 (s, OH, 1 H), 7.03, 7.07 (d, *J* = 2.4 Hz, ArH, 1 H each), 7.08 (m, 5-Py′H, 1 H), 7.16, 7.19 (ABq, *J* = 2.4 Hz, ArH, 2 H), 7.37–7.74 (m, PhCO, 3-PyH, 4-PyH, and 4-Py′H, 8 H), 8.22 (d, *J* = 4.9 Hz, 6-PyH, 1 H), 8.38 (d, *J* = 7.8 Hz, 3-Py′H, 1 H), and 8.42 (d, *J* = 4.9 Hz, 6-Py′H, 1 H); ^{13}C NMR δ 30.69, 31.32, 31.54 (t, ArCH$_2$Ar), 30.99, 31.64, 31.72 [q, C(CH$_3$)$_3$], 33.71, 33.78, 34.13 [s, C(CH$_3$)$_3$], 76.89, 77.14, 78.58 (t, OCH$_2$), 121.96, 122.51, 122.90, 124.28, 125.00, 125.04, 125.09, 125.23, 125.31, 125.64, 125.85, 127.76, 128.57, 133.38 (d), 127.70, 128.31, 131.97, 132.12, 132.23, 132.35, 134.58, 135.07, 135.47 (s, bridgehead-C and C$_{sp2}$CO), 136.55, 136.75 (d, 4-Py and 4-Py′), 140.97, 145.56, 146.01, 146.07 (s), 147.27, 148.76 (d, 6-Py and 6-Py′), 150.74, 151.13, 151.45, 153.02 (s), 157.00, 158.01 (s, 2-Py and 2-Py′), and 193.96 (s, PhCO); MS *m/z* 948 (M$^+$, 15). Anal. Calcd for C$_{64}$H$_{72}$N$_2$O$_5$: C, 80.98; H, 7.64; N, 2.95: Found: C, 80.33; H, 7.99; N, 3.08.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-(benzyloxy)-28-hydroxycalix[4]arene (3i). Reaction of **2** with benzyl bromide (1 equiv) under standard conditions produced triether **3i** in 81% yield: mp 219–221 °C (MeCN-DCM); ^{1}H NMR δ 0.82, 0.89, 1.32, 1.35 [s, C(CH$_3$)$_3$, 9 H each], 3.05, 4.18 (ABq, *J* = 12.4 Hz, ArCH$_2$Ar, 2 H), 3.11, 4.07 (ABq, *J* = 13.5 Hz, ArCH$_2$Ar, 2 H), 3.21, 4.40 (ABq, *J* = 12.9 Hz, ArCH$_2$Ar, 4 H), 4.48, 4.53 (ABq, J = 11.1 Hz, OCH$_2$, 2 H), 4.74, 4.79 (ABq, *J* = 12.0 Hz, OCH$_2$, 2 H), 4.89, 5.02 (ABq, *J* = 13.6 Hz, OCH$_2$, 2 H), 6.52, 6.63 (ABq, *J* = 2.4 Hz, ArH, 2 H), 6.57, 6.70 (ABq, *J* = 2.3 Hz, ArH, 2 H), 6.61 (s, OH, 1 H), 6.99–7.20 (m, ArH, PhH, 5-PyH and 5-Py′H, 11 H), 7.32 (d, *J* = 7.4 Hz, 3-PyH, 1 H), 7.39, 7.43 (td, *J* = 7.7, 1.6 Hz, 4-PyH and 4-Py′H, 1 H each), 8.40 (m, 6-PyH and 6-Py′H, 2 H), and 8.45 (d, *J* = 7.8 Hz, 3-Py′H, 1 H); ^{13}C NMR δ 30.53, 30.60, 31.24 (t, ArCH$_2$Ar), 31.01, 31.65, 31.71 [q, C(CH$_3$)$_3$], 33.68, 33.76, 33.80, 34.14 [s, C(CH$_3$)$_3$], 77.00, 78.11, 78.57 (t, OCH$_2$), 121.89, 122.44, 122.72, 124.19, 124.82, 124.97, 125.03, 126.16, 125.21, 125.67, 125.73, 127.98, 128.15, 129.17 (d), 127.69, 128.52, 131.92, 132.00, 132.25, 132.82, 135.26, 135.59 (s, bridgehead-C), 136.19, 136.30 (d, 4-Py and 4-Py′), 136.43 (s, Ph), 141.24, 145.50, 145.91, 146.14 (s), 147.17, 148.78 (d, 6-Py and 6-Py′), 150.19, 150.68, 151.23, 152.95 (s), 156.99 and 158.13 (s, 2-Py and 2-Py′); MS *m/z* 920 (M$^+$, 59). Anal. Calcd for C$_{63}$H$_{72}$N$_2$O$_4$: C, 82.13; H, 7.88; N, 3.04. Found: C, 82.20; H, 8.37; N, 3.24.