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# Highly Distorted *Cone* Calix[4]arenes Through Intramolecular Mc Murry Coupling Reaction

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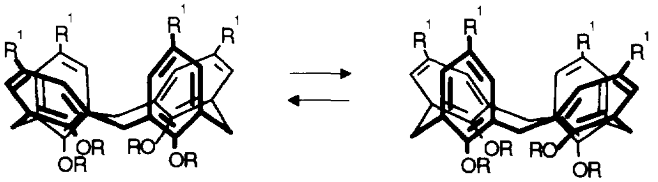
***Abstract:*** Highly distorted and rigid cone conformers of calix[4]arene have been synthesized by low-valent titanium promoted *intra*-molecular coupling of aldehydes **1a-d**. The reaction outcome strongly depends on the substituents present at the upper rim and reaction time. In all cases examined *intra*-molecular coupled compounds, having a bridge only two atoms long, were obtained in about 30% yield.

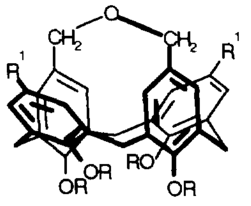
## INTRODUCTION

Calix[4]arenes have been conveniently used as molecular platforms for the synthesis of artificial receptors for ions[1] and neutral molecules.[2] The mobility of the calix[4]arene backbone can be blocked by introducing four substituents bulkier than ethyl at the lower rim (phenolic oxygens) and the stereochemical outcome is determined by the reaction conditions and the metal ion used. In this way it is possible to prevent the interconversion between the isomers formed so that each conformer (cone, partial cone, 1,3-alternate, 1,2-alternate) is considered to be blocked.[3] There is however a further aspect which has often been neglected: that is the residual flexibility of the different conformers. In fact, it is known by solid state data[4] and by molecular modeling studies[5] that symmetrical cone isomers adopt a flattened cone conformation showing $C_{2v}$ symmetry. We and others[6] have recently shown that also in solution the cone isomer of tetraalkoxycalix[4]arenes can adopt a flattened structure, thus verifying that the $C_{4v}$ symmetry observed in the $^1$H NMR spectra is the result of a fast interconversion on the NMR timescale, between two $C_{2v}$ conformations.



This residual flexibility strongly influences the complexation properties of calix[4]arene-based hosts blocked in the cone conformation toward neutral organic molecules.[7]

Less studied is the role played by this flexibility on the *intra*-molecular reactivity of functional groups attached at the upper rim of the macrocycle, which could be exploited to modulate the angles between the four aromatic rings. During the synthesis of double calix[4]arenes, we observed the formation of three atoms intramolecularly bridged products (**I**) as the main reaction pathway.[8]



I

$R^1 = H, tBu$

$R = CH_2CH_2OCH_2CH_3$

This prompted us to explore the possibility of synthesizing more distorted calix[4]arene structures which could be of interest from the stereochemical and spectroscopic viewpoint and also for further synthetic elaborations. For this purpose the intramolecular reductive coupling *via* Mc Murry[9] reaction of calix[4]arenes bearing aldehyde groups at the upper rim was studied.

