

## Novel Routes for the Synthesis of Upper Rim Amino and Methoxycarbonyl Functionalized Calix[4]arenes Carrying Other Types of Functional Groups

Peter Timmerman,<sup>a</sup> Willem Verboom,<sup>a</sup> David N. Reinhoudt,<sup>\*a</sup> Arturo Arduini,<sup>b</sup> Stefania Grandi,<sup>b</sup> Anna R. Sicuri,<sup>b</sup> Andrea Pochini,<sup>\*b</sup> Rocco Ungaro<sup>\*b</sup>

<sup>a</sup> Laboratory of Organic Chemistry, University of Twente, NL-7500 AE Enschede, The Netherlands

<sup>b</sup> Dipartimento di Chimica Organica e Industriale dell'Università, Viale delle Scienze 78, I-43100 Parma, Italy

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The selective functionalization of calix[4]arenes **1** by iodination at the upper rim in the presence of other functionalities is described. The resulting (partly) iodinated calix[4]arenes **2** are good starting materials for the preparation of both the corresponding carboxylic ester and amino derivatives **3** and **6**, respectively.

Calix[4]arenes<sup>1,2</sup> have become a useful building block<sup>3</sup> in supramolecular chemistry due to their easy availability and the possibility of selective functionalization. For more specific complexation in the hydrophobic cavity, functionalization of the upper rim has been extensively studied, resulting in methods for the facile introduction of a variety of functional groups, like allyl,<sup>3,4</sup> keto,<sup>5,6</sup> cyano,<sup>5</sup> formyl<sup>4,7</sup> and nitro<sup>8</sup> groups. However, other important functional groups, like carboxylic acid,<sup>5</sup> ester<sup>5</sup> and amide moieties<sup>9</sup> can only be introduced via multi-step chemical transformations, often in low yields. The reaction conditions required for the introduction of functional groups are not always compatible with other functionalities in the same molecule. In this paper we describe new procedures for the introduction of both amino and carboxylic ester groups at the upper rim of calix[4]arenes in the presence of several other functional groups.

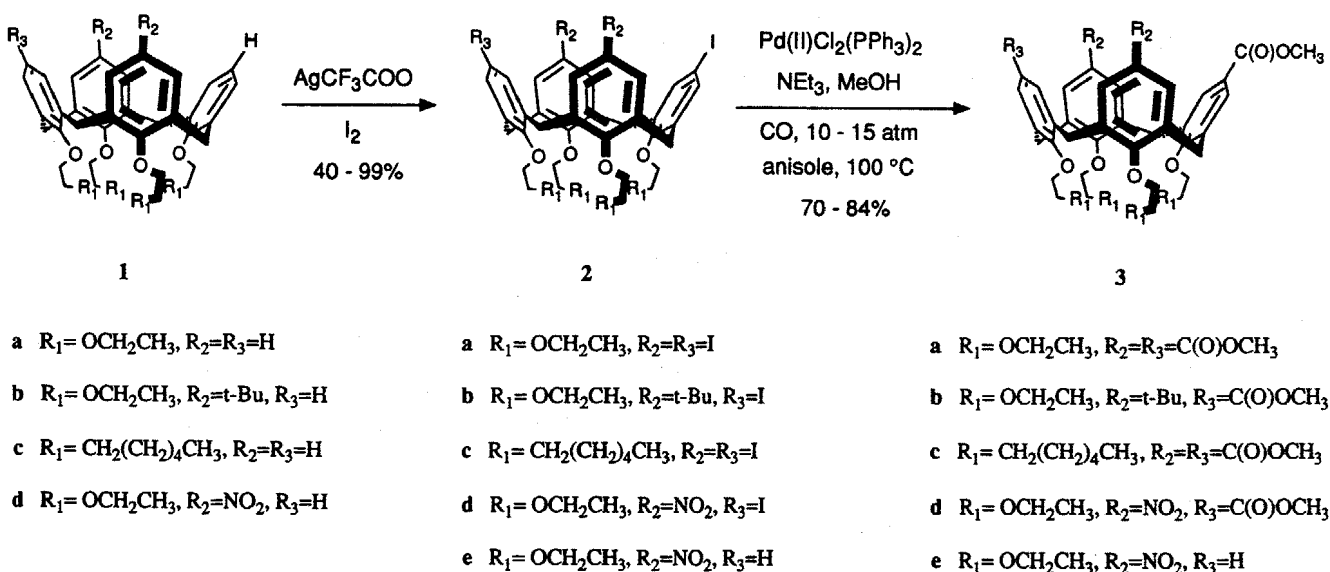
The methodology starts with the iodination of calix[4]arenes. This reaction was previously carried out with Hg(TFA)<sub>2</sub>/I<sub>2</sub> or Tl(TFA)<sub>3</sub>/KI<sup>10</sup> in modest yields of ≤ 40%. As part of a study to introduce alkynyl groups into calix[4]arenes, it was found that with silver trifluoroacetate and I<sub>2</sub> in CHCl<sub>3</sub>, 25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (**1a**)<sup>10</sup> and 5,17-bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene

(**1b**)<sup>8</sup> gave **2a**<sup>10</sup> and **2b**,<sup>11</sup> respectively, in quantitative yield. The scope of this reaction was studied with other calix[4]arenes. We found that the reaction affords good yields with all the substrates used. In this way compounds **1c**,<sup>8</sup> **1d**<sup>12</sup> and **1f**<sup>13</sup> could be converted to the corresponding tetra- or diiodo derivatives **2c**, **2d** and **2f**, respectively. Treatment of **1d** with only 1 equiv of AgTFA/I<sub>2</sub> gave the partly iodinated calix[4]arene **2e** in 40% yield.