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[(2-quinolylmethyl)oxy]-28-hydroxycalix[4]arene (3j). Reaction of **2** with QuinCl·HCl (1 equiv) and Cs$_2$CO$_3$ (2 equiv) under standard conditions gave triether **3j** in 79% yield: mp 210–213 °C (*n*-hexane); ^{1}H NMR δ 0.85 [s, C(CH$_3$)$_3$, 18 H], 1.33, 1.36 [s, C(CH$_3$)$_3$, 9 H each], 3.16–3.28 (m, *exo*-ArCH$_2$Ar, 4 H), 4.33 (d, *J* = 13.1 Hz, *endo*-ArCH$_2$Ar, 2 H), 4.43 (t, *J* = 12.5 Hz, *endo*-ArCH$_2$Ar, 2 H), 4.73, 4.92, 4.96 (s, OCH$_2$, 2 H each), 6.56 (d, *J* = 2.3 Hz, ArH, 2 H), 6.60 (m, 5-PyH, 1 H), 6.61 (s, OH, 1 H), 6.67 (d, *J* = 2.4 Hz, ArH, 2 H), 7.03 (m, 5-Py′H, 1 H), 7.08 (s, ArH, 2 H), 7.12 (td, *J* = 7.7, 1.7 Hz, 4-PyH, 1 H), 7.20 (s, ArH, 2 H), 7.21 (d, *J* = 7.7 Hz, 3-PyH, 1 H), 7.37 (td, *J* = 7.6, 1.8 Hz, 4-Py′H, 1 H), 7.43 (d, *J* = 8.4 Hz, QuinH, 1 H), 7.52 (t, *J* = 7.1 Hz, QuinH, 1 H), 7.66 (bt, *J* = 8.4 Hz, QuinH, 1 H), 7.74 (d, *J* = 8.2 Hz, QuinH, 1 H), 7.95 (d, *J* = 8.6 Hz, QuinH, 1 H), 7.98 (d, *J* = 8.6 Hz, QuinH, 1 H), 8.16 (d, *J* = 4.9 Hz, 6-PyH, 1 H), 8.30 (d, *J* = 8.1 Hz, 3-Py′H, 1 H), and 8.38 (d, *J* = 4.9 Hz, 6-Py′H, 1 H); ^{13}C NMR δ 30.55, 30.69, 31.44, 31.56 (t, ArCH$_2$Ar), 31.03, 31.69, 31.75 [q, C(CH$_3$)$_3$], 77.08, 78.70, 79.22 (t, OCH$_2$), 120.63, 121.46, 122.48, 122.71, 123.79, 125.09, 125.18, 125.82, 126.35, 127.45, 129.24, 129.40 (d), 128.22, 128.29, 131.77, 131.84, 132.26, 132.30, 135.43, 135.48 (s, bridgehead-C), 135.81, 136.31 (d, 4-Py and 4-Py′), 141.29, 145.70, 145.75, 146.14 (s), 147.07, 148.82 (d, 6-Py and 6-Py′), 147.34, 150.75, 150.86, 151.18, 153.03, 156.71, 157.22, and 157.92 (s); MS *m/z* 971 (M$^+$, 10). Anal. Calcd for C$_{66}$H$_{73}$N$_3$O$_4$: C, 81.53; H, 7.57; N, 4.32. Found: C, 81.76; H, 7.98; N, 4.49.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-[[2-(*N*-methylimidazolyl)methyl]oxy]-28-hydroxycalix[4]arene (3k). Reaction of **2** with 2-(chloromethyl)-*N*-methylimidazole hydrochloride (1 equiv) and Cs_2CO_3 (2 equiv) under standard conditions afforded triether **3j** in 93% yield: mp 233–235 °C (*n*-hexane-DCM); ^{1}H NMR δ 0.80, 0.86, 1.32, 1.36 [s, C(CH$_3$)$_3$, 9 H each], 3.09, 4.14 (ABq, *J* = 13.4 Hz, ArCH$_2$Ar, 2 H), 3.15, 4.27 (ABq, *J* = 12.7 Hz, ArCH$_2$Ar, 4 H), 3.23, 4.35 (ABq, *J* = 13.0 Hz, ArCH$_2$Ar, 2 H), 3.24 (s, *N*-CH$_3$, 3 H), 4.58, 4.65 (ABq, *J* = 12.4 Hz, OCH$_2$, 2 H), 4.69, 4.76 (ABq, *J* = 11.7 Hz, OCH$_2$, 2 H), 4.91, 5.02 (ABq, *J* = 13.8 Hz, OCH$_2$, 2 H), 6.47, 6.56, 6.59, 6.69 (d, *J* = 2.4 Hz, ArH, 1 H each), 6.61 (s, OH, 1 H), 6.86, 7.20 (ABq, *J* = 1.1 Hz, 4,5-ImidH, 2 H), 7.02–7.22 (m, ArH, 5-PyH, 5-Py′H, and 3-PyH, 7 H), 7.40 (td, *J* = 7.6, 1.7 Hz, 4-PyH and 4-Py′H, 2 H), 8.40 (m, 6-PyH and 6-Py′H, 2 H), and 8.45 (d, *J* = 7.9 Hz, 3-Py′H, 1 H); ^{13}C NMR δ 30.35, 30.48, 30.71, 31.47 (t, ArCH$_2$Ar), 30.97, 31.66, 31.70 [q, C(*C*H$_3$)$_3$], 32.34 (q, *N*-CH$_3$), 33.66, 33.72, 33.80, 34.15 [s, *C*(CH$_3$)$_3$], 67.79 (t, OCH$_2$Imid), 76.84, 78.87 (t, OCH$_2$Py and OCH$_2$Py′), 121.76, 121.82, 122.55, 122.73, 123.78, 124.89, 125.06, 125.18, 125.79, 125.83, 127.70 (d), 127.86, 128.50, 131.62, 132.10, 132.28, 132.36, 135.38, 135.45 (s, bridgehead-C), 136.13, 136.32 (d, 4-Py and 4-Py′), 141.28, 143.64, 145.74, 145.94, 146.22 (s), 147.31, 148.90 (d, 6-Py and 6-Py′), 150.15, 150.63, 152.96, 156.34, and 158.30 (s); MS *m*/*z* 924 (M$^+$, 45). Anal. Calcd for $C_{61}H_{72}N_4O_4$: C, 79.18; H, 7.84; N, 6.06. Found: C, 79.52; H, 8.36; N, 6.05.

