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# New Calix[4]arenes Having Electron Donating Groups at the Upper Rim as Molecular Platforms and Host Molecules

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*Abstract*: a new and general synthetic procedure for the exhaustive and selective introduction of hydroxy groups at the upper rim of calix[4]arenes in the *cone* conformation is reported. The aldehyde-derivatives of tetraalkoxycalix[4]arenes have been oxidized by Baeyer-Villiger reaction. The introduction of amino and hydroxy groups on calix[4]arene having a rigid *cone* conformation has been achieved for the first time. Copyright © 1996 Elsevier Science Ltd

## INTRODUCTION

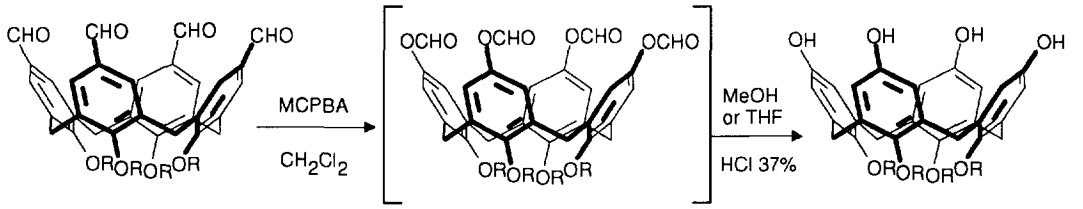
Calix[4]arenes[1] are easily available ditopic molecular platforms extensively used in supramolecular chemistry to build up more complex synthetic receptors for ions[2] and neutral molecules[3]. The complexing ability of these hosts can be tuned by changing either the nature and the number of the binding sites introduced at both rims, or by controlling the conformational properties of the calix.

As part of a general project aimed at enhancing the π-donor ability of the three-dimentional lipophilic cavity experienced by *cone* conformers of calix[4]arenes, we have been looking for efficient procedures to introduce electron-donating groups (e.g. OH and $NH_2$) at the upper rim of the these macrocycles, which could also be suitable for further functionalization. Recently Reinhoudt et al. have reported on the synthesis of *cone* amino tetraalkoxy calix[4]arenes starting from the corresponding nitro[4] or iodo[5] derivatives which were used to synthesize receptors having binding sites at the upper rim. Less studied has been the introduction of the OH function on calix[4]arenes and no example exists in the literature for the exhaustive and selective hydroxylation of calix[4]arenes already blocked in the *cone* conformation.

It was therefore important to devise new synthetic procedures to introduce the OH groups on *cone*-tetraalkoxycalix[4]arenes both in exhaustive and selective ways. Particularly important was to introduce hydroxy and amino functions on calix[4]arenes blocked in a rigid *cone* conformation[6] by two short ether bridges connecting two adjacent oxygens of the lower rim. In fact in these rigid *cone*-macrocycles intramolecular reactions occurring during the synthetic manipulation of functional groups already present at the upper rim[7], usually experienced by simple tetraalkoxycalix[4]arenes, can be prevented. Moreover the rigidity of the macrocycle can be used to block the relative position of the binding sites present at the upper rim of the host.

***Hydroxylation of flexible cone-tetraalkoxycalix[4]arenes***

The formyl derivatives of calix[4]arenes have been chosen as precursors for the synthesis of hydroxycalix[4]arenes because they can easily be obtained by several methods.[7a,8] We started by studying the Baeyer-Villiger[9] oxidation of tetra aldehydes **1a,b**. In both cases the groups present at the lower rim, which have different coordination properties, prevent the interconversion of the *cone* conformer to other stereoisomers, but are not able to block it completely so that the macrocycle still maintains a residual flexibility.[6,10] Thus reacting aldehydes (**1a, 1b**) with *m*-chloroperbenzoic acid (MCPBA) followed by hydrolysis of the formate intermediates (**2a, b**), 80% overall yield of the corresponding tetrahydroxycalix[4]arenes (**3a, 3b**) was obtained (see Scheme 1).