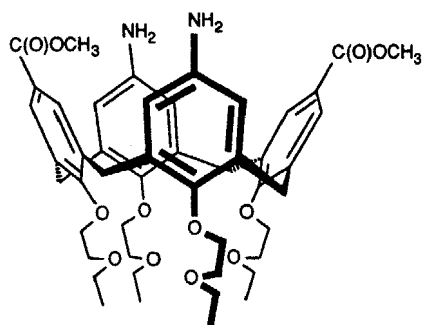
Subsequently, we studied the conversion of iodinated calix[4]arenes into calix[4]arenes bearing carboxylic ester groups, according to the procedure developed by Heck for the synthesis of benzoic esters.<sup>14</sup> Reaction of tetraiodocalix[4]arene **2a**<sup>10</sup> with CO and MeOH using NEt<sub>3</sub> as a base and Pd[(PPh)<sub>3</sub>]<sub>2</sub>Cl<sub>2</sub> as a catalyst at 100 °C and 10–15 atm in anisole for 24 hours, afforded the corresponding tetraester derivative **3a** in 70% yield. In the <sup>1</sup>H NMR spectrum, the singlet at δ = 3.78 clearly proved the formation of the product. In a similar way, compounds **3b–e** (70–84%) could be synthesized, indicating that *tert*-butyl and nitro groups are compatible with the reaction conditions.

Compound **3d**, a calix[4]arene carrying two nitro and two carboxylic ester functions, was submitted to reduction with hydrazine in the presence of a catalytic amount of Raney nickel. The nitro groups were cleanly reduced without affecting the ester functions to give **4** in 98% yield.

So far, reduction of nitrocalix[4]arenes is the only convenient route for the introduction of amino groups at



Scheme 1



4

the upper rim of calix[4]arenes.<sup>8</sup> Our recent interest in calix[4]arenes carrying both amino and nitro groups obviously requires another strategy. Several attempts to nitrate the two remaining para positions of diamino-calix[4]arenes failed in our hands and as an alternative, we have studied the Gabriel reaction for the synthesis of 5,11-diamino-17,23-dinitrocalix[4]arenes, e. g. **6b**. To the best of our knowledge, this reaction has hardly been used for aromatic compounds. When **2e** was reacted with 0.75 equiv of  $\text{Cu}_2\text{O}$  and 1.5 equiv of phthalimide in refluxing collidine for 24 hours,<sup>15</sup> we isolated **5a** in 55% yield together with 13% unreacted starting material. In the same way, **2f** was converted to **5b** in 59% yield. Deprotection of the masked amino groups in **5a** and **5b** was carried out using hydrazine and HCl in EtOH.<sup>16</sup> In this way, **6a** and **6b** were formed in quantitative yield, as

could be seen from the absorption at  $\delta = 5.9$  in the  $^1\text{H}$ NMR spectrum, characteristic of aromatic protons ortho to an amino group.