***Syn-Distal* 5,11,17,23-Tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-27-[(2-quinolylmethyl)oxy]-26,28-dihydroxycalix[4]arene (6).** A mixture of **5** (0.37 g, 0.5 mmol), QuinCl·HCl (0.22 g, 1 mmol), and anhydrous K_2CO_3 (0.14 g, 1 mmol) in DMF (15 mL) was heated at 70 °C for 10 h. The solvent was evaporated in vacuo, and the residue was partitioned between water and DCM. The organic layer was dried (Na_2SO_4) and concentrated to give an oily residue, which was chromatographed on a SiO_2 column (eluent cyclohexane–AcOEt (5:1)) to afford **6** (0.31 g, 70 %): mp 115–117 °C (MeCN); R_f = 0.63 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 0.95, 0.96 [s, C(CH$_3$)$_3$, 9 H each], 1.30 [s, C(CH$_3$)$_3$, 18 H], 3.36, 3.39, 4.32, 4.40 (d, *J* = 13.1 Hz, ArCH$_2$Ar, 2 H each), 5.19, 5.36 (s, OCH$_2$, 2 H each), 6.82, 6.84 (s, ArH, 2 H each), 7.09 (s, ArH, 4 H), 7.16 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 5-PyH, 1 H), 7.28 (td, *J* =7.6, 1.8 Hz, 4-PyH, 1 H), 7.36 (s, OH, 2 H), 7.58 (ddd, *J* = 8.0, 7.0, 1.1 Hz, QuinH, 1 H), 7.74 (ddd, *J* = 8.4, 6.9, 1.4 Hz, Quin H 1 H), 7.83 (dd, *J* = 8.1, 1.0 Hz, QuinH, 1 H), 8.03 (d, *J* = 8.5 Hz, 4-QuinH, 1 H), 8.10 (d, *J* = 7.9 Hz, QuinH, 1 H), 8.25 (d, *J* = 7.7 Hz, 3-PyH, 1 H), 8.47 (d, *J* = 8.5 Hz, 3-QuinH, 1 H), and 8.60 (ddd, *J* = 4.9, 1.7, 0.8 Hz, 6-PyH, 1 H); ^{13}C NMR δ 30.93, 31.66 [q, C(*C*H$_3$)$_3$], 31.51 (t, ArCH$_2$Ar), 33.81, 33.92 [s, *C*(CH$_3$)$_3$], 78.14, 78.49 (t, OCH$_2$), 119.57, 121.37, 122.33, 125.06, 125.66, 126.46, 127.58, 129.01, 129.71 (d), 132.36 (s, bridgehead-C), 137.26, 137.35 (d, 4-Py and 4-Quin), 141.65, 147.28(s), 148.81 (d, 6-Py), 149.45, 150.60 (s), 157.50 and 158.06 (s, 2-Py and 2-Quin); MS *m*/*z* 880 (M$^+$, 18). Anal. Calcd for $C_{60}H_{68}N_2O_4$·MeCN: C, 80.74; H, 7.76; N, 4.56. Found: C, 80.26; H, 8.02; N,4.47.

Chiral Tetra-O-alkylated Calix[4]arenes, Partial Cone Conformers. General Procedures. Method A. A stirred mixture of **2** (0.3 mmol), the alkylating agent (4 equiv), and Cs_2CO_3 (1.2 mmol) in dry DMF (10 mL) was heated at 60 °C for 20 h. The solvent was removed under reduced pressure, and the residue was partitioned between water and DCM. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed (column, SiO_2) by eluting with a gradient of AcOEt in *n*-hexane to give the desired tetraether.

Method B. A stirred mixture of **6** (0.3 mmol), the alkylating agent (15 equiv), and Cs_2CO_3 (4.5 mmol) in dry DMF (10 mL) was heated at 60 °C for 48 h. Usual workup, followed by chromatographic purification, led to the desired product.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-bis[[(methoxycarbonyl)methyl]oxy]calix[4]arene (4a). Obtained in 41% yield by alkylation of **2** with methyl bromoacetate according to method A: mp 196–199 °C (*n*-hexane); ^{1}H NMR δ 1.10, 1.13, 1.16, 1.26 [s, C(CH$_3$)$_3$, 9 H each], 2.89, 2.99 [ABq, *J* = 15.5 Hz, inverted OC*H*$_2$CO$_2$CH$_3$, 2 H], 3.02, 4.14 (ABq, *J* = 12.4 Hz, ArCH$_2$Ar, 2 H), 3.06, 4.30 (ABq, *J* = 12.6 Hz, ArCH$_2$Ar, 2 H), 3.43 (s, inverted OCH$_2$CO$_2$C*H*$_3$, 3 H), 3.68 (s, OCH$_2$CO$_2$C*H*$_3$, 3 H), 3.82, 3.92 (ABq, *J* = 15.4 Hz, ArCH$_2$Ar, 2 H), 3.91, 3.98 (ABq, *J* = 14.2 Hz, ArCH$_2$Ar, 2 H), 4.30, 4.39 [ABq, *J* = 15.7 Hz, OC*H*$_2$CO$_2$CH$_3$, 2 H], 4.69, 4.88 (ABq, *J* = 12.6 Hz, OCH$_2$Py, 2 H), 4.74, 4.80 (ABq, *J* = 13.2 Hz, OCH$_2$Py′, 2 H), 6.87, 6.89 (d, *J* = 2.5 Hz, ArH, 1 H each), 6.98 (t, *J* = 2.5 Hz, ArH, 2 H), 7.02–7.46 (m, ArH and PyH, 10 H), 8.37 and 8.49 (d, *J* = 4.8 Hz, 6-PyH and 6-Py′H, 1 H each); ^{13}C NMR δ 26.83, 30.78, 37.88 (t, ArCH$_2$Ar), 31.30, 31.46 [q, C(CH$_3$)$_3$], 33.81, 33.94, [s, *C*(CH$_3$)$_3$], 51.23, 51.53 (q, OCH$_2$CO$_2$*C*H$_3$), 68.01, 70.77 (t, O*C*H$_2$CO$_2$CH$_3$), 76.35, 76.49 (t, O*C*H$_2$Py and O*C*H$_2$Py′), 121.78, 122.22, 122.97, 123.69 (3,5-Py and 3,5-Py′), 125.39, 125.50, 125.69, 125.89, 126.20, 127.30, 127.55 (d, Ar), 132.35, 132.77, 133.42, 133.75, 134.02, 134.25, 134.43 (s, bridgehead-C), 135.75, 136.21 (d, 4-Py and 4-Py′), 144.43, 145.34 [s, *C*-C(CH$_3$)$_3$], 148.12, 148.48 (d, 6-Py and 6-Py′), 151.92, 153.11, 153.60, 153.75 (s, *C*-OCH$_2$), 157.64, 158.08 (s, 2-Py and 2-Py′), 169.56 and 170.21 (s, OCH$_2$*C*O$_2$CH$_3$); MS, *m*/*z* 974 (M$^+$, 65). Anal. Calcd for $C_{62}H_{74}N_2O_8$: C, 76.35; H, 7.65; N, 2.87. Found: C, 76.72; H, 7.88; N, 2.96.