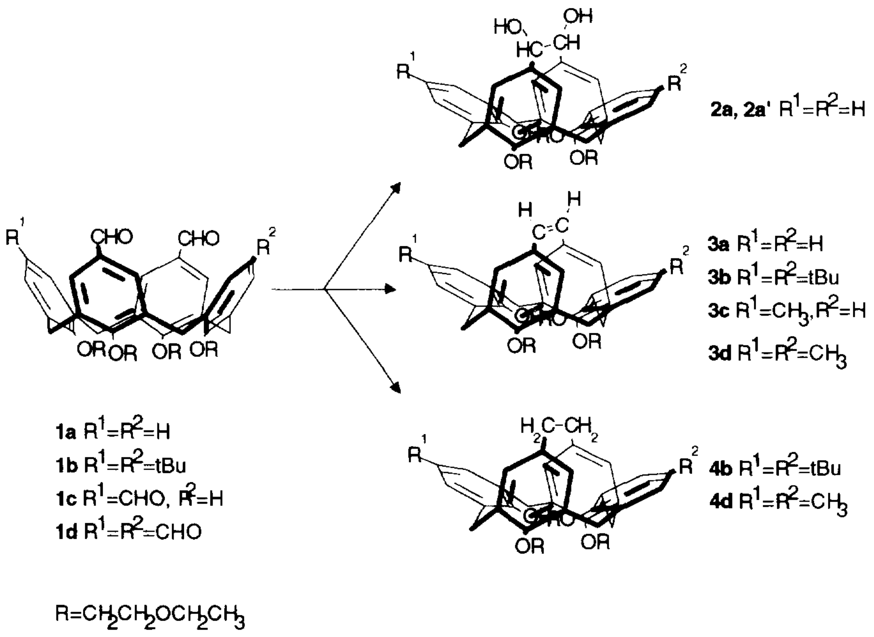
## RESULTS AND DISCUSSION

Low-valent titanium promoted cross-coupling of aldehydes is a powerful method for carbon-carbon bond formation and it can be applied for the synthesis of pinacols or alkenes by changing the reaction conditions and the method by which low-valent titanium is generated.[10] Because of a better reproducibility and milder reaction conditions the procedure reported by Corey was used.[11]

Thus the reaction of aldehydes **1a-d**,[8] in THF with low-valent titanium generated from Mg/Hg amalgam and $TiCl_4$ at room temperature was studied.

In all cases *ca.* 30% yield of intramolecularly coupled compounds was obtained. Variation in concentration of the reactants does not affect the yield and product distribution, in agreement with the Mc Murry hypothesis that the reaction takes place on the titanium surface.[10]

A more systematic study of this reaction was performed using the dialdehyde **1a**. Running the reaction for 5 h at room temperature, a 1:1 mixture of the two diastereomeric diols **2a** and **2a'** was isolated and characterized by $^1H$ NMR. The main feature of the spectra is the unusually high-field shift experienced by the aromatic protons involved in the bridge ( δ 5.22 and 5.82 for **2a** and δ 5.38 and 5.96 for **2a'**) while the other two aromatics absorb at the normal value of about 7 ppm. A similar behaviour has also been observed by Böhmer et al.[12] in upper rim diametrically bridged calix[4]arenes where the aromatic protons of the host bearing the shortest (5 atoms long) bridge absorb at δ 6.27 ppm. The higher up-field shift observed in compounds **2a** and **2a'** suggest that, because of the shorter bridge, the molecules are forced to adopt a highly distorted flattened cone structure. It is in fact reasonable to assume that the more the cone is distorted the more the protons of the bridged aromatics are shielded by the π–electrons of the two other nuclei.[13]



**2a, 2a'** $R^1=R^2=H$

**3a** $R^1=R^2=H$
**3b** $R^1=R^2=tBu$
**3c** $R^1=CH_3, R^2=H$
**3d** $R^1=R^2=CH_3$

**4b** $R^1=R^2=tBu$
**4d** $R^1=R^2=CH_3$

**1a** $R^1=R^2=H$
**1b** $R^1=R^2=tBu$
**1c** $R^1=CHO, R^2=H$
**1d** $R^1=R^2=CHO$

$R=CH_2CH_2OCH_2CH_3$

Increasing the reaction time up to 18 h, the alkene **3a** was isolated instead of the diols. Also in this case the $^1$H NMR spectrum shows the presence of a peak at δ 5.43 ppm experienced by the protons of the aromatics involved in the unsaturated bridge.

Interestingly the reaction of the dialdehyde **1b** with low valent titanium yields a different product distribution. In fact, after HPLC separation, the expected alkene **3b** was obtained together with the alkane **4b** in 1:4 ratio. This type of reactivity, through not common, has been shown to occur when the congestion around the reactive center increases.[14] It is therefore likely to assume that the t-butyl groups present in close proximity to the reactive centers favour the formation of the alkane.