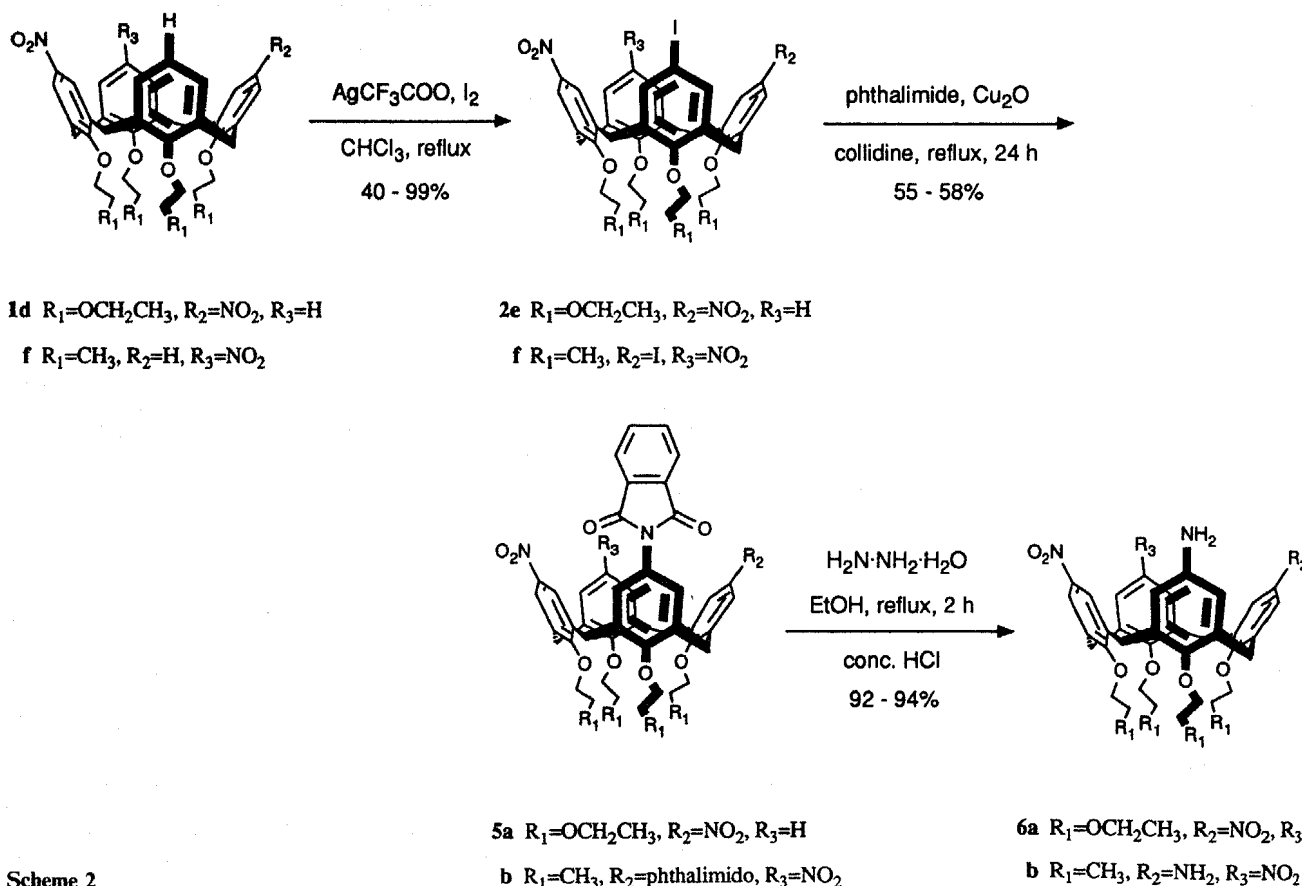
Melting points are uncorrected.  $^1\text{H}$ NMR and  $^{13}\text{C}$ NMR were recorded on Bruker instruments. TMS was used as an internal standard. Preparative column chromatography separations were performed on Merck silica gel 60 (230–400 mesh) or 60 H, while pre-coated silica gel plates (Merck, 60 F<sub>254</sub>) were used for analytical TLC. FAB mass spectra were performed on a Finnigan MAT 90 spectrometer, with *meta*-nitrobenzyl alcohol as a matrix; CI mass spectra were recorded on a Finnigan MAT 8400 spectrometer. All solvents were purified by standard procedures. Petroleum ether refers to the fraction with bp 60–80°C. All other chemicals were analytically pure, and were used without further purification. All reactions were carried out in an inert atmosphere ( $\text{N}_2$  or Ar).

#### Iodocalix[4]arenes **2**; General Procedure:

To a suspension of  $\text{CF}_3\text{COOAg}$  (1.0–1.5 equiv per iodo incorporated) in refluxing  $\text{CHCl}_3$  (25 mL) was added a solution of calix[4]arene **1c–e** in  $\text{CHCl}_3$  (25 mL) and the cloudy solution was refluxed for 15 min. Then  $\text{I}_2$  (1.0–1.5 equiv per iodo incorporated) was added in portions until the deep purple color was permanent. During the addition, AgI precipitated from the solution as a yellow powder. The reaction mixture was refluxed another 15 min, cooled to r. t., filtered over Celite and evaporated to dryness. The residue was dissolved in EtOAc (25 mL), washed with 10% aq  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL), washed with  $\text{H}_2\text{O}$  ( $3 \times 10$  mL), with brine (10 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed under vacuo to give **2**.

#### 5,11,17,23-Tetraiodo-25,26,27,28-tetraoctoxycalix[4]arene (**2c**):

The reaction was carried out using **1c** (0.5 g, 0.57 mmol),  $\text{CF}_3\text{COOAg}$  (0.5 g, 2.28 mmol) and  $\text{I}_2$  (0.57 g, 2.28 mmol) to give the crude product which was purified by column chromatography ( $\text{SiO}_2$ , hexane–EtOAc, 95:5); yield: 0.55 g (70%); mp 99–100°C. MS (CI):  $m/z = 1377 [(M^+ + H), \text{calc. } 1377.2]$ .



Scheme 2

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.98 (s, 8H, ArH), 4.27 and 3.04 (ABq, 8H,  $J$  = 13.4 Hz,  $\text{ArCH}_2\text{Ar}$ ), 3.82 [t, 8H,  $J$  = 7.6 Hz,  $\text{ArOCH}_2(\text{CH}_2)_6\text{CH}_3$ ], 1.83 [m, 8H,  $\text{ArOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ ], 1.32–1.27 [m, 40H,  $\text{ArOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ ], 0.88 [t, 12H,  $J$  = 6.6 Hz,  $\text{ArOCH}_2(\text{CH}_2)_6\text{CH}_3$ ].

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.4 (s, Ar 25,26,27,28-C), 137.1 (s, Ar 1,3,7,9,13,15,19,21-C), 136.8 (d, Ar 4,6,10,12,16,18,22,24-C), 86.1 (s, Ar 5,11,17,23-C), 30.4 (t,  $\text{ArCH}_2\text{Ar}$ ).