From this reaction the achiral cone isomer **4aa** was also isolated (28%): mp 159–162 °C; ^{1}H NMR δ 1.09 [s, C(CH$_3$)$_3$, 36 H], 3.12, 4.40 (ABq, *J* = 12.6 Hz, ArCH$_2$Ar, 2 H), 3.18, 4.57 (ABq, *J* = 12.8 Hz, ArCH$_2$Ar, 4 H), 3.21, 4.89 (ABq, *J* = 12.9 Hz, ArCH$_2$Ar, 2 H), 3.66 (s, OCH$_2$CO$_2$C*H*$_3$, 6 H), 4.67, 4.74 (ABq, *J* = 15.8 Hz, OC*H*$_2$CO$_2$CH$_3$, 4 H), 4.98, 5.04 (ABq, *J* = 12.6 Hz, OC*H*$_2$Py, 4 H), 6.82 (m, ArH, 8 H), 7.14 (ddd, *J* = 7.3, 4.9, 0.9 Hz, 5-PyH, 2 H), 7.49 (td, *J* = 7.6, 1.8 Hz, 4-Py, 2 H), 7.78 (d, *J* = 7.8 Hz, 3-PyH, 2 H), and 8.51 (dd, *J* = 4.9, 0.8 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.91, 31.75 (t, ArCH$_2$Ar), 31.35 [q, C(CH$_3$)$_3$], 33.77 [s, *C*(CH$_3$)$_3$], 51.26 (q, OCH$_2$CO$_2$CH$_3$), 71.00 (t, OCH$_2$CO$_2$CH$_3$), 77.92 (t, O*C*H$_2$Py), 122.13, 123.15 (d, 3,5-Py), 125.26, 125.38 (d, Ar), 133.27, 133.39, 133.57 (s, bridgehead-C), 136.08 (d, 4-Py), 144.92, 145.02 [s, *C*C(CH$_3$)$_3$], 148.60 (d, 6-Py), 152.70, 152.91 (*C*OCH$_2$), 158.24 (2-Py), and 170.91 (s, OCH$_2$CO$_2$CH$_3$); MS *m*/*z* 974 (M$^+$, 36). Anal. Calcd for $C_{62}H_{74}N_2O_8$: C, 76.35; H, 7.65; N, 2.87. Found: C, 76.57; H, 7.76; N, 2.79.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-bis[[(*tert*-butoxycarbonyl)methyl]oxy]calix[4]arene (4b). Obtained in 25% yield by alkylation of **2** with *tert*-butyl bromoacetate according to method A: mp 92–94 °C (*n*-hexane); ^{1}H NMR δ 1.03, 1.07, 1.24, 1.31 [s, C(CH$_3$)$_3$, 9 H each], 1.44, 1.45 (s, OC(CH$_3$)$_3$, 9 H each], 2.93, 3.85 (ABq, *J* = 12.8 Hz, ArCH$_2$Ar, 2 H), 3.07, 4.18 (ABq, *J* = 12.8 Hz, ArCH$_2$Ar, 2 H), 3.77, 3.90 (ABq, *J* = 14.1 Hz, ArCH$_2$Ar, 2 H), 3.99, 4.07 (ABq, *J* = 14.2 Hz, ArCH$_2$Ar, 2 H), 4.05 and 4.15 (ABq, *J* = 15.5 Hz, OCH$_2$CO, 2 H), 4.19, 4.26 (ABq, *J* = 15.0 Hz, OCH$_2$CO, 2 H), 4.68, 4.92 (ABq, *J* = 13.0 Hz, OCH$_2$Py, 2 H), 4.76, 4.89 (ABq, *J* = 12.1 Hz, OCH$_2$Py′, 2 H), 6.58, 6.64 (d, *J* = 2.4 Hz, ArH, 1 H each), 6.99–7.14 (m, ArH and PyH, 8 H), 7.36 (td, *J* = 7.6, 1.7 Hz, 4-PyH, 1 H), 7.39–7.54 (m, ArH and PyH, 3 H), 8.35 (d, *J* = 4.6 Hz, 6-PyH, 1 H), and 8.54 (d, *J* = 4.8 Hz, 6-Py′H, 1 H); ^{13}C NMR δ 28.08 [q, OC(CH$_3$)$_3$], 31.34, 31.58, 31.65 [q, C(CH$_3$)$_3$], 33.77, 34.01, [s, *C*(CH$_3$)$_3$], 36.93, 37.36 (t, ArCH$_2$Ar), 70.20, 71.82 (t, OCH$_2$CO), 75.68, 77.17 (t, OCH$_2$Py and OCH$_2$Py′), 81.02 [s, OC(CH$_3$)$_3$], 121.70, 122.41, 122.96, 124.57, 125.37, 125.56, 125.68, 125.77, 125.93, 126.40, 127.70, 128.17 (d), 131.37, 131.58, 131.81, 132.18, 132.72, 134.99 (s, bridgehead-C), 136.03, 136.34 (d, 4-Py and 4-Py′), 143.50, 144.11, 144.35, 144.89 (s), 147.81, 148.91 (d, 6-Py and 6-Py′), 152.63, 153.03, 153.93, 155.14 (s), 157.68, 158.38 (s, 2-Py and 2-Py′), and 168.76 (OCH$_2$*C*O); MS *m*/*z* 1058 (M$^+$, 58). Anal. Calcd for $C_{68}H_{86}N_2O_8$: C, 77.10; H, 8.18; N, 2.64. Found: C, 76.82; H, 8.38; N, 2.57.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-bis[[(aminocarbonyl)methyl]oxy]-28-hydroxycalix[4]arene (4c). Obtained in 52% yield by alkylation of **2** with 2-iodoacetamide according to method A: mp 241–244 °C; ^{1}H NMR δ 1.22, 1.23, 1.29, 1.34 [s, C(CH$_3$)$_3$, 9 H each], 2.84, 3.09, 5.87, 6.74 (bs, OCH$_2$CON*H*$_2$, 1 H each), 3.10, 3.38, 4.07, 4.42 (d, *J* = 12.1 Hz, ArCH$_2$Ar, 1 H each), 3.55, 3.62 (ABq, *J* = 14.3 Hz, OC*H*$_2$CONH$_2$, 2 H), 3.67, 3.77 (ABq, *J* = 16.8 Hz, ArCH$_2$Ar, 2 H), 3.84, 3.95 (ABq, *J* = 17.5 Hz, ArCH$_2$Ar, 2 H), 4.01 (s, OC*H*$_2$CONH$_2$, 2 H), 4.67, 5.06 (ABq, *J* = 11.1 Hz, OCH$_2$Py, 2 H), 4.78, 4.86 (ABq, *J* = 12.2 Hz, OCH$_2$Py′, 2 H), 6.70 (bs, ArH, 1 H), 6.86 (bs, ArH, 2 H), 7.02, 7.14, 7.20 (d, *J* = 2.0 Hz, ArH, 1 H each), 7.2–7.4 (m, ArH and PyH, 6 H), 7.67, 7.77 (td, *J* = 7.6, 1.5 Hz, 1 H each), 8.51 and 8.74 (d, *J* = 4.6 Hz, 6-PyH and 6-Py′H, 1 H each); ^{13}C NMR δ 29.63, 30.29, 38.73, 39.22 (t, ArCH$_2$Ar), 31.28, 31.36, 31.59 q, C(*C*H$_3$)$_3$, 33.91, 34.02, 34.09 s, *C*(CH$_3$)$_3$, 66.62, 69.16 (t, OCH$_2$CO), 77.94, 79.07 (t, OCH$_2$Py and OCH$_2$Py′), 123.12,