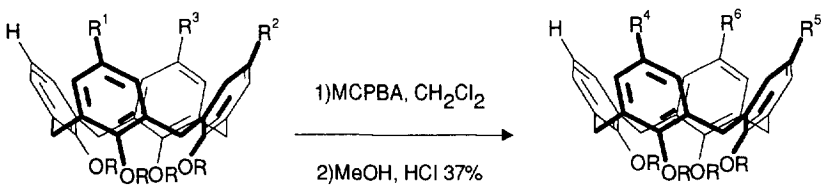

**1(a-b)** **2(a-b)** **3(a-b)**

**a:** R=$CH_2CH_2OCH_2CH_3$

**b:** R=$CH_2CH_2CH_3$

Scheme 1

The interest for the selective functionalization of the upper rim[11] prompted us to extend this synthetic method to the preparation of partially and selectively hydroxylated calix[4]arenes (see Scheme 2).




**4** $R^1$ = CHO, $R^2 = R^3$ = H

**5** $R^1 = R^3$ = CHO, $R^2$ = H

**6** $R^1 = R^2 = R^3$ = CHO

R = $CH_2CH_2OCH_2CH_3$

**7** $R^4$ = OH, $R^5 = R^6$ = H

**8** $R^4 = R^6$ = OH, $R^5$ = H

**9** $R^4 = R^5 = R^6$ = OH

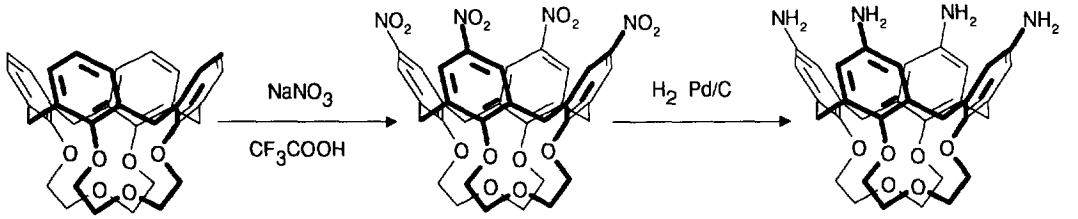
Scheme 2

Therefore taking advantage of our previous results on the partial and selective Gross formylation of calix[4]arenes[7a], the synthesis of partially hydroxylated tetraethoxyethoxycalix[4]arenes (**7-9**) has been performed using the same reaction conditions used for tetrahydroxy derivatives.

***Hydroxylation and amination of rigid cone-calix[4]arene***

Recently we devised several synthetic procedures to increase the preorganization of calix[4]arenes both by lower rim (phenolic OH)[6] and upper rim (aromatic nuclei)[12] functionalization and shown that when the macrocycle is blocked in a rigid cone conformation its cavity is able to bind neutral organic molecules in the gas phase[12] and in organic media.[13]

In order to introduce electron donating groups on rigidified calixarene we first tried to use the classical nitration procedures of calix[4]arenes[4]. Both the ipso nitration of p-*tert*-butylcalix[4]arene-biscrown-3 and the nitration of the unsubstituted biscrown-3 **10** were unsuccessfull. After several attempts we found that reacting **10** with an excess of $NaNO_3$ in $CF_3COOH$,[14] 60% yield of tetranitro derivative **11** could be isolated after column chromatography (see Scheme 3).

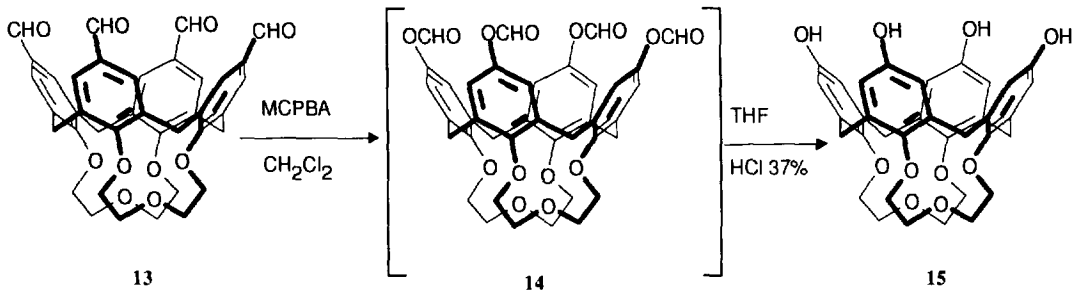



**10** **11** **12**

Scheme 3

Reduction of the tetranitro **11** using $H_2$ and Pd/C gave in almost quantitative yield the corresponding tetraamino-biscrown-3 **12**.

