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Resolution of inherently chiral calix[4]arenes with AABB and CDCD substitution patterns on the upper and lower rims, respectively

Salvatore Caccamese,[a,*] Alessandra Bottino,[b] Francesca Cunsolo,[b] Silvia Parlato[a] and Placido Neri[c,*]

[a]*Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy*
[b]*Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, CNR, Via del Santuario 110, I-95028 Valverde (CT), Italy*
[c]*Dipartimento di Chimica, Università di Salerno, Via S. Allende, I-84081 Baronissi (SA), Italy*

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Abstract

Proximal di-*tert*-butylcalix[4]arene (5,11-di-*tert*-butylcalix[4]arene-25,26,27,28-tetrol) **1b**, obtained by direct partial removal of *tert*-butyl groups from *p*-*tert*-butylcalix[4]arene, gave high yields of inherently chiral derivatives upon 'symmetry breaking' by *syn*-distal di-*O*-alkylation or di-*O*-acylation in the presence of K_2CO_3. The chirality of these compounds was proven by the splitting of ^1H NMR signals in the presence of Pirkle's reagent and in some cases by HPLC enantiomeric resolution using chiral stationary phases and corroborated by mirror-image CD spectra.

1. Introduction

The intrinsic recognition ability of cavity-shaped calix[4]arenes macrocycles[1] can be enhanced and variously modulated to give more sophisticated molecular receptors. Thus, for example, by introducing chirality it is possible to obtain receptors with chiral discrimination ability.[2] Chiral calix[4]arenes can be obtained simply by the introduction of chiral substituents on the 'lower rim' or on the 'upper rim' of the macrocycle[2,3] or by generation of inherent chirality exploiting their non-planar molecular structure.[4] Obviously, in the latter instance, the calix[4]arene conformation has to be fixed in order to avoid racemization.

Inherently chiral calix[4]arenes can be obtained eliminating any symmetry plane or inversion center by combining a proper substitution pattern with any given conformation[4,5] or producing C_2- or C_4-dissymmetric derivatives.[6] Thus, for a calix[4]arene in the cone conformation at least

* Corresponding authors. E-mail: scaccamese@dipchi.unict.it, neri@unisa.it

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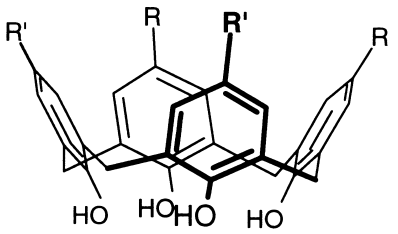
three kinds of aromatic rings are required to give inherent chirality. This condition can be met with a 'fragment' macrocyclization of three or four differently *p*-substituted rings[7] or by a proper differentiating functionalization of a 'native' calix[4]arene (e.g. *p-tert*-butylcalix[4]arene **1a**). In this latter instance various approaches based on the regio- and stereoselective functionalization at the lower rim have been proposed.[4,5,8]



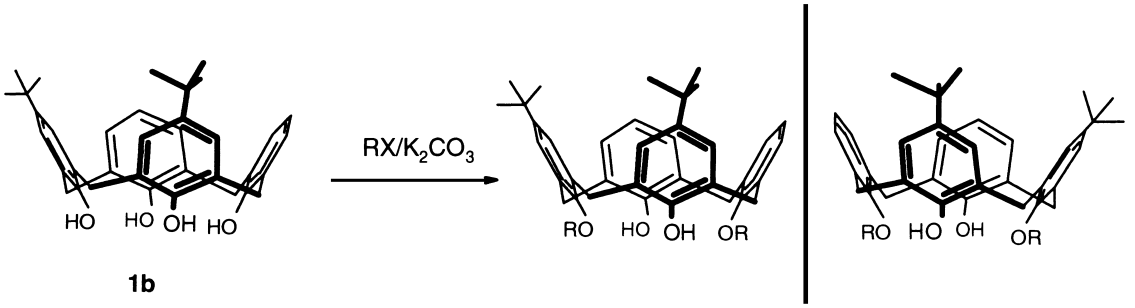
1 R = R' = H
1a R = R' = Bu^t
1b R = H, R' = Bu^t

A different interesting approach requires a calix[4]arene-tetrol proximally disubstituted on the upper rim (AABB substitution) which can be easily and efficiently *syn*-distally derivatized on the lower rim (CDCD substitution) using weak-base promoted standard reactions. This idea was originally realized by Böhmer who prepared the starting AABB-calix[4]arene-tetrol using a multistep fragment condensation.[9] It occurred to us that a more convenient procedure would be realizable by exploiting as starting calix[4]arene-tetrol the proximal de-*tert*-butylated-calix[4]arene **1b**, recently described in the literature.[10] Therefore, we undertook an independent investigation on the preparation of **1b** and on its distal di-*O*-functionalization to give inherently chiral calix[4]arenes. In this paper we wish to report on the results of this study and on the first resolution by enantioselective HPLC of inherently chiral calix[4]arenes with AABB and CDCD substitution patterns on the upper and lower rims, respectively.