123.32, 123.97, 124.25 (d, 3,5-Py and 3,5-Py'), 125.00, 125.28, 125.34, 125.58, 126.06, 126.32 (d, Ar), 130.60, 131.34, 132.03, 133.76, 134.12, 134.96, 135.14 (s, bridgehead-C), 136.67, 136.87 (d, 4-Py and 4-Py'), 146.00, 146.58, 147.23, 147.49 s, $ArCC(CH_3)_3$, 149.22, 149.81 (d, 6-Py and 6-Py'), 150.02, 150.87, 151.56, 154.09 (s, $ArCOCH_2$), 156.25, 157.09 (s, 2-Py and 2-Py'), 169.20, 170.30 (s, OCH_2CO); MS *m/z* 944 (M^+, 45). Anal. Calcd for $C_{60}H_{72}N_4O_6$: C, 76.24; H, 7.68; N, 5.93. Found: C, 76.52; H, 7.87; N, 5.80.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-bis[(2-quinolylmethyl)oxy]calix[4]arene (4d). Reaction of **2** with QuinCl·HCl according to method A produced partial cone tetraether **4d** in 60% yield: mp 169–170 °C (MeCN); ^1H NMR δ 0.44, 0.45, 1.11, 1.47 [s, $C(CH_3)_3$, 9 H each], 3.05 (d, *J* = 12.2 Hz, *exo*-$ArCH_2Ar$, 2 H), 3.83, 3.94 (ABq, *J* = 16.5 Hz, $ArCH_2Ar$, 2 H), 3.85, 4.00 (ABq, *J* = 16.3 Hz, $ArCH_2Ar$, 2 H), 4.26 (t, *J* = 12.5 Hz, *endo*-$ArCH_2Ar$, 2 H), 4.60 (s, inverted OCH_2-Quin, 2 H), 4.69, 4.75 (ABq, *J* = 12.8 Hz, OCH_2, 2 H), 4.78 (d, *J* = 8.4 Hz, inverted 3-QuinH, 1 H), 4.74, 4.82 (ABq, *J* = 12.8 Hz, OCH_2, 2 H), 4.92, 5.02 (ABq, *J* = 12.6 Hz, OCH_2, 2 H), 6.55 (t, *J* = 2.8 Hz, ArH, 2 H), 6.80 (m, 5-PyH, 1 H), 6.85–8.01 (m, ArH, QuinH, and PyH, 22 H), 8.20 (dd, *J* = 4.0, 0.8 Hz, 6-PyH, 1 H), and 8.48 (d, *J* = 4.7 Hz, 6-Py'H, 1 H); ^{13}C NMR δ 30.54, 31.45, 31.82 [q, $C(CH_3)_3$], 31.33, 39.16, 39.26 (t, $ArCH_2Ar$), 33.24, 34.02, 34.33 [s, $C(CH_3)_3$], 69.89 (t, inverted OCH_2Quin), 75.71, 76.50, 76.81 (t, OCH_2), 118.56, 121.30, 121.58, 122.21, 123.17, 123.89, 124.96, 125.08, 125.31, 125.44, 126.02, 126.15, 126.68, 127.53, 128.30, 128.46, 129.08, 129.23 (d), 127.34, 132.14, 133.35, 133.41, 133.59, 135.29 (s, bridgehead-C), 135.53, 135.73, 136.30, 136.54 (d, 4-Py, 4-Py', 4-Quin, and 4-Quin'), 145.23, 145.43, 146.68 (s), 147.74, 148.47 (d, 6-Py and 6-Py'), 152.57, 153.13 (s), 157.61, 158.04, 158.68, and 159.01 (s, 2-Py, 2-Py', 2-Quin, and 2-Quin'); MS *m/z* 1112 (M^+, 3). Anal. Calcd for $C_{76}H_{80}N_4O_4·H_2O$: C, 80.67; H, 7.30; N, 4.95. Found: C, 80.20; H, 7.46; N, 5.19.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris[(2-pyridylmethyl)oxy]-28-[(2-quinolylmethyl)oxy]calix[4]arene (7a). Reaction of **6** with PicCl·HCl according to method A afforded partial cone tetraether **7a** in 37% yield: mp 206–208 °C (*n*-hexane); ^1H NMR δ 0.72, 0.73, 1.07, 1.35 [s, $C(CH_3)_3$, 9 H each], 3.03 (d, *J* = 12.2 Hz, *exo*-$ArCH_2Ar$, 2 H), 3.80, 3.91 (ABq, *J* = 16.7 Hz, $ArCH_2$-Ar, 2 H), 3.82, 3.98 (ABq, *J* = 16.6 Hz, $ArCH_2Ar$, 2 H), 4.19 (d, *J* = 12.4 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.25 (d, *J* = 12.3 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.43 (s, inverted OCH_2Py, 2 H), 4.67, 4.73 (ABq, *J* = 12.9 Hz, OCH_2, 2 H), 4.71 (d, *J* = 7.7 Hz, inverted 3-PyH, 1 H), 4.75, 4.84 (ABq, *J* = 12.7 Hz, OCH_2, 2 H), 4.94, 5.02 (ABq, *J* = 12.6 Hz, OCH_2, 2 H), 6.49 (td, *J* = 7.7, 1.6 Hz, inverted 4-PyH, 1 H), 6.58 (bt, *J* = 