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Regioselective intramolecular bridging of *p-tert*-butylcalix[7]arene

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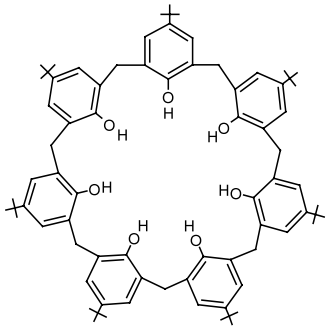
Abstract—The first examples of singly bridged calix[7]arenes **2**–**4** have been obtained by base-promoted direct *O*-alkylation of *p-tert*-butylcalix[7]arene with a variety of bis-electrophiles including $BrCH_2Cl$, oligoethylene glycol ditosylates, and 1,4-bis(bromomethyl)benzene. 1,2-Bridging was favored with 'short bite' spanning elements, while the 1,4-isomer predominated with the others (yields up to 72% in the presence of Cs_2CO_3). Assignment of bridging pattern was mainly based on chemical shift of OH groups, in some cases confirmed by 2D NMR experiments. A hampered conformational mobility, depending on the position and nature of the bridge, was observed for compounds **2**–**4**.

In contrast to the 'major' calix[*n*]arenes ($n=4$, 6, 8),[1] the chemical modification of the 'minor' calix[7]arenes has remained largely less studied[2] and only very recently the first examples of selectively *O*-substituted derivatives were reported by our group.[3] Obviously, also the intramolecular bridging, intensively investigated as a very convenient method to shape and preorganize calixarene macrocycles,[1] still remains unstudied in the case of calix[7]arenes. Therefore, we decided to investigate this aspect of calix[7]arene chemistry and we wish to report here the first examples of calix[7]arenes intramolecularly bridged at the lower rim.



1

As a first step we studied the intrabridging of *p-tert*-butylcalix[7]arene[4] **1** by direct alkylation with bromochloromethane, which has been widely used in the scaffolding of resorcinarenes, to give cavitands and carcerands,[5] and in the synthesis of dioxamethylene-bridged calix[4]- and calix[6]-arenes.[6] Thus, treatment of **1** with $BrCH_2Cl$ in the presence of K_2CO_3 as a base, in refluxing CH_3CN, under the conditions reported in Table 1 (entry 1),[7] afforded 1,2-methylene-bridged calix[7]arene **2a** in 15% yield, after column chromatography of the crude reaction mixture.[8]

This result induced us to extend the procedure to some oligo(ethylene glycol) ditosylates, which would give rise to hybrid compounds belonging to the class of calixcrowns,[9] whose members have often shown remarkable cation complexing abilities.[10] Therefore, the alkylation of **1** with ethylene glycol ditosylate (Table 1, entry 2) was performed under the above conditions to obtain 1,2-ethylene-bridged calix[7]arenes **2b** (1,2-calix[7]-crown-2) in 20% yield. The extension of these conditions (Table 1, entry 3) to alkylation with di(ethylene glycol) ditosylate afforded 1,2-, 1,3-, and 1,4-calix[7]crown-3 **2c**, **3a**, and **4a** in 25, 4, and 14%, respectively.

Very interesting was the alkylation of *p-tert*-butylcalix[7]arene **1** with tri(ethylene glycol) ditosylate in the presence of Cs_2CO_3 in acetone (Table 1, entry 4), which gave 1,4-calix[7]crown-4 **4b** in good yield (72%). The use of tetra(ethylene glycol) ditosylate as alkylating agent under similar condition (Table 1, entry 5) led to