**25,26,27,28-Tetrakis(2-ethoxyethoxy)-5,17-diiodo-11,23-dinitrocalix[4]arene (2d):**

The reaction was carried out using **1d** (0.27 g, 0.34 mmol),  $\text{CF}_3\text{COOAg}$  (0.23 g, 1.02 mmol) and  $\text{I}_2$  (0.26 g, 1.02 mmol) to give pure **2d** as a yellow solid; yield: 0.35 g (99%); mp 184°C ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ).

MS (FAB):  $m/z$  = 1054.9 [(M + H)<sup>+</sup>, calc. 1055.1].

$^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.71 (s, 4H, ArH ortho to  $\text{NO}_2$ ), 6.90 (s, 4H, ArH ortho to I), 4.54 and 3.21 (ABq, 8H,  $J$  = 13.7 Hz,  $\text{ArCH}_2\text{Ar}$ ), 4.31, 4.04 (2 t, 4H each,  $J$  = 4.9 and 4.8 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.79, 3.74 (2 t, 4H each,  $J$  = 5.0 and 4.5 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.52, 3.45 (2 q, 4H each,  $J$  = 7.0 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 1.20, 1.12 (2 t, 6H each,  $J$  = 7.0 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 162.5 (s, Ar 25,27-C), 155.9 (s, Ar 26,28-C), 143.1 (s, Ar 11,23-C), 137.3 (d, Ar 4,6,16,18-C), 136.3, 135.8 (s, Ar 1,3,7,9,13,15,19,21-C), 123.9 (d, Ar 10,12,22,24-C), 30.6 (t,  $\text{ArCH}_2\text{Ar}$ ).

**25,26,27,28-Tetrakis(2-ethoxyethoxy)-11-iodo-5,17-dinitrocalix[4]arene (2e):**

The reaction was carried out using **1d** (1.13 g, 1.40 mmol),  $\text{CF}_3\text{COOAg}$  (0.31 g, 1.40 mmol) and  $\text{I}_2$  (0.43 g, 1.70 mmol) to give **2e** after column chromatography ( $\text{SiO}_2$ , petroleum ether–EtOAc, 80:20); yield 0.52 g (40%); an additional 14% product slightly contaminated with starting compound was isolated as well; mp 131–133°C (EtOH).

MS (FAB):  $m/z$  = 929.4 [(M + H)<sup>+</sup>, calc. 929.2].

$^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.77, 7.72 (2 d, 2H each,  $J$  = 2.7 Hz, ArH ortho to  $\text{NO}_2$ ), 6.62 (t, 1H,  $J$  = 7.6 Hz, ArH), 6.56 (s, 2H, ArH ortho to I), 6.31 (d, 2H,  $J$  = 7.6 Hz, ArH), 4.52, 4.46 and 3.22, 3.13 (2 ABq, 4H each,  $J$  = 13.9 Hz,  $\text{ArCH}_2\text{Ar}$ ), 4.35–4.20 (m, 4H,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 4.00–3.90 (m, 4H,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.80–3.65 (m, 8H,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.55–3.35 (m, 8H,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 1.20–1.00 (m, 12H,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 163.3 (s, Ar 26,28-C), 155.5, 155.2 (s, Ar 25,27-C), 142.4 (s, Ar 5,17-C), 137.4, 136.6, 135.7 (s, Ar 3,7,9,13,15,19-C), 137.0 (d, Ar 10,12-C), 132.8 (s, Ar 1,21-C), 128.3 (d, Ar 22,24-C), 124.2, 123.7, 123.5 (d, Ar 4,6,16,18,23-C), 86.8 (s, Ar 11-C), 31.0, 30.6 (t,  $\text{ArCH}_2\text{Ar}$ ).

**5,11-Diiodo-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (2f):**

The reaction was carried out using **1f** (0.78 g, 1.14 mmol),  $\text{CF}_3\text{COOAg}$  (0.76 g, 3.42 mmol) and  $\text{I}_2$  (0.87 g, 3.42 mmol) to give pure **2f**; yield: 1.06 g (99%); mp 254–255°C ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ).

MS (FAB):  $m/z$  = 934.1 ( $\text{M}^+$ , calc. 934.0).

$^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.63 (s, 4H, ArH ortho to  $\text{NO}_2$ ), 6.94 (s, 4H, ArH ortho to I), 4.53, 4.40, 4.28 and 3.37, 3.22, 3.06 [3 ABq, 8H (1:2:1),  $J$  = 13.7 and 13.8 Hz,  $\text{ArCH}_2\text{Ar}$ ], 4.05–3.75 (m, 8H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ), 1.95–1.80 (m, 8H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ), 1.05–0.95 (m, 12H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 162.0 (s, Ar 25,26-C), 156.3 (s, Ar 27,28-C), 142.7 (s, Ar 17,23-C), 137.5, 137.0 (d, Ar 4,6,10,12-C), 124.2, 123.7 (d, Ar 16,18,22,24-C), 86.1 (s, Ar 5,11-C), 31.1, 30.7, 30.3 (t,  $\text{ArCH}_2\text{Ar}$ ).