2. Result and discussion

Partial de-*tert*-butylation of *p-tert*-butylcalix[4]arene **1a** was recently obtained by a Nafion-H catalyzed *trans*-butylation of toluene, used as the acceptor.[10] Under these conditions proximal di-*tert*-butylcalix[4]arene **1b** could be isolated in 5% yield by chromatography. We found that better yields of **1b** (23% with respect to **1a**) can be obtained by conventional $AlCl_3$-catalyzed *trans*-butylation[11] using *p-H*-calix[4]arene **1** as acceptor in anhydrous $CHCl_3$. Obviously, the consequent butylation of **1** contributes to the observed improvement of the yield of **1b**.

Calix[4]arene **1b**, possesses C_s symmetry which can be 'broken' by introducing two distal substituents on the lower rim and thus generating asymmetric inherently chiral calix[4]arenes.[9] It is well known that this substitution can be efficiently achieved using weak-base promoted alkylation.[12] Therefore, calix[4]arene **1b** was subjected to alkylation in acetonitrile or acetone in the presence of K_2CO_3 using *n*-PrI or *p*-X-benzyl bromide (X = Bu^t, NO_2, Br,) as alkylating agent. The corresponding *syn*-distal dialkylated calix[4]arenes **2**–**5** (Scheme 1) were isolated in 46–82% yield. The conditions used for the K_2CO_3-promoted alkylation were successfully extended to



1b

2-7

2 R = $CH_2CH_2CH_3$
3 R = *p*-$CH_2C_6H_4Bu^t$
4 R = *p*-$CH_2C_6H_4NO_2$
5 R = *p*-$CH_2C_6H_4Br$
6 R = $COCH_3$
7 R = COC_6H_5

Scheme 1.

acylation reaction with acetyl or benzoyl chloride which afforded 1,3-*syn*-diacetate **6** and 1,3-*syn*-dibenzoate **7** in 75 and 63% yield, respectively.

The presence of two *O*-substituents in compounds **2**–**7** was proved by FAB (+) mass spectra, while their distal positioning was confirmed by ^1H and ^{13}C NMR spectra. In fact, these spectra clearly demonstrate asymmetric structures only compatible with the AABB–CDCD substitution, whereas the alternative 1,2-di-*O*-substitution (AABB–CCDD pattern) would lead to C_s-symmetric structures. Thus, in their ^1H NMR spectra, apart from the obvious difference due to substituents, two separate singlets attributable to two different *tert*-butyl groups and four AX systems for $ArCH_2Ar$ groups are present. These data and the presence of four different $ArCH_2Ar$ signals in the 32–34 ppm range of ^{13}C NMR spectra indicate that all derivatives are in the *cone* conformation.[13]

Inherent chirality of calix[4]arenes **2**–**7** is a direct consequence of their asymmetry. In these cases racemization cannot occur because the inversion of alkylated rings, by passage through the calix[4]arene annulus, is prevented for bulkiness reasons. Of course, the residual mobility of OH-bearing rings has no influence in this respect. Further evidence of chirality was obtained by the doubling of resonances in the ^1H NMR spectra upon addition of Pirkle's reagent [(*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol], as exemplified by Fig. 1 for compound **7**, which shows the splitting of the $ArCH_2Ar$ AX systems.

Definite proof of chirality was obtained by resolution using enantioselective HPLC. The chromatographic results are presented in Table 1 and typical HPLC chromatograms are shown in Fig. 2. The separation factor (α) and resolution factor (R_s) are much better for esters **6** and **7** with respect to ether **2**. This behavior can be attributed to the presence of carbonyls in **6** and **7** that can interact via hydrogen bond with the carbamate moiety of the chiral stationary phase (CSP), Chiralcel OD. Indeed, compound **2** is very weakly adsorbed on the CSP, exhibiting a lower capacity factor K'_1 yet at a much lower polarity of the mobile phase. Compounds **3** and **5** exhibit a behavior very similar to that of compound **2**. Compound **4** is instead totally retained on the CSP also at high polarity of the mobile phase (hexane:2-propanol, 7:3) giving a very high K'