2.8 Hz, ArH, 2 H), 6.74 (m, inverted 5-PyH, 1 H), 6.81 (m, 5-Py'H, 1 H), 6.87 (bs, ArH, 2 H), 6.88 (d, *J* = 7.7 Hz, 3-Py'H, 1 H), 7.03–7.14 (m, ArH, 4-Py'H and 5-Py''H, 4 H), 7.17 (s, ArH, 2 H), 7.21 (d, *J* = 7.8 Hz, 3-Py''H, 1 H), 7.35 (d, *J* = 8.5 Hz, 4-QuinH, 1 H), 7.51 (td, *J* = 7.0, 1.0 Hz, 6-QuinH, 1 H), 7.59 (td, *J* = 7.7, 1.8 Hz, 4-Py''H, 1 H), 7.68 (td, *J* = 8.4, 1.4 Hz, 7-QuinH, 1 H), 7.75 (dd, *J* = 8.2, 0.9 Hz, 5-QuinH, 1 H), 7.99 (d, *J* = 8.4 Hz, 3-QuinH, 1 H), 8.00 (d, *J* = 8.2 Hz, 8-QuinH, 1 H), 8.20 (bt, *J* = 4.4 Hz, inverted 6-PyH and 6-Py'H, 2 H), and 8.49 (dd, *J* = 4.8, 0.8 Hz, 6-Py''H); ^{13}C NMR δ 30.89, 31.34, 31.62 [q, $C(CH_3)_3$], 31.16, 39.07, 39.13 (t, $ArCH_2Ar$), 33.43, 33.84, 34.18 [s, $C(CH_3)_3$], 69.61 (t, inverted OCH_2Py), 75.62, 76.39, 76.75 (t, OCH_2), 120.11, 120.71, 121.28, 121.62, 122.18, 123.15, 123.82, 124.97, 125.31, 126.03, 126.11, 127.48, 128.98, 129.19 (d), 132.05, 133.27, 133.55, 135.09 (s, bridgehead-C), 135.71, 136.31, 136.42, 136.55 (4-Py, 4-Py', 4-Py'', and 4-Quin), 145.12, 145.25 (s), 147.11, 147.74, 148.40 (d, 6-Py, 6-Py', and 6-Py''), 152.39, 153.01, 153.14, 153.22 (s), 157.50, 157.72, 158.01, and 158.63 (s, 2-Py, 2-Py', 2-Py'', and 2-Quin); MS *m/z* 1062 (M^+, 95). Anal. Calcd for $C_{72}H_{78}N_4O_4·H_2O$: C, 79.96; H, 7.46; N, 5.18. Found: C, 79.96; H, 7.85; N, 5.27.

5,11,17,23-Tetra-*tert*-butyl-25,26,28-tris[(2-quinolylmethyl)oxy]-27-[(2-pyridylmethyl)oxy]calix[4]arene (7b). Reaction of **6** with QuinCl·HCl according to method B gave partial cone tetraether **7b** in 28% yield: mp 105–107 °C; ^1H NMR d 0.43, 0.44, 1.19, 1.49 [s, $C(CH_3)_3$, 9 H each], 3.08, 4.31 (ABq, *J* = 12.2 Hz, $ArCH_2Ar$, 2 H), 3.11, 4.41 (ABq, *J* = 12.2 Hz, $ArCH_2$-Ar, 2 H), 3.85, 4.02 (ABq, *J* = 16.9 Hz, $ArCH_2Ar$, 2 H), 3.87, 4.07 (ABq, *J* = 16.6 Hz, $ArCH_2Ar$, 2 H), 4.62 (s, inverted OCH_2Quin, 2 H), 4.67, 4.77 (ABq, *J* = 12.4 Hz, OCH_2, 2 H), 4.79 (d, *J* = 8.6 Hz, inverted 3-QuinH, 1 H), 4.88, 4.99 (ABq, *J* = 12.3 Hz, OCH_2, 2 H), 4.90, 4.97 (ABq, *J* = 13.3 Hz, OCH_2, 2 H), 6.5–7.9 (m, aromatic, 20 H), and 8.34 (d, *J* = 4.4 Hz, 6-PyH); ^{13}C NMR δ 30.85, 31.88, 32.18 [q, $C(CH_3)_3$], 31.57, 39.62 (t, $ArCH_2Ar$), 33.55, 34.36, 34.71 [s, $C(CH_3)_3$], 70.17 (t, inverted OCH_2Quin), 76.19, 77.00, 77.44 (t, OCH_2), 118.98, 121.42, 122.35, 123.38, 125.30, 125.42, 125.58, 125.75, 125.99, 126.43, 127.01, 127.41, 127.71, 128.60, 128.79, 129.00, 129.24 (d), 129.46, 132.47, 133.79, 135.67 (s, bridgehead-C), 135.51, 135.82, 136.39, 136.55 (d, 4-Py, 4-Quin, 4-Quin', and 4-Quin''), 145.56, 145.96, 146.99 (s), 148.65 (d, 6-Py), 151.53, 153.05, 153.55, 153.76 (s), 157.95, 158.56, 158.94, and 159.33 (s, 2-Py, 2-Quin, 2-Quin', and 2-Quin''); MS *m/z* 1162 (M^+, 27). Anal. Calcd for $C_{80}H_{82}N_4O_4$: C, 82.58; H, 7.10; N, 4.81. Found: C, 82.86; H, 7.43; N, 4.67.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris[(2-pyridylmethyl)oxy]-28-(benzyloxy)calix[4]arene (7c). A mixture of **3i** (0.28 g, 0.3 mmol), PicCl·HCl (0.2 g, 1.2 mmol), and Cs_2CO_3 (0.78 g, 2.4 mmol) in dry DMF (10 mL) was heated at 60 °C for 20 h. Usual workup, followed by chromatography, gave tetraether **7c** in 75% yield: mp 195–196 °C (MeOH); ^1H NMR δ 0.69, 0.71, 1.29, 1.36 [s, $C(CH_3)_3$, 9 H each], 2.95, 4.12 (ABq, *J* = 12.2 Hz, $ArCH_2Ar$, 2 H), 3.01, 4.06 (ABq, *J* = 12.2 Hz, $ArCH_2Ar$, 2 H), 3.61, 3.69 (ABq, *J* = 16.3 Hz, $ArCH_2Ar$, 2 H), 3.79, 3.98 (ABq, *J* = 16.5 Hz, $ArCH_2Ar$,2 H), 4.40, (s, inverted OCH_2Py, 2 H), 4.44, 4.48 (ABq, *J* = 12.0 Hz, OCH_2, 2 H), 4.59, 4.70 (ABq, *J* = 12.5 Hz, OCH_2, 2 H), 4.73 (d, *J* = 7.8 Hz, 3-PyH, 1 H), 4.74, 4.79 (ABq, *J* = 12.2 Hz, 2 H), 6.43 (bt, *J* = 7.7 Hz, 4-PyH, 1 H), 6.54 (t, *J* = 2.6 Hz, ArH, 2 H), 6.73 (m, 5-PyH, 1 H), 6.80 (t, *J* = 2.9 Hz, ArH, 2 H), 6.91 (bd, *J* = 6.7 Hz, 3-Py'H and 3-Py''H, 2 H),