**Methoxycarbonylcalix[4]arenes 3; General Procedure:**

A mixture of **2**,  $\text{NEt}_3$  (1.25–4.4 equiv per ester group incorporated),  $\text{MeOH}$  (5 mL) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (5–8 mol%) in anisole (40 mL)

was heated at 90–100°C for 24 h under 10 atm CO pressure in an autoclave. The reaction mixture was cooled down to r. t. The black powder formed was filtered off and the solvent was removed under vacuo. The residue was dissolved in EtOAc (100 mL), washed with 0.2 N HCl (3 × 25 mL) and  $\text{H}_2\text{O}$  (25 mL) till neutrality, washed with brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$  and evaporated to dryness. The crude product was separated with column chromatography or by recrystallization to give pure **3**.

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

The reaction was carried out using **2a** (0.40 g, 0.33 mmol),  $\text{NEt}_3$  (0.50 g, 5.8 mmol),  $\text{MeOH}$  (0.5 g, 14.5 mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (70 mg, 0.11 mmol) to give crude **3a**, which was further purified by column chromatography ( $\text{SiO}_2$ , hexane–EtOAc, 60:40); yield: 0.21 g (67%); mp 193–195°C.

MS (CI):  $m/z$  = 945 [(M + H)<sup>+</sup>, calc. 945.4].

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.33 (s, 8H, ArH), 4.52 and 3.23 (ABq, 8H,  $J$  = 13.7 Hz,  $\text{ArCH}_2\text{Ar}$ ), 4.14 (t, 8H,  $J$  = 4.8 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.78 [s, 12H,  $\text{C}(\text{O})\text{OCH}_3$ ], 3.76 (t, 8H,  $J$  = 4.8 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.47 (q, 8H,  $J$  = 6.8 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 1.15 (t, 12H,  $J$  = 6.8 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 166.7 [s,  $\text{C}(\text{O})\text{OCH}_3$ ], 160.4 (s, Ar 25,26,27,28-C), 134.7 (s, Ar 1,3,7,9,13,15,19,21-C), 130.1 (d, Ar 4,6,10,12,16,18,22,24-C), 124.4 (s, Ar 5,11,17,23-C), 51.6 [q,  $\text{C}(\text{O})\text{OCH}_3$ ], 30.7 (t,  $\text{ArCH}_2\text{Ar}$ ).

**5,17-Bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(2-ethoxyethoxy)-11,23-bis(methoxycarbonyl)calix[4]arene (3b):**

The reaction was carried out using **2b** (0.40 g, 0.29 mmol),  $\text{NEt}_3$  (0.30 g, 2.9 mmol),  $\text{MeOH}$  (0.27 g, 8.7 mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (80 mg, 0.11 mmol) to give crude **3b**, which was further purified by column chromatography ( $\text{SiO}_2$ , hexane–EtOAc, 75:25); yield: 0.21 g (75%); mp 116–117°C.

MS (CI):  $m/z$  = 941 ( $\text{M}^+$ , calc. 940.5).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.01 (s, 8H, ArH), 4.48 and 3.15 (ABq, 8H,  $J$  = 13.3 Hz,  $\text{ArCH}_2\text{Ar}$ ), 4.18, 4.05 (2 t, 4H each,  $J$  = 6.1 and 5.2 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.87, 3.80 (2 t, 4H each,  $J$  = 6.1 and 5.2 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 3.68 [s, 6H,  $\text{C}(\text{O})\text{OCH}_3$ ], 3.56, 3.54 (2 q, 4H each,  $J$  = 6.9 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ), 1.29 [s, 18H,  $\text{C}(\text{CH}_3)_3$ ], 1.23, 1.20 (2 t, 6H each,  $J$  = 7.0 Hz,  $\text{ArOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 166.7 [s,  $\text{C}(\text{O})\text{OCH}_3$ ], 159.4 (s, Ar 25,27-C), 154.9 (s, Ar 26,28-C), 145.6 (s, Ar 5,17-C), 134.9, 134.7 (s, Ar 1,3,7,9,13,15,19,21-C), 129.7 (d, Ar 10,12,22,24-C), 126.2 (d, Ar 4,6,16,18-C), 124.2 (s, Ar 11,23-C), 51.6 [q,  $\text{C}(\text{O})\text{OCH}_3$ ], 34.3 [s,  $\text{C}(\text{CH}_3)_3$ ], 31.8 [q,  $\text{C}(\text{CH}_3)_3$ ], 31.3 (t,  $\text{ArCH}_2\text{Ar}$ ).

**5,11,17-23-Tetrakis(methoxycarbonyl)-25,26,27,28-tetraoctyloxy-calix[4]arene (3c):**

The reaction was carried out using **2c** (0.40 g, 0.29 mmol),  $\text{NEt}_3$  (0.50 g, 5.0 mmol),  $\text{MeOH}$  (0.5 g, 13.0 mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (80 mg, 0.11 mmol) to give crude **3c** as a brown oil, which was further purified by column chromatography ( $\text{SiO}_2$ , hexane–EtOAc, 60:40); yield: 0.22 g (70%).