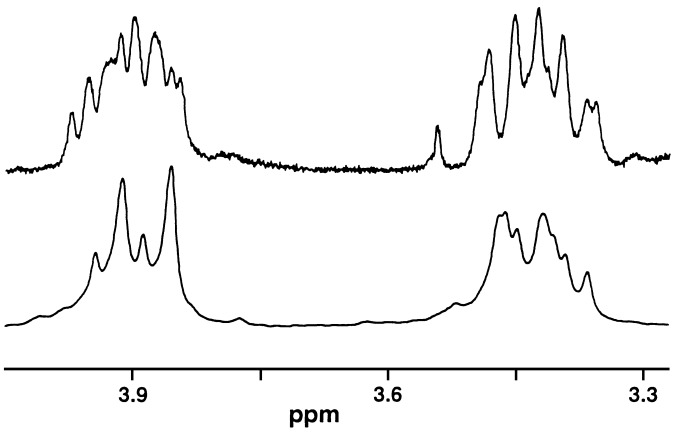


Figure 1. Methylene region of the ^{1}H NMR spectra (250 MHz, $CDCl_3$, 295 K) of **7** in the presence (top) or in the absence (bottom) of Pirkle's reagent

(5.07) and a unique chromatographic peak. Enantioseparation of compounds **2**, **6** and **7** was also tried using Chiralpak AD as CSP but the results were totally negative under either similar or different conditions (polarity of mobile phase and flow rate). The strong difference in chiral recognition of cellulose and amylose derivatives (Chiralcel OD and Chiralpak AD, respectively) is due to a different chiral environment around the carbamate residue and to the greater width and compactness of the helix in the amylose derivative.[14] For other calixarene derivatives, with much larger dimensions as 1,4:2,5-calix[8]bis-crowns[15] and calix[5]crowns,[16] some of us experienced that Chiralpak AD was instead much more effective than Chiralcel OD in the enantiomeric separation. Other features of compounds **2**, **6** and **7** that can be extracted from the results in

Table 1
HPLC behaviour of inherently chiral calix[4]arenes **2**, **6** and **7** on Chiralcel OD

Compd	R	A(%)[a]	FR[b]	K'$_1$[c]	α	R_s
6	-$COCH_3$	20	1.0	0.87	1.26	0.8
6		10	1.0	1.32	1.29	1.2
6		5[d]	1.0	2.11	1.30	1.6
7	-COC_6H_5	20[d]	1.4	1.55	1.64	2.5
7		20	1.2	1.68	1.67	3.0
7		20	1.0	2.03	1.63	3.1
7		10	0.7	3.00	1.67	3.7
2	-$(CH_2)_2CH_3$	1	0.7	0.50	NS[e]	–
2		1	0.4	0.69	1.08	<0.4

[a]Percentage of 2-propanol in *n*-hexane. [b]Flow rate (mL/min), FR = 1.4, t_0 = 2.7 min; FR = 1.2, t_0 = 2.9 min; FR = 0.7, t_0 = 4.81 min; FR = 0.4, t_0 = 7.93 min. [c]Capacity factor of the first-eluted enantiomer. [d]Experimental conditions used for semipreparative isolation, t_1 = 9.96 min, t_2 = 12.00 min for compound **6**, t_1 = 6.90 min, t_2 = 9.60 min for compound **7**. [e]Not separated.

Table 1 and Fig. 2 are that: (i) a decrease in the polarity of mobile phase has a beneficial effect on enantioselectivity α and resolution factor R_s; and (ii) a decrease in the flow rate of the mobile phase also has a beneficial effect on these parameters and this is crucial for obtaining enantioseparation of compound **2**.