The introduction of the OH function was performed by Baeyer-Villiger oxidation of tetraaldehyde **13**, obtained by Duff formylation of **10** in 60% yield, followed by hydrolysis of the formate **14**, gave 36% overall yield of rigid *cone*-tetrahydroxycalix[4]arene **15** (see Scheme 4).




**13** **14** **15**

Scheme 4

## CONCLUSIONS

The new host molecules synthesized **3a,b**, **7-9**, **12** and **15** have an electron-rich apolar cavity and can be used as molecular platforms for the synthesis of more complex receptors. The introduction of $NO_2$, $NH_2$ and OH functions on calix[4]arenes having a rigid *cone* conformation discloses also the possibility to study the effect of the substituents present at the upper rim on the complexing properties of these new hosts.

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## EXPERIMENTAL

Melting points were recorded on Electrotermal apparatus and are uncorrected. Mass spectra were recorded on Finnigan Mat SSQ 710 in the CI mode ($CH_4$). $^1$H NMR were recorded on Bruker instruments operating at 300 and 400 MHz while $^{13}$C NMR at 75 or 25 MHz using TMS as internal standard. Preparative column chromatography were performed on silica gel (Merck, particle size 0.040-0.063 nm, 230-240 mesh). Analytical TLC were performed on precoated silica gel plates (Merck, 60 $F_{254}$). Elemental analyses[15] were performed at Dipartimento di Chimica Generale e Inorganica, Chimica Analitica, Chimica Fisica of the University of Parma using a Carlo Erba EA 1108-Elemental Analyzer.

Compounds **1a**[7a], **1b**[8], **4-6**[7a], and **10**[6,13] were synthesized according to literature procedures. Commercial $CH_2Cl_2$ was washed twice with water, dried over $CaCl_2$ and then stored for at least 3 h over molecular sieves 3Å prior to use; *m*-chloroperbenzoic acid (MCPBA) was washed with a buffer solution at pH 7.5 obtained by dissolving 1.8 g $KH_2PO_4$ and 10.4 g of $Na_2HPO_4$ in 100 mL $H_2O$. THF was freshly distilled from sodium benzophenone and stored over molecular sieves 4Å.

***5,11,17,23-tetraformyl-biscrown-3-calix[4]arene* 13:**

under nitrogen atmosphere hexamethylenetetraamine (11.2 g, 79.9 mmol) was suspended in $CF_3COOH$ (45 mL) and stirred at room temperature up to complete homogeneity (*ca.* 2 h) then **10** (1 g, 1.77 mmol) was added and the mixture refluxed for 24 h. The resulting mixture was then poured into ice/water (100 mL), neutralized with $Na_2CO_3$ (caution!) and extracted with ethyl acetate. The organic phase was washed twice with water, dried over sodium sulphate and the solvent evaporated. Separation by column chromatography (eluent hexane/ethyl acetate 1/4) gave 0.69 g (60% yield) of **13**; m.p. 300°C (dec.); MS (CI) *m/z* = 677 ($MH^+$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.76 (s, 4H, ArCHO), 7.61 and 7.57 (2d, 8H, $J$ = 2.4 Hz, ArH), 4.57 and 5.21 (2d, 4H, $J$ = 12.4 Hz, $ArCH_2Ar$ axial), 3.9-4.4 (m, 16H, $OCH_2CH_2O$), 3.41 and 3.46 (2d, 4H, $J$ = 12.4 Hz,

$ArCH_2Ar$ equatorial). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 161.11 (ArCHO), 130.62, 131.66, 133.10, 136.50 (Ar), 74.37, 76.67 ($CH_2CH_2$), 30.00, 30.05 ($ArCH_2Ar$). IR (NaCl): ν ($cm^{-1}$) 1685 (s, CHO). Anal. Calcd for $C_{40}H_{36}O_{10}\cdot H_2O$: C, 69.15; H, 5.51. Found: C, 69.70; H, 5.98.

**Oxidation of calix[4]arene aldehydes, general procedure:**

In a two necked flask equipped with $CaCl_2$ valve and nitrogen inlet the appropriate aldehyde (0.68 mmol) was dissolved in dichloromethane (50 mL) and MCPBA (2.72 mmol each CHO group) was added. The reaction mixture was stirred at room temperature up to disappearance of starting material (TLC, hexane/ethyl acetate 3/2). The excess of MCPBA was then eliminated with aqueous $Na_2S_2O_5$ (10%) and the two phases separated, the organic phase washed twice with water and then evaporated. The resulting material was dissolved in methanol (30 mL) then HCl (37%, 27 mmol each OCHO) was added and the mixture stirred overnight at room temperature. The solvents were then completely evaporated, the residue taken up with ethyl acetate and the solution washed twice with water. The organic phase was separated, dried over sodium sulphate and the solvent evaporated to give a residue which was purified by column chromatography.