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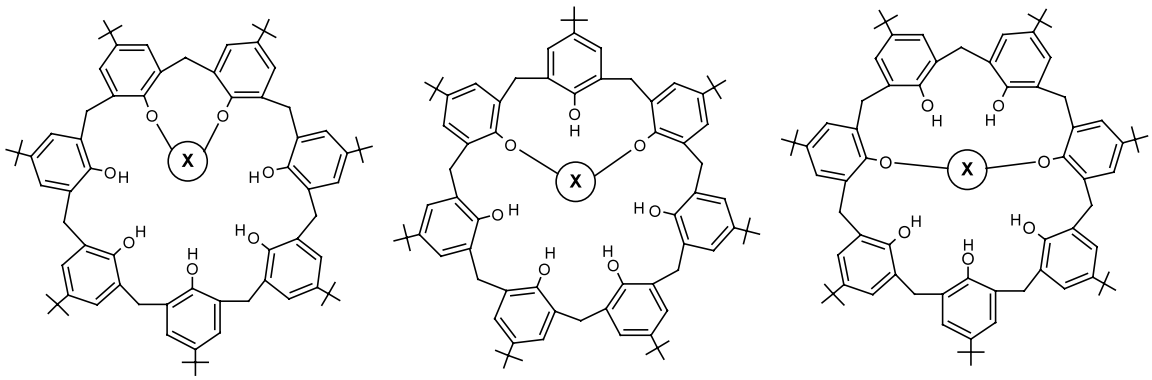

2

a X = CH_2
b X = CH_2CH_2
c X = $CH_2CH_2OCH_2CH_2$
d X = $CH_2(CH_2OCH_2)_3CH_2$

3

a X = $CH_2CH_2OCH_2CH_2$

4

a X = $CH_2CH_2OCH_2CH_2$
b X = $CH_2(CH_2OCH_2)_2CH_2$
c X = $CH_2(CH_2OCH_2)_3CH_2$
d X = $CH_2(CH_2OCH_2)_4CH_2$
e X = CH_2–C$_6$H$_4$–CH_2

Table 1. Yield of bridged calix[7]arenes in the direct alkylation of **1** in acetonitrile or acetone at reflux

Entry	Alkylating agent (equiv.)	Base (equiv.)	Solvent	Isolated compd (yield%)
1	$BrCH_2Cl$ (1)	K_2CO_3 (15)	Acetonitrile	**2a** (15)
2	$TsOCH_2CH_2OTs$ (1)	K_2CO_3 (15)	Acetonitrile	**2b** (20)
3	$TsO(CH_2CH_2O)_2Ts$ (1)	K_2CO_3 (15)	Acetonitrile	**2c** (25), **3a** (4), **4a** (14)
4	$TsO(CH_2CH_2O)_3Ts$ (2)	Cs_2CO_3 (15)	Acetone	**4b** (72)
5	$TsO(CH_2CH_2O)_4Ts$ (2)	Cs_2CO_3 (15)	Acetone	**2d** (5), **4c** (30)
6	$TsO(CH_2CH_2O)_5Ts$ (2)	Cs_2CO_3 (15)	Acetone	**4d** (20)
7	1,4-$C_6H_4(CH_2Br)_2$ (1)	Cs_2CO_3 (15)	Acetone	**4e** (40)

the isolation of 1,2- and 1,4-calix[7]crown-5 **2d** and **4c** (5 and 30% yield, respectively). Analogously, penta(ethylene glycol) ditosylate gave 1,4-calix[7]crown-6 **4d** in 20% yield (Table 1, entry 6).

The scaffolding of **1** with an aromatic unit was also obtained by Cs_2CO_3-promoted alkylation with 1,4-bis-(bromomethyl)benzene, which afforded the corresponding 1,4-(*p*-xylylene)-bridged calix[7]arene **4e** in 40% yield (Table 1, entry 7).

The structure assignment for intrabridged calix[7]arenes **2**–**4** was mainly based on spectral data.[8] In particular, elemental analysis and ESI(+) MS confirmed the molecular formula, while ^{1}H and ^{13}C NMR spectroscopy were used to determine the bridging pattern. In fact, three singly bridged calix[7]arenes, namely 1,2-, 1,3-, or 1,4-bridged, are possible, which all possess a symmetry plane bisecting one aromatic ring and the opposite $ArCH_2Ar$ group (Ar–CH_2 symmetry). Consequently, a very similar ^{1}H NMR spectrum, containing four *t*-Bu and four $ArCH_2Ar$ signals in a 2:2:2:1 ratio, is expected for all the three bridging patterns, if conformational mobility is assumed. Therefore, as for the case of selectively *O*-substituted calix[7]arenes,[3] we used the chemical shift of OH groups for assignment of the bridging pattern. In fact, this value is neatly increasing in accordance with the number of H-bonds with proximal OH groups, allowing their classification as 'isolated' (i), 'singly-H-bonded' (s), and 'doubly-H-bonded' (d).[11] In this way, a 1,2-bridged calix[7]arenes should give rise to three 's,d,d' OH signals in a 2:2:1 ratio, while the 1,3- and 1,4-isomers would give to 'i,s,d' (1:2:2), or 's,s,d' (2:2:1) patterns, respectively.