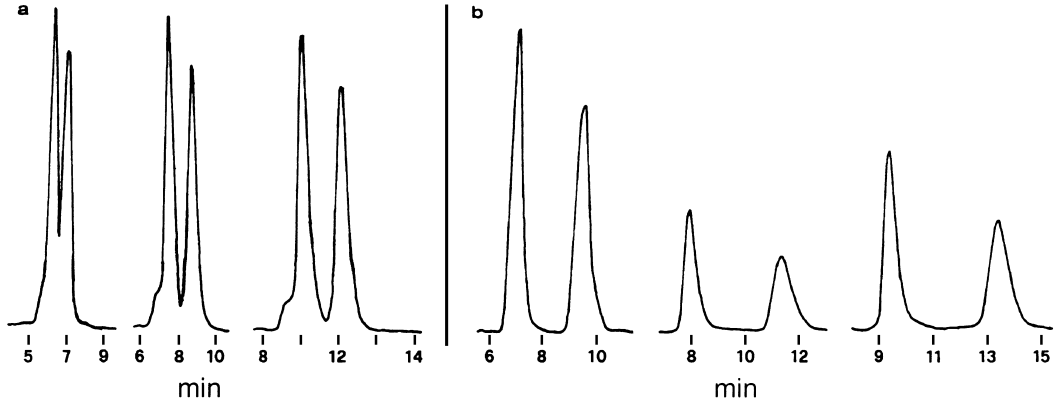


Figure 2. Chiralcel OD HPLC enantioresolution of compounds **6** (a) and **7** (b). Chromatograms in (a) show the relationship between enantioselectivity and polarity of mobile phase: flow rate 1 mL/min, eluant *n*-hexane:2-propanol 8:2, 9:1 and 95:5, from left to right. Chromatograms in (b) show the relationship between enantioselectivity and flow rate of mobile phase (8:2 *n*-hexane:2-propanol): 1.4, 1.2 and 1.0 mL/min, from left to right

The good resolution factors observed for **6** and **7** (Table 1) allowed a separation of their enantiomers by repeated 50 μl injections (0.2÷0.3 mg) and collection of the eluates corresponding to the two chromatographic peaks. Analytical HPLC reruns of these peaks in any case gave values >99% for the enantiomeric excess (ee). The conditions for these experiments are those which gave good R_s (1.6 and 2.5 for **6** and **7**, respectively) and reasonable elution times (9.96 and 6.90 min) for the first peak of **6** and **7**, respectively (Table 1).

The CD spectra of both eluates were measured and they were mirror images of each other (Fig. 3) indicating their enantiomeric nature. The shape and the absorption maxima of the CD curves of compounds **6** and **7** are very similar indicating that the chromophores contributing to the CD spectrum are similar. Only a slight difference is present at lower wavelengths for compound **7**, possessing benzoyl group as an additional chromophore. Remarkably, the chromatographic peak giving a positive CD at λ 287 nm is the second eluted in the case of compound **6**, whereas it is the first eluted for compound **7**. This behavior can be due, in our opinion, to an inversion of elution order of the enantiomer possessing the same absolute configuration for compounds **6** and **7**. This fact could originate from an additional chiral recognition process of the π-acid benzoyl group in **7** with the π-basic carbamate moiety of the CSP. This hypothesis is supported by the much stronger interaction of the enantiomeric pair of **7** with the CSP, as shown by the comparison of the capacity factors in 8:2 *n*-hexane:2-propanol at a flow rate of 1 mL/min ($K'_1 = 0.87$ and 2.03 for compounds **6** and **7**, respectively). This 'crossing effect' in chiral HPLC has to be taken into account to avoid incorrect assignment of absolute configuration by extrapolating the relationship elution-order/CD-spectrum obtained experimentally for a single compound of a homologous series.

In accordance with the above results, a specific rotation $[\alpha]_D^{25}$ +7.4 (*c* 0.6, EtOH) was measured for the first-eluted sample of compound **6**, while the second one afforded an experimental $[\alpha]_D^{25}$

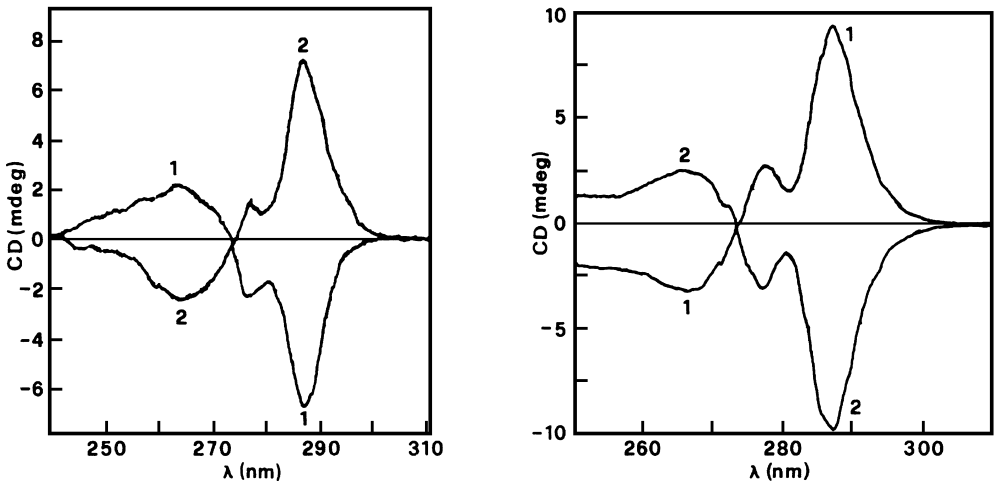


Figure 3. CD spectra (ethanol, 295 K) of the enantiomers of compound **6** (left) and **7** (right) obtained from the first (1) and the second (2) eluted peaks