***5-hydroxy-25,26,27,28-tetrakis-(2-ethoxyethoxy)-calix[4]arene* 7:**

eluent hexane/ethyl acetate 3/2; $R_f$ = 0.66; 0.15 g (30% yield) of **7**; m.p. = 107-110° C; MS (CI) *m/z* = 729 ($MH^+$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, 4H, *J* = 7.1 Hz, ArH 10,12,22,24), 6.66 (t, 2H, ArH 11,23), 6.55-6.50 (m, 3H, 16,17,18), 5.94 (s, 2H, ArH 4,6), 4.51 and 4.45 (2d, 4H, *J* = 13.4 Hz, $ArCH_2Ar$ axial), 4.16 (t, 4H, *J* = 6.0 Hz, $ArOC\underline{H}_2CH_2O$-), 4.08 and 4.02 (2t, 4H, *J* = 5.7 Hz, $ArOCH_2C\underline{H}_2O$-), 3.87 (t, 4H, $ArOC\underline{H}_2CH_2O$-), 3.84 (t, 4H, $ArOCH_2C\underline{H}_2O$-), 3.60-3.52 (m, 8H, $-OC\underline{H}_2CH_3$), 3.16 and 3.06 (2d, 4H, $ArCH_2Ar$ equatorial), 1.27-1.18 (m, 12H, $-OCH_2C\underline{H}_3$). $^{13}C$ NMR (25 MHz, $CDCl_3$): δ = 156.9, 156.0, 150.3, 149.9, 135.6, 135.3, 134.6, 128.3, 128.1, 122.1, 114.6, 73.4, 73.3, 72.9, 69.7, 66.4, 66.3, 31.0, 15.3. Anal. Calcd for $C_{44}H_{56}O_9$: C, 72.51; H, 7.74. Found: C, 71.81; H, 7.86.

***5,17-dihydroxy-25,26,27,28-tetrakis-(2-ethoxyethoxy)-calix[4]arene* 8:**

eluent hexane/ethyl acetate 3/2; $R_f$ = 0.45; 0.152 g (30% yield) of **8**; m.p. = 105-108° C; MS (CI) *m/z* = 745 ($MH^+$); $^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.97 (d, 4H, *J* = 7.4 Hz, ArH 10,12,22,24), 6.78 (t, 2H, ArH 11,23), 5.61 (s, 4H, ArH 4,6,16,18), 4.45 (d, 4H, *J* = 13.5 Hz, $ArCH_2Ar$ axial), 4.23 (t, 4H, *J* = 6.2 Hz, $ArOC\underline{H}_2CH_2O$-), 3.91-3.84 (m, 8H, $ArOCH_2C\underline{H}_2O$- and $ArOC\underline{H}_2CH_2O$-), 3.77 (t, 4H, $ArOCH_2C\underline{H}_2O$-), 3.58 and 3.50 (2q, 8H, *J* = 7 Hz, $-OC\underline{H}_2CH_3$), 3.07 (d, 4H, $ArCH_2Ar$ equatorial), 1.24 and 1.16 ( 2t, 12H, $-OCH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 158.1, 149.1, 148.8, 136.4, 134.7, 128.8, 122.1, 114.6, 73.8, 72.3, 69.6, 66.5, 31.0, 15.3. Anal. Calcd for $C_{44}H_{56}O_{10}\cdot H_2O$: C, 69.27; H, 7.66. Found: C, 70.11; H, 8.43.