In order to verify whether the intramolecular reductive coupling could take place between two adjacent (1-2) aldehyde groups, the reactivity of the tri- and tetra-aldehydes **1c** and **1d** was studied. In both cases only the aldehyde groups in the 1-3 positions show coupling, aldehyde **1c** giving the alkene **3c** and the tetraaldehyde **1d** a 1:1 mixture of the alkene **3d** and alkane **4d**. This indicates that the presence of two additional aldehyde groups, although less demanding than t-butyl groups present in **1b**, are bulky enough to allow the formation of the alkane. Unexpectedly the carbonyls not involved in the bridge were reduced to methyl.

The separation between the *axial* and *equatorial* protons of the methylene bridge ($Ar-CH_2-Ar$) is always very high ($\Delta\delta > 1$ ppm) and we have no indication from the $^1H$ NMR spectra of compounds **2-4** that the flattening of the cone causes a substantial reduction of this value, as previously suggested[15]. Therefore it seems that the $\Delta\delta$ separation between axial and equatorial protons is more sensitive to the mobility of the calix conformation and to other effects rather than indicative of a distortion from the symmetrical cone structure.

## CONCLUSIONS

The residual flexibility of tetra-alkoxycali[4]arene cone conformers has been exploited to synthesize highly distorted and rigid cone structures having a two atoms long bridge. They all show in the $^1H$ NMR spectrum an unusually high-field shift for the aromatic protons of the bridged nuclei. By changing the reaction time of the low valent titanium promoted coupling of **1a** it has been possible to obtain the diols **2a** and **2a'** or the alkene **3a** in 30 % overall yield. The aldehyde **1b** behaves differently because of the presence of the two *t*-butyl groups in close proximity to the aldehyde groups and a mixture of alkene **3b** and alkane **3d** was isolated. In the tri- and tetra aldehydes **1c** and **1d** the coupling reaction takes place only between two opposite (diametrical) formyl groups, while the other two groups present are reduced to methyl. Differently from what was suggested by other authors[15] for mobile cone conformers of calix[4]arenes, the $\Delta\delta$ separation between the chemical shifts of *axial* and *equatorial* protons of the methylene bridge cannot be used as a tool to indicate the distortion from the symmetrical cone conformations.

## EXPERIMENTAL SECTION

All reactions were carried out under argon, THF was freshly distilled from sodium benzophenone prior to use, whereas all other reagents and solvents were of reagent grade quality, obtained from commercial suppliers, and used without further purification. $^1$H NMR spectra were recorded in $CDCl_3$ on Bruker AC 100 and Bruker AMX 400 instruments (at 400 MHz) while $^{13}$C NMR were recorded at 25 MHz. Chemical shifts ($\delta$) are expressed in ppm from the internal reference tetramethylsilane (TMS). Mass spectra were determined in the CI mode ($CH_4$) using a Finnigan-MAT SSQ70 spectrometer. Analytical thin layer chromatography was performed on precoated silica gel plates (Merck, 60 $F_{256}$), column chromatography was performed with silica gel (Merck, particle size 0.040-0.063 mm, 230-240 mesh). Elemental analyses were performed at Dipartimento di Chimica Generale e Inorganica, Chimica Analitica, Chimica Fisica of the University of Parma.