–7.3 (*c* 0.5, EtOH), in agreement with a 99% ee. A similar result was also obtained for compound **7**, which gave specific rotations $[\alpha]_D^{25}$ –20.0 (*c* 0.3, EtOH) and $[\alpha]_D^{25}$ +9.8 (*c* 0.2, EtOH) for the first and second eluted samples, respectively.

3. Conclusion

In the present paper we have demonstrated that $AlCl_3$-catalyzed partial *trans*-de-*tert*-butylation of *p*-*tert*-butylcalix[4]arene affords acceptable amounts of proximal di-*tert*-butylcalix[4]arene. This compound, because of its AABB-substitution pattern at the upper rim, provides an easy access to inherently chiral calix[4]arenes of the AABB–CDCD-type by standard weak-base-promoted *syn*-distal di-*O*-alkylation or di-*O*-acylation. Enantiomeric resolution by HPLC of some racemic mixtures furnished the first optically active calix[4]arenes of this type. The inherently chiral calix[4]arenes of the AABB–CDCD-type described here, because of their two hydroxy groups yet available for further functionalization, can be considered versatile substrates for the preparation of more elaborated chiral calix[4]arene derivatives.

4. Experimental

4.1. General

NMR spectra were taken on a Bruker ARX-250 spectrometer operating at 250.13 (^{1}H) and 62.9 (^{13}C) MHz, using Me_4Si as internal standard. FAB(+) MS spectra were recorded on a VG-ZAB 2-SE instrument, using 3-nitrobenzyl alcohol as matrix. Elemental analyses were obtained from the Department of Pharmaceutical Sciences, University of Catania. Column chromatography was performed using silica gel (Kieselgel-60, 63–200 μm, Merck). Preparative TLC was performed using silica gel plates (Kieselgel 60 F_{254}, 1 mm Merck). All chemicals were reagent

grade and were used without further purification. Anhydrous $CHCl_3$ (Sure/Seal™) was purchased from Aldrich. *p-tert*-Butylcalix[4]arene **1a**[17] and *p-H*-calix[4]arene **1**[11] were prepared according to literature procedures. The HPLC system consisted of a Varian 5060 liquid chromatograph with Valco sample loops, a Jasco Uvidec III spectrophotometric detector operating at 240 nm, and a Hewlett–Packard 3395 integrator or Omniscribe Houston recorder for fraction collecting. The columns (250×4.6 mm) used were Chiralcel OD (cellulose tris-3,5-dimethylphenylcarbamate) and Chiralpak AD (amylose tris-3,5-dimethylphenylcarbamate) coated on 10 μm silica gel, both from Daicel (Tokyo). Column void volume (t_0) was measured by injection of tri-*tert*-butylbenzene as a non-retained compound.[18] HPLC chromatographic parameters were given as usual.[19] Retention times (t_R) were mean values of two replicate determinations. All separations were carried out at room temperature. CD spectra were recorded on a Jasco 600 spectropolarimeter. Optical rotation measurements were performed on a Jasco DIP-370 digital polarimeter.

4.2. *Partial* trans-*de*-tert-*butylation of* p-tert-*butylcalix[4]arene*

Anhydrous $AlCl_3$ (2.5 g, 18 mmol) was added to a suspension of *p-H*-calix[4]arene **1** (1.3 g, 3.1 mmol) and *p-tert*-butylcalix[4]arene **1a** (2.0 g, 3.1 mmol) in anhydrous $CHCl_3$ (50 mL). The mixture was stirred at room temperature for 4 h. After quenching by addition of 1N HCl (50 mL), the reaction mixture was extracted four times with 50 mL portions of $CHCl_3$. The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent, the crude product was taken up in CH_3CN and the suspension filtered to remove unreacted *p-tert*-butylcalix[4]arene. The filtrate was taken to dryness under reduced pressure and the residue washed with MeOH to give 2.40 g of a mixture of partially butylated calix[4]arenes. These compounds were separated using the Chromatotron (hexane:THF, 9:1),[10] whereas analytical samples of **1b** (ca. 25 mg each) were obtained by preparative TLC (acetone:hexane, 1:9). 5,11-Di-*tert*-butylcalix[4]arene-25,26,27,28-tetrol **1b** was obtained in 23% yield with respect to starting *p-tert*-butylcalix[4]arene. All analytical and spectral data of **1b** were identical to those reported.[10]