Table I. Summary of Data Collection, Structure Solution, and Refinement Details for 3i

(a) Crystal Data	
empirical formula	$C_{68}H_{74}O_4N_2$
fw	923.3
color, habit	colorless, block
crystal size, mm	0.20 × 0.25 × 0.35
cryst syst	monoclinic
a, Å	10.199(1)
b, Å	47.547(11)
c, Å	12.271(2)
α, deg	90
β, deg	111.14(1)
γ, deg	90
V, Å^3	5550(2)
space group	$P2_1/a$
Z	4
molecular symmetry	none
F(000)	1992
d_{calc}, g cm^{-3}	1.10
μ, cm^{-1}	0.6
(b) Data Acquisition[a]	
temp, °C	21
unit-cell reflcns (2θ-range (deg))	25 (16–38)
max 2θ (deg) for reflcns	40
hkl range of reflcns	−9 9, 0 45, 0 11
variation in three std reflcns	4% decay
reflcns measured	5518
unique reflcns	5156
R_{int}	0.02
reflcns with $I > 2\sigma(I)$	2349
(c) Structure Solution and Refinement[b]	
solution method	direct methods (SHELXS86)
H-atom treatment	riding
no. of variables in LS	653 (block-diagonal)
k in $w = 1/(\sigma^2F_o + kF_o^2)$	0.005
R, R_w, gof	0.103, 0.141, 1.63
density range in final Δ-map, e Å^{-3}	−0.30, 0.43
final shift/error ratio	<0.05
sec. extnct. correctn	1.63(52)

[a] Data collection on an Enraf Nonius CAD4 diffractometer with graphite monochromatized Mo Kα radiation (λ 0.7093 Å). [b] All calculations were done on a Silicon Graphics 4D-35TG computer system with the NRCVAX system of programs (Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384–389).

7.0–7.3 (m, ArH, PhH and PyH, 13 H), 8.18 (d, J = 4.8 Hz, 6-PyH, 1 H), 8.35 (d, J = 4.9 Hz, 6-Py′H, 1 H), and 8.40 (d, J = 4.7 Hz, 6-Py2H, 1 H); ^{13}C NMR δ 29.68, 31.41, 38.98, 39.12 (t, $ArCH_2Ar$), 30.85, 30.90, 31.65 [q, $C(CH_3)_3$], 33.41, 33.45, 34.10, 34.23 [s, $C(CH_3)_3$], 69.64 (t, inverted OCH_2Py), 75.45, 75.74, 76.57 (t, OCH_2), 120.38, 120.81, 121.53, 122.10, 123.09, 124.29, 124.71, 124.88, 125.01, 125.25, 126.04, 126.31, 127.84, 129.99, 129.61 (d), 132.06, 132.57, 133.26, 133.46, 133.54, 133.72, 135.28, 135.43 (s, bridgehead-C), 136.09, 136.28, 136.39 (d, 4-Py), 137.48 (s, Ph), 144.88, 145.01, 145.06, 145.50 (s),147.05, 147.28, 148.21 (d, 6-Py), 152.32, 152.80, 152.98, 153.10 (s), 157.70, and 157.91 (2-Py); MS m/z 1011 (M^+, 14). Anal. Calcd for $C_{69}H_{77}N_3O_4$: C, 81.86; H, 7.67; N, 4.15. Found: C, 81.31; H, 7.94; N, 4.31.

The reaction also produced the achiral cone conformer **7ca** (12%): mp 210–211 °C (MeOH); ^{1}H NMR δ 1.05, 1.13 [s, $C(CH_3)_3$, 18 H each], 2.96, 3.04, 4.29, 4.38 (d, J = 12.6 Hz, $ArCH_2Ar$, 2 H each), 4.82, 4.95 (s, OCH_2, 2 H each), 4.99, 5.03 (ABq, J = 12.2 Hz, OCH_2Py, 4 H), 6.75, 6.78 (s, ArH, 2 H each), 6.85, 6.86 (ABq, J = 2.4 Hz, ArH, 4 H), 7.0–7.3 (m, PyH and PhH, 11 H), 7.72 (d, J = 7.8 Hz, 3-PyH, 1 H), 7.74 (d, J = 7.9 Hz, 3-Py′H, 2 H), and 8.49 (d, J = 4.9 Hz, 6-PyH and 6-Py′H, 3 H); ^{13}C NMR δ 30.72, 30.92 (t, $ArCH_2Ar$), 31.37, 31.47 [q, $C(CH_3)_3$], 33.82, 33.87 [s, $C(CH_3)_3$], 77.10, 77.86, 77.91 (t, OCH_2), 122.18, 122.91, 123.37, 125.06, 125.27, 125.41, 127.56, 127.90, 129.39 (d), 133.31, 133.62, 133.75, 133.87 (s, bridgehead-C), 136.26, 136.36 (4-Py and 4-Py′), 137.79 (s, Ph), 144.67, 144.86, 144.90 (s), 148.39, 148.48 (6-Py and 6-Py′), 152.10, 152.37, 152.91 (s), 158.24 and 158.30 (2-Py and 2-Py′); MS m/z 1011 (M^+, 7). Anal. Calcd for $C_{69}H_{77}N_3O_4 \cdot CH_3OH$: C, 80.52; H, 7.82; N, 4.02. Found: C, 80.58; H, 7.76; N, 4.22.