The application of this approach is well illustrated by 1,2-methylene-bridged calix[7]arene **2a** whose ^{1}H NMR spectrum ($CDCl_3$, 328 K) shows three OH singlets at 8.45, 9.57, and 9.91 ppm in a 2:2:1 ratio (Fig. 1). These values

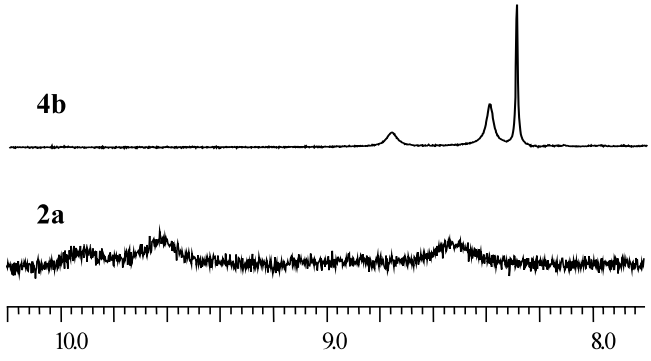

Figure 1. OH region of the ^{1}H NMR spectra of 1,2-methylene-bridged calix[7]arene **2a** (400 MHz, $CDCl_3$, 328 K) and 1,4-calix[7]-crown-4 **4b** (400 MHz, acetone-d_6, 300 K).

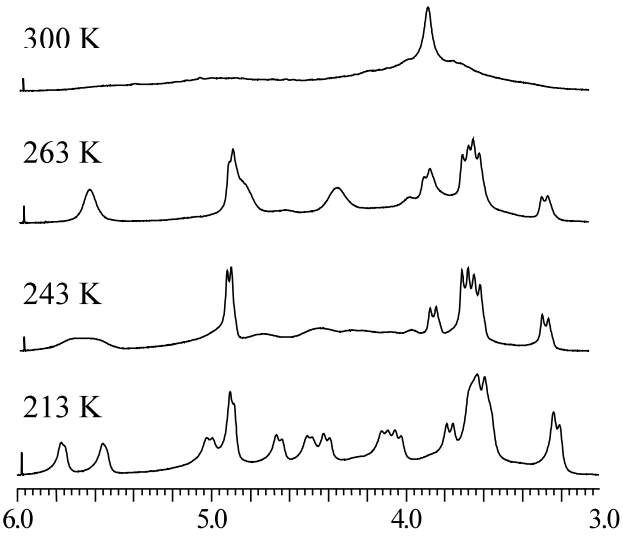

Figure 2. Methylene region of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1,4-(*p*-xylylene)-bridged calix[7]arene **4e** at relevant temperatures.

are fully consistent with an 's,d,d' OH pattern and consequently the 1,2-bridging can be confidently assigned to **2a**. This conclusion is well in line with the finding that only the 1,2-bridging has been observed in the reported alkylation with $BrCH_2Cl$ of other calixarenes,[6] probably due to the short 'bite' of the OCH_2Cl group in the ring-closure step.

In a similar way the structure of 1,2-ethylene-bridged calix[7]arene was assigned to **2b** because three OH signals are present in its ^{1}H NMR spectrum ($CDCl_3$, 293 K) at 8.63, 9.37, and 9.65 ppm (2:2:1 ratio), consistently with the expected 's,d,d' OH pattern. Also in this case, the proximal bridging appears to be favored for geometrical reasons. The structure of the other isolated 1,2-bridged derivatives, namely 1,2-calix[7]-crown-3 **2c** and 1,2-calix[7]crown-5 **2d**, was easily assigned as a simple extension of above method because they give rise to singly- and doubly-H-bonded OH signals at δ 8.29–8.62 and δ 9.26–9.42, respectively.