4.3. *General procedure for* syn-*distal di*-O-*alkylation or di*-O-*acylation of* ***1b***

A suspension of **1b** (100 mg, 0.18 mmol) and K_2CO_3 (77 mg, 0.56 mmol) in CH_3CN (10 mL) (or acetone, in the preparation of **6**) was refluxed for 0.5 h under stirring. Then the alkyl- or acyl-halide (0.56 mmol) was added and the reaction mixture was refluxed for additional 3 h under stirring. After cooling, the solvent was removed under vacuum to leave a residue that was suspended in 1N HCl. The insoluble material was collected by filtration, washed with MeOH, dried and purified by chromatography when required.

4.3.1. *5,11-Di*-tert-*butyl-26,28-bis[propyloxy]calix[4]arene-25,27-diol* ***2***

Compound **2** was isolated by column chromatography (acetone:petroleum ether, 1:9 v/v) as a white powder, 52 mg (yield 46%); mp 112–114°C; $R_f = 0.29$ (acetone:petroleum ether, 1:9 v/v); ^1H NMR ($CDCl_3$, 295 K) δ 1.10, 1.25 [s, $C(CH_3)_3$, 9H each], 1.29 (t, $J = 3.1$ Hz, $CH_3CH_2CH_2$, 3H), 1.30 (t, $J = 3.0$ Hz, $CH_3CH_2CH_2$, 3H), 2.06 (overlapped, $CH_3CH_2CH_2$, 4H), 3.31 and 4.25 (AX, $J = 12.9$ Hz, $ArCH_2Ar$, 2H), 3.36 and 4.30 (AX, $J = 13.1$ Hz, $ArCH_2Ar$, 2H), 3.36 and 4.35 (AX, $J = 12.9$ Hz, $ArCH_2Ar$, 2H), 3.37 and 4.39 (AX, $J = 12.7$ Hz, $ArCH_2Ar$, 2H), 3.95 (t, $J = 6.1$ Hz, $CH_3CH_2CH_2O$, 2H), 3.97 (t, $J = 6.3$ Hz, $CH_3CH_2CH_2O$, 2H), 6.61 (t, $J = 7.4$ Hz, ArH, 1H), 6.77 (t, $J = 7.7$ Hz, ArH, 1H), 6.88 (d, $J = 2.5$ Hz, ArH, 2H), 6.95–7.05 (overlapped, ArH, 6H), 8.19,

8.43 (s, OH, 1H each). ^{13}C NMR ($CDCl_3$, 295 K) δ 10.9 (q), 23.4 (t), 31.2 (q), 31.3 (t), 31.6 (q), 31.8, 32.0 (t), 33.8, 34.7 (s), 78.2, 78.4 (t), 119.0, 124.8, 125.4, 125.5, 126.1 (d), 127.1 (s), 128.1 (d), 128.3, 128.4 (s), 128.6 (d), 132.2, 133.1, 134.1, 134.2, 141.5, 147.0, 149.7, 150.6, 152.2, 153.3 (s). FAB (+) MS m/z 621 (MH^+). Anal. calcd for $C_{42}H_{52}O_4$: C, 81.29; H, 8.39. Found: C, 81.45; H, 8.15.

4.3.2. 5,11-Di-tert-*butyl-26,28-bis[(4*-tert-*butylbenzyl)oxy]calix[4]arene-25,27-diol* ***3***

The crude product was washed twice with CH_3OH to give **3** as a white powder, 110 mg (yield 73%); mp 185–186°C; R_f = 0.23 (acetone:petroleum ether, 1:9 v/v); ^{1}H NMR ($CDCl_3$, 295 K) δ 1.05, 1.29, 1.38, 1.39 [s, $C(CH_3)_3$, 9H each], 3.26 and 4.24 (AX, J = 12.8 Hz, $ArCH_2Ar$, 4H), 3.28 and 4.32 (AX, J = 13.3 Hz, $ArCH_2Ar$, 2H), 3.29 and 4.35 (AX, J = 13.2 Hz, $ArCH_2Ar$, 2H), 5.07, 5.09 (s, OCH_2, 2H each), 5.08 (s, OH, 1H), 6.64 (t, J = 7.5 Hz, ArH, 1H), 6.70–7.72 (overlapped, ArH and OH, 18H). ^{13}C NMR ($CDCl_3$, 295 K) δ 31.1, 31.4, 31.6 (q), 31.8, 31.9 (t), 33.8, 34.0, 34.6 (s), 78.0, 78.2 (t), 118.9, 124.7, 124.8, 125.4, 126.1 (d), 127.3 (s), 127.6, 127.8, 128.1, 128.5, 128.6 (d), 132.1, 132.9, 133.9, 134.1, 141.5, 147.0, 150.2, 150.6, 150.9, 151.1, 152.4, 153.2 (s). FAB (+) MS m/z 839 (MH^+). Anal. calcd for $C_{58}H_{68}O_4$: C, 84.06; H, 8.21. Found: C, 84.2; H, 8.1.