5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27-(benzyloxy)-28-propoxycalix[4]arene (8). A mixture of triether 3i (0.276 g, 0.3 mmol) and NaH (0.015 g, 0.6 mmol) in anhydrous THF (10 mL) was stirred at rt for 0.5 h. *n*-Propyl bromide (0.07 g, 0.6 mmol) was then added, and the reaction mixture was refluxed for 1.5 h. The excess NaH was destroyed by addition of MeOH (1 mL), and the solvent was evaporated. The residue was partitioned between water and DCM. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by recrystallization from MeOH to afford asymmetrical tetraether as white prisms (0.23 g, 80%): mp 196–197 °C; ^{1}H NMR δ 0.60 (t, J = 7.5 Hz, $OCH_2CH_2CH_3$, 3 H), 0.94, 0.95 [s, $C(CH_3)_3$, 9 H each], 1.23 [s, $C(CH_3)_3$, 18 H], 1.78 (m, $OCH_2CH_2CH_3$, 2 H), 3.05 (d, J = 12.6 Hz, *exo*-$ArCH_2Ar$, 2 H), 3.09 (d, J = 12.6 Hz, *exo*-$ArCH_2Ar$, 1 H), 3.10 (d, J = 12.4 Hz, *exo*-$ArCH_2Ar$, 1 H), 3.73 (m, $OCH_2CH_2CH_3$, 2 H), 4.37 (d, J = 12.2 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.40 (d, J = 12.4 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.41 (d, J = 12.5 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.42 (d, J = 12.1 Hz, *endo*-$ArCH_2Ar$, 1 H), 4.72, 4.79 (ABq, J = 11.1 Hz, OCH_2, 2 H), 4.83, 4.93 (ABq, J = 12.3 Hz, OCH_2, 2 H), 5.01, 5.08 (ABq, J = 13.3 Hz, OCH_2, 2 H), 6.61–7.35 (m, PhH, ArH and PyH, 21 H), 7.44 (td, J = 7.7, 1.8 Hz, 4-PyH, 1 H), 7.63 (d, J = 7.8 Hz, 3-PyH, 1 H), 7.91 (d, J = 7.6 Hz, 3-Py′H, 1 H), 8.47 (ddd, J = 4.8, 1.8, 0.9 Hz, 6-PyH, 1 H), and 8.52 (ddd, J = 4.9, 1.8, 0.9 Hz, 6-Py′H, 1 H); ^{13}C NMR δ 9.77 (q, $OCH_2CH_2CH_3$), 22.78 (t, $OCH_2CH_2CH_3$), 30.90, 30.98, 31.19 (t, $ArCH_2Ar$), 31.30, 31.61 [q, $C(CH_3)_3$], 33.73, 33.95 [s, $C(CH_3)_3$], 76.39, 77.60, 78.31 (t, OCH_2), 121.92, 122.30, 123.07, 123.24 (d, 3,5-Py and 3,5-Py′), 124.79, 124.89, 124.92, 125.08, 125.22, 125.28, 125.53, 125.63, 127.71, 128.04, 129.52 (d, Ph and Ar), 132.65, 132.76, 132.91, 133.00, 134.30, 134.38, 134.88, 134.92 (s, bridgehead-C), 135.97, 136.18 (d, 4-Py and 4-Py′), 137.92 (s, Ph), 144.54, 144.60, 144.65, 144.84 [s, $ArCC(CH_3)_3$], 148.27, 148.80 (d, 4-Py and 4-Py′), 152.23, 152.38, 153.55. 153.84 (s, $ArCOCH_2$), 158.18 and 158.83 (s, 2-Py and 2-Py′); MS m/z 962 (M^+, 47). Anal. Calcd for $C_{68}H_{78}N_2O_4$: C, 82.29; H, 8.16; N, 2.91. Found: C, 82.33; H, 8.28; N, 3.07.

Structural Analysis for Calixarene 3i. Details of the X-ray experimental conditions, cell data, data collection, and refinement for molecule **3i** are summarized in Table I. Molecule **3i** crystallized in the monoclinic system, and the space group was uniquely determined from the systematic absences ($0k0$ absent if $k = 2n + 1$, $h0l$ absent if $h = 2n + 1$) and subsequent successful refinement as $P2_1/a$. The crystal diffracted weakly (only 42% of the measured data could be labeled "observed" in the 2–20° θ range, ($I > 2\sigma(I)$). The structure was solved by direct methods using SHELXS86[24] which revealed the non-hydrogen atoms of the calixarene core and refined using the NRCVAX[25] suite of programs. One pyridinyl ring was disordered (80/20) over two orientations. The remaining non-hydrogen atoms were located in subsequent difference Fourier syntheses. Hydrogen atoms (visible in difference maps at an intermediate stage of the refinement) were included at geometrically idealized positions but restrained to ride on the carbon atom to which they were bonded (C–H 0.95 Å) (the phenolic hydrogen was not clearly resolved). The decision as to which was a nitrogen atom and which was a carbon atom in the pyridine rings was made unequivocally in each case from difference maps (by unambiguous location of all pyridine H atoms). Refinement was by block-diagonal least-squares calculations on F, initially with isotropic and later with anisotropic thermal parameters for all non-hydrogen atoms (except the non-hydrogen atoms of the minor orientation of the disordered pyridinyl group attached to ring C which was refined isotropically). The figures were prepared with the aid of ORTEPII.[26] Atomic coordinates and full details of molecular dimensions have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Copies of the structure factor listing are available from the authors.

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