***5,11,17-trihydroxy-25,26,27,28-tetrakis-(2-ethoxyethoxy)-calix[4]arene* 9:**

eluent hexane/ethyl acetate 1/1; $R_f$ = 0.35; 0.144 g (28% yield) of **9**; m.p.= 83-85° C (taken from a nitrogen fluxed sealed capillary tube); MS (CI) *m/z* = 761 ($MH^+$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, 2H, *J* = 7.4 Hz, ArH 22,24), 6.73 (t, 1H, ArH 23), 6.37 (s, 2H, ArH 10, 12), 5.86 (s, 2H, ArH 6,16), 5.76 (s, 2H, ArH 4, 18), 4.43 and 4.36 (2d, 4H, *J* = 13.4 Hz, $ArCH_2Ar$ axial), 4.21 and 4.14 (2t, 4H, *J* = 6 Hz, $ArOC\underline{H}_2CH_2O$-), 3.90-3.84 (m, 8H, $ArOCH_2C\underline{H}_2O$- and $ArOC\underline{H}_2CH_2O$-), 3.78 (t, 4H, $ArOCH_2C\underline{H}_2O$-), 3.60-3.48 (m, 8H, -$OC\underline{H}_2CH_3$), 3.06 and 2.93 (2d, 4H, *J* = 13.4 Hz, $ArCH_2Ar$ equatorial), 1.26-1.15 (m, 12H, -$OCH_2C\underline{H}_3$); $^{13}$C NMR (25 MHz, $CDCl_3$): δ = 157.6, 151.3, 150.3, 150.0, 149.6, 136.6, 136.1, 135.0, 134.7, 128.7, 114.9, 75.8, 73.6, 72.5, 69.7, 66.5, 66.4, 66.2, 31.1, 15.2. Anal. Calcd for $C_{44}H_{56}O_{11}\cdot H_2O$: C, 67.84; H, 7.50. Found: C, 68.52; H, 7.95.

***5,11,17,23-tetrahydroxy-25,26,27,28-tetrakis-(2-ethoxyethoxy)-calix[4]arene* 3a:**

recrystallization from $CH_2Cl_2$; 0.42 g (80% yield) of **3a**; m.p. = 148-150° C; MS (CI) *m/z* = 777 ($MH^+$); $^1$H NMR (300 MHz, $CD_3OD$): δ = 6.23 (s, 8H, ArH), 4.46 (d, 4H, *J* = 13 Hz, $ArCH_2Ar$ axial), 4.06 (t, 8H, *J* = 5.6 Hz, , $ArOC\underline{H}_2CH_2O$-), 3.91 (t, 8H, $ArOCH_2C\underline{H}_2O$-), 3.61 (q, 8H, *J* = 7 Hz, -$OC\underline{H}_2CH_3$), 2.99 (d, 4H, *J* = 13 Hz, $ArCH_2Ar$ equatorial), 1.25 (t, 12H, -$OCH_2C\underline{H}_3$); $^{13}$C NMR (75 MHz, $CD_3OD$): δ = 152.5, 150.9, 136.7, 115.9, 74.4, 71.1, 67.4, 32.1, 15.7. Anal. Calcd for $C_{44}H_{56}O_{12}\cdot H_2O$: C, 66.48; H, 7.35. Found: C, 67.41; H, 7.63.

***5,11,17,23-tetrahydroxy-25,26,27,28-tetrapropoxy-calix[4]arene* 3b:**

variation at the general procedure: THF instead of methanol was used as solvent for the hydrolysis reaction. The compound was purified by precipitation from dichloromethane/hexane; 0.357 g (80% yield) of **3b**; m.p.>300°C; MS (CI) *m/z* = 657 ($MH^+$); $^1$H NMR (300 MHz, $CD_3OD$): δ = 6.15 (s, 8H, ArH), 4.36 (d, 4H, *J* = 12.9 Hz, $ArCH_2Ar$ axial), 3.75 (t, 8H, *J* = 7.4 Hz, $ArOCH_2$), 2.93 (d, 4H, *J* = 12.9 Hz, $ArCH_2Ar$ equatorial), 1.86 (m, 8H, $ArOCH_2C\underline{H}_2CH_3$), 0.99 (t, 12H, $ArOCH_2CH_2C\underline{H}_3$); $^{13}$C NMR (75 MHz, $CD_3OD$): δ = 152.4, 151.0, 130.8, 115.9, 78.0, 32.2, 24.4, 10.9. Anal. Calcd for $C_{40}H_{48}O_8\cdot H_2O$: C, 71.19; H, 7.47. Found: C, 71.56; H, 7.99.