The assignment of 1,4-bridging is well exemplified by 1,4-calix[7]crown-4 **4b**, which shows (acetone-d_6, 300 K) three OH singlets at 8.28, 8.39, and 8.75 ppm (2:2:1) clearly attributable to an 's,s,d' pattern representative of 1,4-bridging (Fig. 1). It is worth pointing out that the doubly-H-bonded signal appears at higher field with respect to compounds **2** because of the reduced cooperativity in the shorter 'semicircular' H-bond.[11d] An independent demonstration of 1,4-bridging in **4b** was obtained by means of 2D NMR (HSQC and HMBC experiments).

The structure of the other 1,4-bridged calix[7]arenes **4a** and **4c–e** was assigned as above on the basis of OH NMR resonances which were commensurate with the 's,s,d' pattern.

Finally, the 1,3-bridging was attributed to calix[7]-crown-3 **3a** resting on the presence in its ^{1}H NMR spectrum ($CDCl_3$, 313 K) of three OH singlets at 7.52, 8.44, and 8.81 ppm (1:2:2) indicative of an 'i,s,d' OH pattern typical of 1,3-substitution.

As concerns the conformational features of bridged calix[7]arenes **2–4**, an intermediate situation between the analogue calix[6]-[12] and -[8]-arene[13] derivatives it is to be expected. In fact, in analogy with the latter, they have a higher mobility with respect to the parent compound **1**, because the stabilizing 'circular' hydrogen bond is partially broken. On the other hand, they are also more mobile of bridged calix[6]arenes for which a single bridge suffices to give compounds conformationally blocked on the NMR time scale. In particular, a dependence on the position and nature of bridge was also observed. In fact, 1,2-bridged calix[7]arenes **2** give rise to broad spectra indicating a conformational mobility slightly higher to that of **1**, because they still have an extended 'quasi-circular' hydrogen bond. Differently, 1,4-bridged derivatives **4** show sharper spectra corresponding to an higher mobility due to less extended hydrogen bond chains.

An exception to this behavior is given by 1,4-(*p*-xylylene)-bridged calix[7]arene **4e**, whose room temperature NMR spectrum (Fig. 2) is at a coalescence temperature, indicating a reduced mobility ascribable to the increased steric hindrance of the bridge. Interestingly, a second coalescence temperature at 243 K was ascertained, below which an asymmetrical spectrum is obtained (Fig. 2). An approximate estimation of the energy barrier for the two conformational processes gives the values of 13.5 and 11.6 kcal/mol, respectively. Obviously, at temperatures above 300 K the molecule is in a fast exchange regime giving rise to a complete equivalence of pertinent protons. The decrease in temperature from 300 to 243 K induces inter alia the splitting of the $ArCH_2Ar$ resonances indicating the freezing of the *through-the-annulus* passage of aryl rings, corresponding to the emergence of a symmetrical conformer. The symmetry of this conformer is due to a fluxional mediacy which ensures the equivalence of several protons as those of the OCH_2 groups (Fig. 2). At temperatures below 243 K these protons become diastereotopical indicating that a single asymmetrical conformer has frozen out, whose 3D structure is currently under investigation.

In conclusion, we have synthesized the first examples of bridged calix[7]arenes, which can be considered useful intermediates for constructing new calix[7]-arene-based hosts. It is expectable that an extension of these procedures could lead to multiply-bridged, permanently shaped calix[7]arenes well preorganized to act as molecular hosts. In these instances, in analogy to calix[8]arenes,[13,14] interesting stereochemical consequences can also be envisioned.

Acknowledgements

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4. (a) Compound **1** was prepared according to the acid-catalyzed one-pot procedure described in: Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, 4136. For additional synthetic procedures, see: (b) Nakamoto, Y.; Ishida, S.-I. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 705; (c) Vocanson, F.; Lamartine, R.; Lanteri, P.; Longeray, R.; Gauvrit, J. Y. *New J. Chem.* **1995**, *19*, 825.
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7. **Typical procedure for the preparation of bridged calix[7]arenes**. A suspension of *p-tert*-butylcalix[7]arene (**1**) (200 mg, 0.176 mmol) and base (K_2CO_3 or Cs_2CO_3, 2.64 mmol, see Table 1) in CH_3CN or Me_2CO (20 mL) was stirred for 2 h under reflux. Then a solution the alkylating agent (1 or 2 equiv., see Table 1) in the same solvent (5 mL) was slowly added. The mixture was stirred for 2 days under reflux, dried under vacuum, and partitioned between CH_2Cl_2 (3×20 mL) and 0.1 M HCl (20 mL). The total organic phase was washed with H_2O (3×20 mL) and dried. The crude product was subjected to column chromatography to give the isolated compounds (Table 1).
8. Satisfactory microanalytical and spectral data were obtained for all new compounds. ^1H and ^{13}C NMR spectra were acquired at 400 and 100 MHz, respectively, in $CDCl_3$, $CDCl_2CDCl_2$, or $(CD_3)_2CO$. ESI(+) MS measurements were performed using a mixture of H_2O/CH_3CN (1:1) and 5% HCOOH as solvent.