4.3.3. 5,11-Di-tert-*butyl-26,28-bis[(4-nitrobenzyl)oxy]calix[4]arene-25,27-diol* ***4***

Compound **4** was isolated by column chromatography (acetone:petroleum ether, 15:85 v/v) as a white powder, 115 mg (yield 79%); mp > 240°C dec.; R_f = 0.25 (acetone:petroleum ether, 2:8 v/v); ^{1}H NMR ($CDCl_3$, 295 K) δ 1.06 [s, $C(CH_3)_3$, 9H], 1.27 [s, $C(CH_3)_3$, 9H], 3.37 and 4.22 (AX, J = 13.3 Hz, $ArCH_2Ar$, 2H), 3.35 and 4.24 (AX, J = 12.2 Hz, $ArCH_2Ar$, 2H), 3.42 and 4.28 (AX, J = 12.4 Hz, $ArCH_2Ar$, 2H), 3.42 and 4.29 (AX, J = 12.1 Hz, $ArCH_2Ar$, 2H), 5.15 (s, OCH_2, 2H), 5.17 (s, OCH_2, 2H), 6.67 (t, J = 7.6 Hz, ArH, 1H), 6.78–7.08 (m, ArH, 9H), 7.44 (s, OH, 1H), 7.60 (s, OH, 1H), 7.94 and 8.10 (AB, J = 8.6 Hz, ArH, 8H). ^{13}C NMR ($CDCl_3$, 295 K) δ 31.1 (q), 31.3, 31.4 (t), 31.6 (q), 31.8 (t), 33.7, 33.9 (s), 76.9, 77.0 (t) 119.5, 123.9, 125.2, 125.5, 125.7, 126.0, 126.5 (d), 126.8 (s), 127.7, 127.8, 128.5, 128.8, 129.1 (d), 131.7, 132.4, 133.4, 142.1, 143.9, 144.1, 148.0, 149.3, 150.3, 151.6, 153.0 (s). FAB (+) MS m/z 807 (MH^+). Anal. calcd for $C_{50}H_{50}N_2O_8$: C, 74.42; H, 6.24; N, 3.47. Found: C, 74.48; H, 6.26; N, 3.46.

4.3.4. 5,11-Di-tert-*butyl-26,28-bis[(4-bromobenzyl)oxy]calix[4]arene-25,27-diol* ***5***

Compound **5** was isolated by column chromatography (gradient acetone/petroleum ether) as a white powder, 129 mg (yield 82%); mp 164–165°C; R_f = 0.24 (acetone:petroleum ether, 1:9 v/v); ^{1}H NMR ($CDCl_3$, 295 K) δ 0.97 (s, $C(CH_3)_3$, 9H), 1.20 [s, $C(CH_3)_3$,9H], 3.24 and 4.13 (AX, J = 13.3 Hz, $ArCH_2Ar$, 2H), 3.25 and 4.15 (AX, J = 12.9 Hz, $ArCH_2Ar$, 2H), 3.26 and 4.21 (2 AX overlapped, J = 13.1 Hz, $ArCH_2Ar$, 4H), 4.89 (s, OCH_2, 2H), 4.92 (s, OCH_2, 2H), 6.57 (t, J = 7.5 Hz, ArH, 1H), 6.67 and 6.68 (AB, J = 6.8 Hz, ArH, 1H), 6.75–7.51 (m, ArH and OH, 17H), 7.59 (s, OH, 1H); ^{13}C NMR ($CDCl_3$, 295 K) δ 31.2 (q), 31.4 (t), 31.7 (q), 31.9, 32.4 (t), 33.9, 34.1 (s), 77.4, 77.6 (t), 119.2 (d), 121.1, 121.2 (s), 121.1, 125.0, 125.1, 125.6 (d), 125.8 (s), 126.3, 126.9, 127.8, 128.0, 128.1, 128.3, 128.7, 128.8, 129.3, 129.4, 130.7, 131.9, 132.0 (d), 133.6, 135.7, 135.9, 141.8, 147.5, 150.0, 151.2, 152.1, 153.4 (s). FAB (+) MS m/z 875 (MH^+). Anal. calcd for $C_{50}H_{50}Br_2O_4$: C, 68.85; H, 5.76. Found: C, 68.87; H, 5.74.