**Reductive coupling: general procedure.** A 25 ml three-necked round bottom flask, equipped with an Argon inlet and stirring bar was charged with $HgCl_2$ (0.070 g, 0.26 mmol), Mg powder (0.24 g, 9.87 mmol) and THF (2 ml) and stirred for 20 min. The reaction was cooled at -10° C and then $TiCl_4$ (0.90 g, 4.8 mmol) was slowly injected through a septum with a syringe. When the reaction mixture had turned to yellow-green the desired aldehyde (0.26 mmol) dissolved in 6 ml of THF was added. The reaction was stirred at -10° C for 20 min and then at room temperature until the starting aldehyde had disappeared (TLC), quenched with $K_2CO_3$ (10% w.) (30 ml), stirred up to complete bleaching (about 3 hours) and the solid removed by suction filtration. The solution was extracted three times with ethyl acetate (10 ml), the combined organic phases washed twice with water, evaporated and purified by column chromatography.

**Diols 2a and 2a'.** Starting aldehyde **1a**, reaction time 5h, eluent hexane/ethyl acetate =6/4. **2a**: 15% yield, viscous oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.07 and 1.15 (2t, 12H, J = 7.0 Hz, $OCH_2CH_3$), 2.70 (bs, 2H, ArCH(O*H*)), 3.07 and 3.11 (2d, 4H, J = 14.6 Hz and J = 14.3 Hz, Heq), 3.39 and 4.49 (2q, 8H, $OCH_2CH_3$), 3.59 and 3.63 (2t, 8H, J = 6.3 Hz and J = 5.1 Hz, $ArOCH_2CH_2$), 3.8-4.0 (m, 8H, $ArOCH_2CH_2$), 4.08 (s, 2H,ArC*H*(OH)), 4.32 and 4.39 (2d, 4H, Hax), 5.22 and 5.82 (2d, 4H, J = 1.9 Hz, Ar 4,6,16,18-H), 6.91 (t, 2H, J = 7.4 Hz, Ar 11, 23-H), 7.0-7.1 (m, 4H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 15.2 (q, $OCH_2CH_3$), 31.0 and 31.3 (t, $ArCH_2Ar$), 66.2, 66.6, 69.4, 69.7, 72.3, 73.4 (t, $ArCH_2CH_2OCH_2$), 82.2 (d, ArCHOH), 121.6, 125.0, 129.3, 129.6, 130.2 (d, Ar 4,6,10,11,12,18,22,23,24-C), 134.6, 134.7, 137.3, 137.8, 155.1, 159.2 (s, Ar 5,17,1,3,7,9,13,15,19,21,25,26,27,28-C); mass spectrum (CI) 771 ($M^+$+1); anal. calcd. for $C_{46}H_{58}O_{10}$: C, 71.66; H, 7.59; found: C, 71.38; H, 7.60. **2a'**: 15% yield, viscous oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.1-1.3 (m, 12H, $OCH_2CH_3$), 3.15 and 3.16 (2d, 4H, J = 14.5 Hz, Heq), 3.4-3.6 (m, 8H, $OCH_2CH_3$), 3.67 and 4.05 (2t, 8H, J = 6.4 Hz, $ArOCH_2CH_2$), 3.71 and 3.90 (2t, 8H, J = 5.7 Hz, $ArOCH_2CH_2$), 4.43 and 4.44 (2d, 4H, Hax), 4.54 (s, 2H, ArC*H*(OH)), 5.38 and 5.96 (2d, 4H, J = 1.8 Hz, Ar 4,6,16,18-H), 6.9-7.1 (m, 6H, Ar 10,11,12,22,23,24-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 15.2 (q, $OCH_2CH_3$), 31.0 and 31.3 (t, $ArCH_2Ar$), 66.2, 66.6, 69.4, 69.7, 72.3, 73.4 (t, $ArOCH_2CH_2OCH_2$), 82.2 (d, ArCHOH), 121.6, 125.0, 129.3, 129.6, 130.2 (d, Ar

4,6,10,11,12,18,22,23,24-C), 134.6, 134.7, 137.3, 137.8, 155.1, 159.2 (s, Ar 5,17,1,3,7,9,13,15,19,21,25,26,27,28-C); mass spectrum (CI) 771 ($M^+$+1); anal. calcd. for $C_{46}H_{58}O_{10}$: C, 71.66; H, 7.59; found: C, 71.40; H, 7.62.