HRMS (FAB):  $m/z$  = 1104.6902 ( $\text{M}^+$ , calc. for  $\text{C}_{68}\text{H}_{96}\text{O}_{12}$ : 1104.6902).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.05 (s, 8H, ArH), 4.47 and 3.28 (ABq, 8H,  $J$  = 13.4 Hz,  $\text{ArCH}_2\text{Ar}$ ), 3.78 [s, 12H,  $\text{C}(\text{O})\text{OCH}_3$ ], 3.69 [t, 8H,  $J$  = 7.6 Hz,  $\text{ArOCH}_2(\text{CH}_2)_6\text{CH}_3$ ], 1.90–1.80 [m, 8H,  $\text{ArOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ ], 1.33–1.27 [m, 40H,  $\text{ArOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ ], 0.86 [t, 12H,  $J$  = 6.8 Hz,  $\text{ArOCH}_2(\text{CH}_2)_6\text{CH}_3$ ].

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 166.6 [s,  $\text{C}(\text{O})\text{OCH}_3$ ], 160.5 (s, Ar 25,26,27,28-C), 134.6 (s, Ar 1,3,7,9,13,15,19,21-C), 129.9 (d, Ar 4,6,10,12,16,18,22,24-C), 124.1 (Ar 5,11,17,23-C), 51.6 [q,  $\text{C}(\text{O})\text{OCH}_3$ ], 30.9 (t,  $\text{ArCH}_2\text{Ar}$ ).

**25,26,27,28-Tetrakis(2-ethoxyethoxy)-5,17-bis(methoxycarbonyl)-11,23-dinitrocalix[4]arene (3d):**

The reaction was carried out using **2d** (2.27 g, 2.15 mmol),  $\text{NEt}_3$  (0.75 mL, 5.4 mmol),  $\text{MeOH}$  (5 mL) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (150 mg,

0.22 mmol). The crude product was filtered over silica ( $\text{CH}_2\text{Cl}_2$ -EtOAc, 80:20) and recrystallized to give pure **12**; yield: 1.46 g (74%); mp 155–156°C (EtOH).

MS (FAB):  $m/z = 887.2$  [(M - OCH<sub>3</sub>)<sup>+</sup>, calc. 887.3].

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.54$  (s, 4 H, ArH ortho to NO<sub>2</sub>), 7.38 [s, 4 H, ortho to C(O)OCH<sub>3</sub>], 4.60 and 3.30 (ABq, 8 H,  $J = 13.9$  Hz, ArCH<sub>2</sub>Ar), 4.22, 4.16 (2 t, 4 H each,  $J = 5.0$  and 4.7 Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.88 [s, 6 H, C(O)OCH<sub>3</sub>], 3.85–3.75 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.55–3.42 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 1.18, 1.15 (2 t, 6 H each,  $J = 6.9$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 166.4$  [s, C(O)OCH<sub>3</sub>], 161.4, 160.7 (s, Ar 25,26,27,28-C), 142.7 (s, Ar 11,23-C), 135.7, 134.8 (s, Ar 1,3,7,9,13,15,19,21-C), 130.4 (d, Ar 4,6,16,18-C), 124.8 (s, Ar 5,17-C), 123.4 (d, Ar 10,12,22,24-C), 52.0 [q, C(O)OCH<sub>3</sub>], 30.9 (t, ArCH<sub>2</sub>Ar).

#### 25,26,27,28-Tetrakis(2-ethoxyethoxy)-11-methoxycarbonyl-5,17-dinitrocalix[4]arene (**3e**):

The reaction was carried out using a 2:1 mixture of **2e** and **2d** (2.60 g, 1.69 mmol of **2e**, 0.75 mmol of **2d**), NEt<sub>3</sub> (0.35 mL, 2.5 mmol), MeOH (5 mL) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (110 mg, 0.16 mmol). The product was separated by column chromatography to give **3e** as a yellow oil and **3d** as a white solid; yield: 1.22 g **3e** (84%; based on the amount of **2e** present) and 0.45 g **3d** (65%; based on the amount of **2d** present).

HRMS (EI):  $m/z = 860.371$  (M<sup>+</sup>, calc. for C<sub>46</sub>H<sub>56</sub>N<sub>2</sub>O<sub>14</sub>: 830.373).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.60$  (s, 4 H, ArH ortho to NO<sub>2</sub>), 7.28 [s, 2 H, ArH ortho to C(O)OCH<sub>3</sub>], 6.60–6.50 (m, 3 H, ArH), 4.61, 4.57 and 3.29, 3.25 (2 ABq, 4 H each,  $J = 13.8$  and 13.9 Hz, ArCH<sub>2</sub>Ar), 4.30–4.05 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.85–3.70 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.82 [s, 3 H, C(O)OCH<sub>3</sub>], 3.60–3.45 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 1.30–1.10 (m, 12 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 166.5$  [s, C(O)OCH<sub>3</sub>], 162.2 (s, Ar 26,28-C), 160.2 (s, Ar 27-C), 155.9 (s, Ar 25-C), 142.6 (s, Ar 5,17-C), 136.7–133.8 (s, Ar 1,3,7,9,13,15,19,21-C), 130.1 (d, Ar 10,12-C), 128.7 (d, Ar 22,24-C), 124.7 (s, Ar 11-C), 123.8–123.1 (d, Ar 4,6,16,18,23-C), 51.9 [q, C(O)OCH<sub>3</sub>], 30.9 (t, ArCH<sub>2</sub>Ar).