***5,11,17,23-tetrahydroxy-biscrown-3-calix[4]arene* 15:**

variation at the general procedure: THF instead of methanol was used as solvent for the hydrolysis reaction. Eluent hexane/ethyl acetate 1/4; 0.256 g (60% yield) of **15**; m.p. > 300° C; MS (CI) *m/z* = 629 ($MH^+$); $^1$H NMR (300 MHz, $CD_3COCD_3$): δ = 7.14 (s, 4H, ArOH), 6.46 and 6.43 (2d, 8H, *J* = 2.9 Hz, ArH), 4.93 and 4.39 (2d, 2H, *J* = 11.9 Hz, $ArCH_2Ar$ axial), 4.29-3.63 (m, 16H, $OCH_2CH_2O$), 3.01 and 2.94 (d, 2H, *J* = 11.9 Hz, $ArCH_2Ar$ equatorial); $^{13}$C NMR (75 MHz, $CD_3COCD_3$): δ = 152.8, 149.3, 136.6, 116.2, 115.2, 77.0, 75.0, 31.3. Anal. Calcd for $C_{36}H_{36}O_{10}\cdot H_2O$: C, 66.86; H, 5.92. Found: C, 67.52; H, 5.98.

***5,11,17,23-tetranitro-biscrown-3-calix[4]arene* 11:**

Under nitrogen atmosphere, 1.0 g of **10** (1.77 mmol) was dissolved in $CF_3COOH$ (3 mL) and then 3.6 g ( 42.4 mmol) $NaNO_3$ were added. The reaction mixture was stirred at room temperature up to disappearance of the dark-blu colour (the reaction can be followed by TLC using ethyl acetate as eluent $R_f$ = 0.3), then poured in 100 mL of ice/water and extracted with $CH_2Cl_2$. The organic phase was washed with water up to neutrality (litmus) and dried over sodium sulphate. After evaporation of the solvent and column chromatography (eluent ethyl acetate; $R_f$ = 0.5) 0.66 g of **11** (60% yield) were obtained; m.p. 275° C (dec.); MS (CI) *m/z* = 744 ($MH^+$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.96 and 7.99 (2d, 8H, *J* = 1.4 Hz, Ar-H), 5.29 and 4.58 (2d, 4H, *J* = 12.0 Hz, $ArCH_2Ar$ axial), 4.4-3.9 (m, 16H, $-CH_2CH_2-$), 3.50 and 3.44 (2d, 4H, *J* = 12.0 Hz, $ArCH_2Ar$ equatorial), $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 161.1, 143.4, 136.5, 124.9, 124.1, 77.1, 73.5, 28.6, 28.2. Anal. Calcd for $C_{36}H_{32}N_4O_{14}\cdot H_2O$: C, 56.69; H, 4.49; N, 7.34. Found: C, 56.87; H, 4.48; N, 7.40.

***5,11,17,23-tetraamino-biscrown-3-calix[4]arene* 12:**

0.5 g (0.67 mmol) of **11** were suspended in a 250 mL hydrogenation Parr flask containing abs. ethanol (20 mL) and $CH_2Cl_2$ (30 mL) and under a gentle nitrogen flux 0.2 g of Pd/C (10%) (**Caution!** adding the catalyst in air atmosphere brings out the self ignition of the mixture). The resulting mixture was shaken under $H_2$ pressure (3.5 barr) at room temperature using a Parr hydrogenation apparatus for 24 h. Then the heterogeneous part was filtered off, the solvent evaporated and after plate chromatography (eluent, methanol/ammonium hydroxide = 4/1, $R_f$ = 0.77) 0.24 g (57% yield) of **12** were obtained; m.p. 185° C (dec., taken from a nitrogen fluxed sealed capillary tube). MS (CI) *m/z* = 625 ($MH^+$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.34 and 6.31 (2d, 8H, *J* = 2.7 Hz, Ar-H), 4.86 and 4.33 (2d, 4H, *J* = 11.9 Hz, $ArCH_2Ar$ axial), 4.2-3.7 (m, 16H, $OCH_2CH_2O$), 3.00 and 2.95 (2d, 4H, *J* = 11.9 Hz, $ArCH_2Ar$, equatorial), 2.8 (bs, 8H, $NH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.2, 141.38, 135.9, 135.6, 116.1, 115.0, 76.2, 74.6, 30.9, 29.9. ; Anal. Calcd for $C_{36}H_{40}N_4O_6\cdot H_2O$: C, 67.27; H, 6.58; N, 8.71. Found: C, 67.10; H, 6.62; N, 8.67.

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