**25,26,27,28-Tetrakis[2-ethoxyethoxy]-5,17-ethylene-calix[4]arene (3a).** Starting aldehyde **1a**, reaction time 16h, eluent hexane/ethyl acetate = 8/2): yield 30%, viscous oil; $^1$H NMR ($CDCl_3$) δ 1.15 and 1.25 (2t, 12H, J = 6.9 Hz, $OCH_2CH_3$), 3.17 (d, 4H, J = 14.5 Hz, Heq), 3.48 and 3.59 (2q, 8H, $OCH_2CH_3$), 3.69 and 3.72 (2t, 8H, J = 6.2 Hz and J = 4.7 Hz, $ArOCH_2CH_2$), 3.94 and 4.07 (2t, 8H, $ArOCH_2CH_2$), 4.46 (d, 4H, Hax), 5.43 (s, 4H, Ar 4,6,16,18-H), 6.55 (s, 2H, ArCH=CH), 6.95 (t, 2H, J = 7.2 Hz, Ar 11,23-H), 7.11 (d, 4H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) 15.3 (q, $OCH_2CH_3$), 31.2 (t, $ArCH_2Ar$), 66.3, 66.6, 69.7, 69.8, 72.3, 73.5 (t, $ArOCH_2CH_2OCH_2$), 128.4 (d, ArCH), 121.7, 129.4,135.0 (d, Ar 4,6,10,11,12,16,18,22,23,24-C), 133.0, 133.7, 137.7, 153.7, 159.3 (s, Ar 5,17,1,3,7,9,13,19,21,25,26,27,28-C); mass spectrum (CI) 737 ($M^+$+1); anal. calcd. for $C_{46}H_{56}O_8$: C,74.97; H, 7.66; found: C, 74.89; H, 7.75.

**11,23-Bis[1,1-dimethylethyl]-25, 26, 27, 28-tetrakis[2-ethoxyethoxy]-5,17-ethylene-calix[4]arene (3b) and 11,23-bis[1,1-dimethylethyl]-5,17-ethano-25,26,27,28-tetrakis[2-ethoxyethoxy]calix[4]arene (4b).** Starting aldehyde **1b**, reaction time 40 min, the crude reaction mixture was purified by column chromatography (hexane/ethyl acetate = 75/25) to afford a mixture of compounds **3b** and **4b**, which were separated by HPLC (RP-18), eluent methanol/water = 99/1, $t_R$(**3b**) = 3.2' $t_R$(**4b**) = 4.4'; $\Delta t_R$ = 1.2'. **3b:** 25% yield, viscous oil; $^1$H NMR ($CDCl_3$) δ 1.14 and 1.24 (2t, 12H, J = 7.2 Hz, $OCH_2CH_3$), 1.37 (s, 18H, $C(CH_3)_3$), 3.11 (d, 8H, J = 14.8 Hz, Heq), 3.47 and 3.59 (2q, 8H, $OCH_2CH_3$), 3.68 and 3.73 (2t, 8H, J = 6.4 Hz and J = 5.5 Hz, $ArOCH_2CH_2O$), 3.92 and 4.0 (2t, 8H, $ArOCH_2CH_2O$), 4.11 (d, 4H, $H_{ax}$), 5.35 (s, 4H, Ar 4,6,16,18-H ), 6.52 (s, 2H, ArCH=CHAr), 7.06 (s, 2H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q, $OCH_2CH_3$), 31.5 (t, $ArCH_2Ar$), 31.8 (q, $ArC(CH_3)_3$), 32.1 (s, $ArC(CH_3)_3$), 60.6-70.4 ($ArOCH_2CH_2OCH_2$), 126.2 (d, Ar 4,6,10,12,16,18,22,24-C), 128.4 (ArCH=CHAr), 132.9, 135.0, 136.7, 144.5 (s, Ar 5,17,11,24,1,3,7,9,13,19,21,25,26,27,28-C); mass spectrum 848 ($M^+$); anal. calcd. for $C_{54}H_{72}O_8$: C, 76.38; H, 8.54; found: C, 76.19; H, 8.64. **4b**: 10% yield, viscous oil; $^1$H NMR ($CDCl_3$) δ 1.14 and 1.23 (2t, 12H, J = 7.0, $OCH_2CH_3$), 1.39 (s, 18H, $C(CH_3)_3$), 2.39 (s, 4H, $ArCH_2CH_2Ar$), 3.10 (4H, J = 14.4 Hz, Heq), 3.48 and 3.58 (2q, 8H, $OCH_2CH_3$), 3.69 and 3.72 (2t, 8H, J = 6.4 Hz and J = 5.2 Hz, $ArCH_2CH_2O$), 3.89 and 4.02 (2t, 8H, $ArOCH_2CH_2O$), 4.40 (d, 4H, $H_{ax}$), 5.36 (s, 4H, Ar 4,6,16,18-H), 7.08 (s, 4H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q, $OCH_2CH_3$), 31.2 (t, $ArCH_2Ar$), 31.6 (q, $ArC(CH_3)_3$), 33.9 (t, $ArCH_2CH_2Ar$), 64.6-73.3 ($ArOCH_2CH_2O$), 126.1, 129.0 (d, Ar 4,6,10,12,16,18,22,24-C) 133.8, 133.8, 136.8, 144.4 (s, Ar 5,17,11,24,1,3,7,9,13,19,21,25,26,27,28-C); mass spectrum 850 ($M^+$); anal. calcd. for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76; found: C, 75.98; H, 8.85.