#### 5,17-Diamino-25,26,27,28-tetrakis(2-ethoxyethoxy)-11,23-bis(methoxycarbonyl)calix[4]arene (**4**):

A suspension of **3d** (1.00 g, 1.09 mmol), hydrazine monohydrate (2.0 mL) and a catalytic amount of Raney Ni in MeOH (50 mL) was refluxed for 3 h. The reaction mixture was filtered through Celite and the solvent was evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 2 M NaOH (10 mL), H<sub>2</sub>O (10 mL) till neutrality, brine (10 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated to give pure **4**; yield: 0.92 g (98%); mp 74–75°C (CHCl<sub>3</sub>).

MS (FAB):  $m/z = 858.3$  (M<sup>+</sup>, calc. 858.4).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.63$  [s, 4 H, ArH ortho to C(O)OCH<sub>3</sub>], 5.55 (s, 4 H, ArH ortho to NH<sub>2</sub>), 4.39 and 3.06 (ABq, 8 H,  $J = 13.5$  Hz, ArCH<sub>2</sub>Ar), 4.24 (t, 4 H,  $J = 5.7$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.85–3.65 (m, 12 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.83 [s, 6 H, C(O)OCH<sub>3</sub>], 3.48, 3.39 (2 q, 4 H each,  $J = 7.0$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 2.87 (bs, 4 H, NH<sub>2</sub>), 1.15, 1.06 (2 t, 6 H each,  $J = 7.0$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 167.8$  [s, C(O)OCH<sub>3</sub>], 162.8 (s, Ar 25,27-C), 148.7 (s, Ar 26,28-C), 141.7 (s, Ar 5,17-C), 137.0 (s, Ar 3,7,15,19-C), 134.0 (s, Ar 1,9,13,21-C), 130.5 (d, Ar 10,12,22,24-C), 123.9 (s, Ar 11,23-C), 116.0 (d, Ar 4,6,16,18-C), 52.2 [q, C(O)OCH<sub>3</sub>], 31.3 (t, ArCH<sub>2</sub>Ar).

#### 25,26,27,28-Tetrakis(2-ethoxyethoxy)-5,17-dinitro-11-phthalimido-calix[4]arene (**5a**):

A mixture of **2e** (50 mg, 54  $\mu$ mol), phthalimide (12 mg, 65  $\mu$ mol) and Cu<sub>2</sub>O (37 mg, 32  $\mu$ mol) in collidine (5 mL) was refluxed for 24 h. The reaction mixture was cooled down to r.t., diluted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL), washed with 5% H<sub>2</sub>SO<sub>4</sub> (2  $\times$  25 mL), 2 M NaOH

(5 mL), H<sub>2</sub>O (5 mL) till neutrality, brine (5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solution was evaporated to dryness. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-EtOAc, 95:5) to give **5a** as a white solid; yield: 28 mg (55%; 13% unreacted starting material was isolated as well); mp 162–163°C (CHCl<sub>3</sub>/EtOH).

MS (FAB):  $m/z = 947.3$  (M<sup>+</sup>, calc. 947.3).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.80$ –7.76 [m, 2 H, Ar(C(O)NC(O)H)], 7.77 (s, 4 H, ArH ortho to phthalimido), 7.66–7.63 [m, 2 H, Ar(C(O)NC(O)H)], 6.50 (s, 2 H, ArH ortho to phthalimido), 6.40–6.28 (m, 3 H, ArH), 4.57, 4.53 and 3.24, 3.22 (2 ABq, 4 H each,  $J = 13.6$  and 13.7 Hz, ArCH<sub>2</sub>Ar), 4.32 (t, 4 H,  $J = 4.9$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 4.00–3.95 (m, 4 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.80–3.70 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.50, 3.49, 3.42 [3 q, 8 H (1:2:1),  $J = 7.0$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>], 1.17, 1.16, 1.08 [3 t, 12 H (1:2:1),  $J = 7.0$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>].

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 166.7$  [s, C(O)NArC(O)], 163.2 (s, Ar 26,28-C), 155.0, 154.5 (s, Ar 25,27-C), 142.4 (s, Ar 5,17-C), 137.4–131.7 [s, Ar 1,3,7,9,11,13,15,19,21-C, C(O)N], 134.2 (d, phthalimide-C), 128.7 (d, Ar 22,24-C), 126.6–123.5 (d, Ar 4,6,10,12,16,18,23-C, phthalimide-C), 31.0 (t, ArCH<sub>2</sub>Ar).

#### 5,11-Dinitro-17,23-bis(phthalimido)-25,26,27,28-tetrapropoxy-calix[4]arene (**5b**):

A mixture of **2f** (1.65 g, 1.77 mmol), phthalimide (0.78 g, 5.3 mmol) and Cu<sub>2</sub>O (0.38 g, 2.7 mmol) in collidine (30 mL) was refluxed for 24 h. The reaction was worked up according to the procedure for **5a**. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-EtOAc, 99:1) and recrystallized from EtOH; yield: 1.00 g (58%); mp > 290°C (phase transition to second crystal phase at 198–200°C).