4.3.5. 5,11-Di-tert-*butyl-26,28-bis-acetyloxycalix[4]arene-25,27-diol* ***6***

Compound **6** was isolated by column chromatography (acetone:petroleum ether, 1:9 v/v) as a white powder, 84 mg (yield 75%); mp 131–133°C; R_f = 0.25 (acetone:petroleum ether, 1:9 v/v); ^{1}H

NMR ($CDCl_3$, 295 K) δ 1.06, 1.32 [s, $C(CH_3)_3$, 9H each], 2.23, 2.25 (s, CH_3CO, 3H each), 3.56 and 3.85 (AX, $J=14.5$ Hz, $ArCH_2Ar$, 4H), 3.58 and 3.86 (AX, $J=14.5$ Hz, $ArCH_2Ar$, 2H), 3.59 and 3.86 (AX, $J=14.5$ Hz, $ArCH_2Ar$, 2H), 4.92, 5.17 (s, OH, 1H each), 6.78 (t, $J=7.6$ Hz, ArH, 1H), 6.84–7.10 (overlapped, ArH, 9H). ^{13}C NMR ($CDCl_3$, 295 K) δ 20.7, 31.1 (q), 31.4 (s), 31.7 (q), 33.7, 34.0, 34.1, 34.2 (t), 119.8, 125.5, 125.8, 126.0, 126.1, 126.4, 126.5 (d), 127.0, 127.5, 127.9, 128.0 (s), 128.8, 129.0, 129.1, 129.4 (d), 131.3, 131.8, 132.6, 132.7, 142.5, 143.8, 146.0, 149.1, 150.4, 152.8, 168.5, 168.7 (s). FAB (+) MS m/z 621 (MH^+). Anal. calcd for $C_{40}H_{44}O_6$: C, 77.39; H, 7.14. Found: C, 77.50; H, 7.25.

*4.3.6. 5,11-Di-*tert*-butyl-26,28-bis[benzoyloxy]calix[4]arene-25,27-diol* **7**

Compound **7** was isolated by column chromatography (acetone:petroleum ether, 1:9 v/v) as a white powder, 85 mg (yield 63%); mp 128–130°C; $R_f=0.26$ (acetone:petroleum ether, 1:9 v/v); ^1H NMR ($CDCl_3$, 295 K) δ 0.96, 1.20 [s, $C(CH_3)_3$, 9H each], 3.48 and 4.00 (AX, $J=14.1$ Hz, 2H), 3.50 and 3.97 (AX, $J=14.1$ Hz, $ArCH_2Ar$, 2H), 3.52 and 3.97 (AX, $J=14.1$ Hz, $ArCH_2Ar$, 2H), 3.53 and 3.97 (AX, $J=14.1$ Hz, $ArCH_2Ar$, 2H), 5.13, 5.27 (s, OH, 1H each), 6.71 (t, $J=7.4$ Hz, ArH, 1H), 6.82 (bs, ArH, 2H), 6.83 (d, $J=3.6$ Hz, ArH, 1H), 6.86 (d, $J=1.6$ Hz, ArH, 1H), 7.01 and 7.06 (AB, $J=2.3$ Hz, ArH, 4H), 7.56 (t, $J=7.3$ Hz, ArH, 4H), 7.70 (t, $J=1.3$ Hz, ArH, 1H), 7.73 (t, $J=1.9$ Hz, ArH, 1H), 7.76 (t, $J=1.2$ Hz, ArH, 1H), 8.34–8.38 (overlapped, ArH, 4H). ^{13}C NMR ($CDCl_3$, 295 K) δ 30.9, 31.5 (s), 32.5, 32.6, 32.8 (t), 33.8, 34.0 (s), 119.7, 125.5, 125.8, 126.0, 126.2, 128.8, 129.1, 129.2, 130.5, (d), 131.3, 131.9, 132.4, 132.6 (s), 133.8, 134.5 (d), 142.6, 143.5, 145.6, 148.9, 150.3, 152.8 (s), 164.7, 164.8 (s). FAB (+) MS m/z 755 (MH^+). Anal. calcd for $C_{50}H_{48}O_6$: C, 80.64; H, 6.45. Found: C, 80.40; H, 6.35.

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