Compound **2a** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 98:2 v/v); ESI(+) MS m/z 1149 (MH^+); ^1H NMR ($CDCl_3$, 328 K): δ 1.26, 1.28 [bs, $C(CH_3)_3$, 27H, 36H], 3.86–3.91 (overlapped, $ArCH_2Ar$, 14H), 5.66 (bs, OCH_2O, 2H), 7.11, 7.15, 7.17, 7.18, 7.21 (bs, ArH, 2H, 6H, 2H, 2H, 2H), 8.45, 9.57, 9.91 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{78}H_{98}O_7$: C, 81.63; H, 8.61. Found: C, 81.59; H, 8.63.

Compound **2b** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1 v/v); ESI(+) MS m/z 1163 (MH^+); ^1H NMR ($CDCl_3$, 293 K): δ 1.24, 1.26, 1.29 [s, $C(CH_3)_3$, 27H, 18H, 18H], 3.88 (bs, $ArCH_2Ar$, 14H), 4.49 (bs, OCH_2, 4H), 7.12, 7.15, 7.21 (bs, ArH, 8H, 2H, 4H), 8.63, 9.37, 9.65 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{79}H_{100}O_7$: C, 81.68; H, 8.68. Found: C, 81.62; H, 8.70.

Compound **2c** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 98:2 v/v); ESI(+) MS m/z 1207 (MH^+); ^1H NMR (acetone-d_6, 303 K): δ 1.13, 1.19, 1.23, 1.24 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 3.84, 3.94, 4.02, 4.27 (s, $ArCH_2Ar$ and OCH_2, 8H, 4H, 4H, 6H), 6.88, 7.11, 7.13, 7.24, 7.28 (bs, ArH, 2H, 2H, 2H, 4H, 4H), 8.30, 9.12, 9.30 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{81}H_{104}O_8$: C, 80.69; H, 8.69. Found: C, 80.63; H, 8.71.

Compound **2d** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 98:2 v/v); ESI(+) MS m/z 1295 (MH^+); ^1H NMR ($CDCl_3$, 300 K): δ 1.21, 1.22, 1.25, 1.26 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 3.79, 3.96, 4.02, 4.37 (bs, $ArCH_2Ar$ and OCH_2, 6H, 4H, 4H, 2H), 7.00, 7.06, 7.10, 7.13 (bs, ArH, 2H, 4H, 4H, 4H), 8.62, 9.40 (bs, OH, 2H, 3H). Anal. calcd for $C_{85}H_{112}O_{10}$: C, 78.91; H, 8.72. Found: C, 78.88; H, 8.74.

Compound **3a** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 85:15 v/v); ESI(+) MS m/z 1207 (MH^+); ^1H NMR ($CDCl_3$, 313 K): δ 1.15, 1.27 [bs, $C(CH_3)_3$, 45H, 18H], 3.70, 3.81, 3.89, 4.02, 4.13 (bs, $ArCH_2Ar$ and OCH_2, 4H, 8H, 4H, 2H, 4H), 6.91, 7.00, 7.08, 7.14, 7.22 (bs, ArH, 2H, 2H, 2H, 6H, 2H), 7.52, 8.44, 8.81 (bs, OH, 1H, 2H, 2H). Anal. calcd for $C_{81}H_{104}O_8$: C, 80.69; H, 8.69. Found: C, 80.63; H, 8.70.