**25,26,27,28-Tetrakis[2-ethoxyethoxy]-5,17-ethylene-11-methyl-calix[4]arene (3c).** Starting aldehyde **1c**, reaction time 10 h, purification by column chromatography ($SiO_2$, eluent hexane / ethyl acetate, 96/4); 27% yield, viscous oil. $^1$H NMR ($CDCl_3$) δ 1.23, 1.40, 1.51 (3t, 12H, J = 7.0 Hz, $OCH_2CH_3$), 2.35 (s, 3H, $ArCH_3$), 3.09 and 3.15 (2d, 4H, J = 14.6 Hz, J = 14.5 Hz, Heq), 3.46, 3.47 and 3.58 (3q, 8H, $OCH_2CH_3$), 3.59 (q, 4H, J = 7.0 Hz, $OCH_2CH_3$), 3.6-3.7 (m, 8H, $ArOCH_2CH_2O$), 3.9-3.4 (m, 8H, $ArOCH_2CH_2O$), 4.39 and 4.43 (2d, 4H, Hax), 5.41 and 5.4 (2d, 4H, J = 1.5 Hz, Ar 4,6,16,18-H), 6.54 (s, 2H, ArCH=CH), 6.89 (s, 2H, Ar 10,12-H), 6.94 (t, 1H, J = 7.36 Hz, Ar23-H), 7.09 (d, 2H, Ar 22, 24-H); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q, $OCH_2CH_3$), 20.9 (q, $ArCH_3$) 31.2 (t, $ArCH_2Ar$), 64.2, 66.6, 69.5, 69.7, 72.2, 73.4 ($ArOCH_2CH_2OCH_2$), 128.4 (d, ArCH=CH), 121.7, 129.5, 134.9 (d, Ar 4,6,10,12,16,18,22,23,24-C) 133.0, 133.7, 137.7, 153.8, 159.3 (s, Ar 5,17,11,1,3,7,9,13,19,21,25,26,27,28-C); mass spectrum (CI) 751 ($M^+$+1); anal. calcd. for $C_{47}H_{58}O_8$: C,75.17; H, 7.78; found: C, 74.89; H, 7.88.