MS (FAB):  $m/z = 973.4$  [(M + H)<sup>+</sup>, calc. 973.3].

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.80$ –7.70 (m, 4 H, ArH phthalimido), 7.65–7.55 (m, 6 H, ArH phthalimido + ArH ortho to NO<sub>2</sub>), 7.57 (d, 2 H,  $J = 2.7$  Hz, ArH ortho to NO<sub>2</sub>), 6.82, 6.73 (2 d, 2 H each,  $J = 2.5$  Hz, ArH ortho to phthalimido), 4.48 and 3.30, 3.28, 3.25 [3 ABq, 8 H (1:2:1),  $J = 13.5$  Hz, ArCH<sub>2</sub>Ar], 4.00–3.80 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.00–1.80 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.05–0.90 (m, 12 H, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 167.2$  [s, C(O)NArC(O)], 162.1 (s, Ar 27,28-C), 155.8 (s, Ar 25,26-C), 143.7 (s, Ar 5,11-C), 126.4–123.9 (d, Ar 4,6,10,12,16,18,22,24-C), 31.5 (t, ArCH<sub>2</sub>Ar).

#### 11-Amino-25,26,27,28-tetrakis(2-ethoxyethoxy)-5,17-dinitrocalix[4]arene (**6a**):

A solution of **5a** (0.24 g, 0.25 mmol) and hydrazine monohydrate (0.125 mL, 2.5 mmol) in EtOH (25 mL) was refluxed for 2 h, followed by treatment with concentrated HCl (0.4 mL, 5 mmol) for 30 min. The reaction mixture was cooled to r.t. and the precipitate formed was filtered off. The filtrate was evaporated to dryness, the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL), washed with 2 M NaOH (10 mL), H<sub>2</sub>O (10 mL) till neutrality, brine (10 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered and evaporated to dryness to give **6a** as a yellow solid; yield 0.19 g (92%); mp 228–229°C (CH<sub>2</sub>Cl<sub>2</sub>/EtOH).

MS (FAB):  $m/z = 817.4$  (M<sup>+</sup>, calc. 817.4).

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.68$  (s, 4 H, ArH ortho to NO<sub>2</sub>), 6.65–6.50 (m, 3 H, ArH), 5.84 (s, 2 H, ArH ortho to NH<sub>2</sub>), 4.59, 4.50 and 3.26, 3.13 (2 ABq, 4 H each,  $J = 13.6$  and 13.7 Hz, ArCH<sub>2</sub>Ar), 4.28, 4.07, 3.97 [3 t, 8 H (1:2:1),  $J = 5.1$  and 5.2 Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>], 3.85–3.70 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.60–3.45 (m, 8 H, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 1.21, 1.15 (2 t, 6 H each,  $J = 7.0$  Hz, ArOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 162.8$  (s, Ar 26,28-C), 155.8 (s, Ar 25-C), 148.5 (s, Ar 27-C), 142.4 (s, Ar 5,17-C), 141.6 (s, Ar 11-C), 136.9 (s, Ar 9,13-C), 133.8, 133.5 (s, Ar 1,3,7,15,19,21-C), 128.6 (d, Ar 22,24-C), 123.6–122.9 (d, Ar 4,6,16,18,23-C), 115.4 (d, Ar 10,12-C), 31.0, 30.9 (t, ArCH<sub>2</sub>Ar).

**5,11-Diamino-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (6b):**

The reaction was carried out following the procedure for **6a**, using **5b** (0.84 g, 0.86 mmol), hydrazine monohydrate (0.21 mL, 4.3 mmol) EtOH (25 mL) and conc. HCl (0.7 mL, 8.6 mmol) to give pure **6b** as a yellow foam; yield: 0.59 g (96%); mp 124–126°C.

MS (FAB):  $m/z = 712.7$  ( $M^+$ , calc. 712.3).

$^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.59, 7.51$  (2 d, 2 H each,  $J = 2.7$  and 2.6 Hz, ArH ortho to  $\text{NO}_2$ ), 5.97, 5.90 (2 d, 2 H each,  $J = 2.6$  and 2.5 Hz, ArH ortho to  $\text{NH}_2$ ), 4.52, 4.38, 4.24 and 3.31, 3.12, 2.90 [3 ABq, 8 H (1:2:1),  $J = 14.0, 13.8$  and 13.5 Hz,  $\text{ArCH}_2\text{Ar}$ ], 4.05–3.60 (m, 8 H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ), 3.15 (bs, 4 H,  $\text{NH}_2$ ), 2.95–2.75 (m, 8 H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ), 1.05–0.90 (m, 12 H,  $\text{ArOCH}_2\text{CH}_2\text{CH}_3$ ).

$^{13}\text{C NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.5$  (s, Ar 25,26-C), 149.2 (s, Ar 27,28-C), 142.2, 141.2 (s, Ar 5,11,17,23-C), 137.1–133.9 (s, Ar 1,3,7,9,13,15,19,21-C), 124.3, 123.2 (d, Ar 16,18,22,24-C), 115.6, 114.5 (d, Ar 4,6,10,12-C), 31.2, 31.0 (t,  $\text{ArCH}_2\text{Ar}$ ).

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