Compound **4a** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 98:2 v/v); ESI(+) MS m/z 1207 (MH^+); ^1H NMR ($CDCl_3$, 300 K): δ 1.26, 1.29 [s, $C(CH_3)_3$, 36H, 27H], 3.84, 3.89, 4.01, 4.09 (bs, $ArCH_2Ar$ and OCH_2, 4H, 6H, 8H, 4H), 6.98, 7.08, 7.10, 7.17, 7.23 (bs, ArH, 2H, 2H, 2H, 6H, 2H), 7.79, 8.62, 8.91 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{81}H_{104}O_8$: C, 80.69; H, 8.69. Found: C, 80.64; H, 8.68.

Compound **4b** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1 v/v); ESI(+) MS m/z 1251 (MH^+); ^1H NMR (acetone-d_6, 301 K): δ 1.16, 1.19, 1.22, 1.24 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 3.78, 3.88 (bs, $ArCH_2Ar$, 2H, 4H), 3.92, 3.96 (bs, OCH_2, 4H, 4H), 4.01, 4.06 (bs, $ArCH_2Ar$, 4H, 4H), 4.18 (bs, OCH_2, 4H), 7.15, 7.21, 7.23, 7.26 (bs, ArH, 2H, 4H, 4H, 4H), 8.28, 8.39, 8.75 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{83}H_{108}O_9$: C, 79.77; H, 8.71. Found: C, 79.73; H, 8.73.

Compound **4c** was isolated by flash chromatography on

silica gel (cyclohexane/ethyl acetate, 96:4 v/v); ESI(+) MS m/z 1295 (MH^+); ^1H NMR (acetone-d_6, 300 K): δ 1.17, 1.20, 1.26, 1.30 [s, $C(CH_3)_3$, 18H, 18H, 18H, 9H], 3.81, 3.88, 3.91, 3.97, 4.00, 4.04 (bs, $ArCH_2Ar$, and OCH_2, 2H, 8H, 6H, 4H, 4H, 6H), 7.08, 7.11, 7.13, 7.19 (d, $J=2.4$ Hz, ArH, 2H, 2H, 2H, 2H), 7.21 (s, ArH, 2H), 7.22, 7.23 (d, $J=2.4$ Hz, ArH, 2H, 2H), 8.34, 8.41, 8.44 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{85}H_{112}O_{10}$: C, 78.91; H, 8.72. Found: C, 78.88; H, 8.73.

Compound **4d** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2 v/v); ESI(+) MS m/z 1339 (MH^+); ^1H NMR ($CDCl_3$, 300 K): δ 1.02, 1.18, 1.24, 1.27 [s, $C(CH_3)_3$, 9H, 18H, 18H, 18H], 3.73, 3.78, 3.82, 3.93, 3.97, 4.05, 4.11, 4.26 (bs, $ArCH_2Ar$ and OCH_2, 4H, 2H, 4H, 4H, 8H, 4H, 4H, 4H), 7.01, 7.06, 7.09, 7.10, 7.13, 7.14, 7.15 (bs, ArH, 2H, 2H, 2H, 2H, 2H, 2H, 2H), 8.21, 8.47, 8.83 (bs, OH, 2H, 2H, 1H). Anal. calcd for $C_{87}H_{116}O_{11}$: C, 78.11; H, 8.74. Found: C, 78.09; H, 8.75.

Compound **4e** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 92:8 v/v); ESI(+) MS m/z 1239 (MH^+); ^1H NMR ($CDCl_2CDCl_2$, 383 K): δ 1.07, 1.14, 1.15 [s, $C(CH_3)_3$, 36H, 9H, 18H], 3.39, 3.67, 3.80, 4.03 (bs, $ArCH_2Ar$, 2H, 4H, 4H, 4H), 5.08 (bs, OCH_2Ar, 4H), 6.83, 6.89, 6.95, 7.00, 7.16, 7.70 (bs, ArH, 2H, 2H, 2H, 6H, 2H, 4H), 7.66, 8.23, 8.39 (bs, OH, 2H, 2H, 1H); the OH signals appear at δ 8.11, 8.84, 8.91 (bs, 2H, 2H, 1H) in $CDCl_3$ at 300 K. Anal. calcd for $C_{85}H_{104}O_7$: C, 82.48; H, 8.47. Found: C, 82.44; H, 8.48.

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