**25,26,27,28-Tetrakis[2-ethoxyethoxy]-5,17-ethylene-11,23-dimethyl-calix[4]arene (3d) and 5,17-Ethano-25,26,27,28-tetrakis[2-ethoxyethoxy]-11,23-dimethyl-calix[4]arene (4d).** Starting aldehyde **1d**, reaction time 10 h, purification by column chromatography ($SiO_2$, eluent hexane / ethyl acetate, 90/10). Since **3d** and **4d** could not be separated by t.l.c., they were separated by HPLC (RP-18), (eluent 99 methanol : 1 water) $t_R$(**3d**) = 3.2'; $t_R$(**4d**) = 4.4'; $\Delta t_R$ = 1.2'. Yield: 15% **3d** and 15% **4d**, viscous oils. **3d:** $^1$H NMR ($CDCl_3$) δ 1.15 and 1.23 (2t, 12H, J = 7.0 Hz, $OCH_2CH_3$ ), 2.36 (s, 6H, $ArCH_3$), 3.08 (d, 4H, J = 14.4 Hz, Heq), 3.48 and 3.59 (2q, 8H, $OCH_2CH_3$), 3.67 and 3.73 (2t, 8H, J = 6.3 Hz and J = 5.2 Hz, $ArOCH_2CH_2O$), 3.91 and 3.99 (2t, 8H, $ArOCH_2CH_2O$), 4.39 (d, 4H, Hax), 5.45 (s, 4H, Ar 4,6,16,18-H), 6.56 (s, 2H, ArCH=CH), 6.89 (s, 4H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q, $OCH_2CH_3$), 20.9 (q, $ArCH_3$) 31.2 (t, $ArCH_2Ar$), 66.2, 66.6, 69.5, 69.7, 72.2, 73.4 (t, $ArOCH_2CH_2OCH_2$), 128.4 (d, ArCH=CH), 129.9, 135.0 (d, Ar 4,6,10,12,16,18,22,24-C) 130.5, 132.5, 133.8, 137.3, 159.3 (s, Ar 5,17,11,1,3,7,9,13,19,21,23,25,26,27,28-C); mass spectrum (CI) 765 ($M^+$+1); anal. calcd. for $C_{48}H_{60}O_8$: C, 75.36; H, 7.90; found: C, 75.15; H, 7.95. **4d:** $^1$H NMR ($CDCl_3$) δ 1.15 and 1.23 (2t, 12H, J = 7.0 Hz, $OCH_2CH_3$), 2.38 (s, 6H, $ArCH_3$), 2.46 (s, 4H, $ArCH_2CH_2Ar$), 3.07 (4H, J = 14.4 Hz, Heq), 3.48 and 3.58 (2q, 8H, $OCH_2CH_3$), 3.68 and 3.72 (2t, 8H, J = 6.4 Hz and J = 4.7 Hz, $ArCH_2CH_2O$), 3.89 and 4.01 (2t, 8H, $ArOCH_2CH_2O$), 4.38 (d, 4H, Hax ), 5.46 (s, 4H, Ar 4,6,16,18-*H*), 6.90 (s, 4H, Ar 10,12,22,24-H); $^{13}$C NMR ($CDCl_3$) δ 15.3 (q, $OCH_2CH_3$), 31.1 (t, $ArCH_2Ar$), 33.6 (t, $ArCH_2CH_2Ar$), 66.2, 66.6, 69.6, 69.7, 72.2, 73.4 (3t, $ArOCH_2CH_2OCH_2$), 129.1, 129.8 (d, Ar 4,6,10,12,16,18,22,24-C), 130.0, 133.6, 133.8, 137.3, 153.3, 157.4 (s, Ar 5,17,11,24,1,3,7,9,13,19,21,25,26,27,28-C); mass spectrum (CI) 767 ($M^+$+1) anal. calcd for $C_{48}H_{62}O_8$: C, 75.16; H, 8.14; found: C, 74.95; H, 8.25.

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