Intramolecular direct arylation in an A,C-functionalized calix[4]arene†

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A recently developed efficient method for intramolecular direct arylation is employed on a doubly functionalized calix[4]arene fixed in the *cone* conformation. The reaction takes place in high yield leading to *meta* substituted calix[4]arenes. The functionalities are located at two opposite aromatic rings and the two possible diastereomers **1a** and **1b** are obtained in a 1 : 1 ratio. Full sets of data including crystal structures for both isomers are presented. The NMR data reveal that even at temperatures up to 120 °C both isomers are fixed in a *flattened cone* conformation with the substituted aromatic units pointing outwards.

Introduction

Phenolcalixarenes are well-established aromatic macrocycles.[1] Their electron-rich aromatic systems provide good conditions for aromatic electrophilic substitution reactions with a regiochemistry governed by the *para* directing effect of the activating phenol group, whereas the *ortho* positions are blocked by the methylene moieties bridging the aromatic units. Therefore the vast majority of phenolcalixarenes functionalized at the wide rim are substituted at the *para* position. However, phenolcalixarenes functionalized at the *meta* position are rare. Of special interest are systems with fused rings because they should expand the calixarene cavity. So far only calix[4]arenes with the expansion of one of the four aromatic units have been described. These systems are inherently chiral, which explains the interest in developing their chemistry. The first system of that kind was synthesized in 1996 by transforming a monoformylcalix[4]arene into a naphthalene-containing calix[4]arene.[2] Recently, inherently chiral calix[4]quinolines were prepared starting from monoaminocalix[4]arenes.[3] A ring expansion employing metal coordination was achieved by the complexation of Mn^{III} and UO_2 with salen calix[4]arene ligands, which were generated from *meta*-formylated monohydroxycalix[4]arenes.[4] Very recently, oxidative photocyclization on monostyrylcalix[4]arenes resulting in the formation of phenanthrene-containing calix[4]arenes was investigated.[5]

In this paper, we present the first application of intramolecular direct arylation to a calixarene system. For this purpose, we adopted a procedure developed by Fagnou *et al*.[6] As a substrate we used the doubly functionalized calix[4]arene **2** fixed in the *cone* conformation (Scheme 1). The reaction centres are located at two opposite aromatic rings, the remaining two aromatic rings bear no functional groups. Therefore ring closure could lead to two diastereomers **1a** and **1b**. In the achiral C_s-symmetric isomer **1a** both newly formed rings reside near the same unfunctionalized aromatic unit B. In the C_2-symmetric isomer **1b** each of the newly formed rings points to a different unfunctionalized aromatic unit. **1b** represents a racemic mixture of inherently chiral calixarenes. We were interested in the question of whether the first ring closure directs the orientation of the second ring closure. In that case one of the isomers **1a** or **1b** should be formed in excess.

Results and discussion

Synthesis

The synthetic route to **1a** and **1b** is outlined in Scheme 1. It starts with the dibromocalix[4]arene **3** which could be prepared according to reported protocols.[7] Compound **3** is fixed in a *cone* conformation due to *O*-alkylation of the phenolic groups with propyl groups which are bulky enough to prevent inversion of the aromatics.[8] Lithiation, arylboronate formation and oxidative carbon–boron bond cleavage led to the formation of dihydroxycalix[4]arene **4** in a yield of 85%. This transformation has been reported before, however without experimental data.[9] Here, we present an experimental procedure with complete characterization. Alkylation of **4** at the phenol groups on the *wide rim* with benzyl bromide **5** *via* a Williamson ether synthesis with Cs_2CO_3 in acetone produced dibenzyl ether **2** in a yield of 65%. Subsequent direct arylation using Fagnou's protocol afforded the *meta* substituted calix[4]arenes **1a** and **1b** in a 1 : 1 ratio in 94% yield.[6] These diastereomers were separated after careful multiple chromatography. In the first flash column chromatography (silica gel, 95% cyclohexane–5% ethyl acetate), most of the impurities were removed, a second flash column chromatography (75% chloroform–25% cyclohexane) yielded slightly impure **1b**, a mixed fraction of **1a** and **1b** and a fraction containing pure **1a**. A final purification step using HPLC (88% cyclohexane–6% chloroform–6% diethyl ether) gave pure **1b**. The ratio of the diastereomers was gathered from the masses of the pure fractions and the ^1H NMR spectrum of the mixed fraction.

NMR studies

The two isomers isolated by column chromatography could be easily distinguished in ^1H as well as ^{13}C NMR spectroscopy. Isomer **1b** was first eluted during the purification process. It is expected

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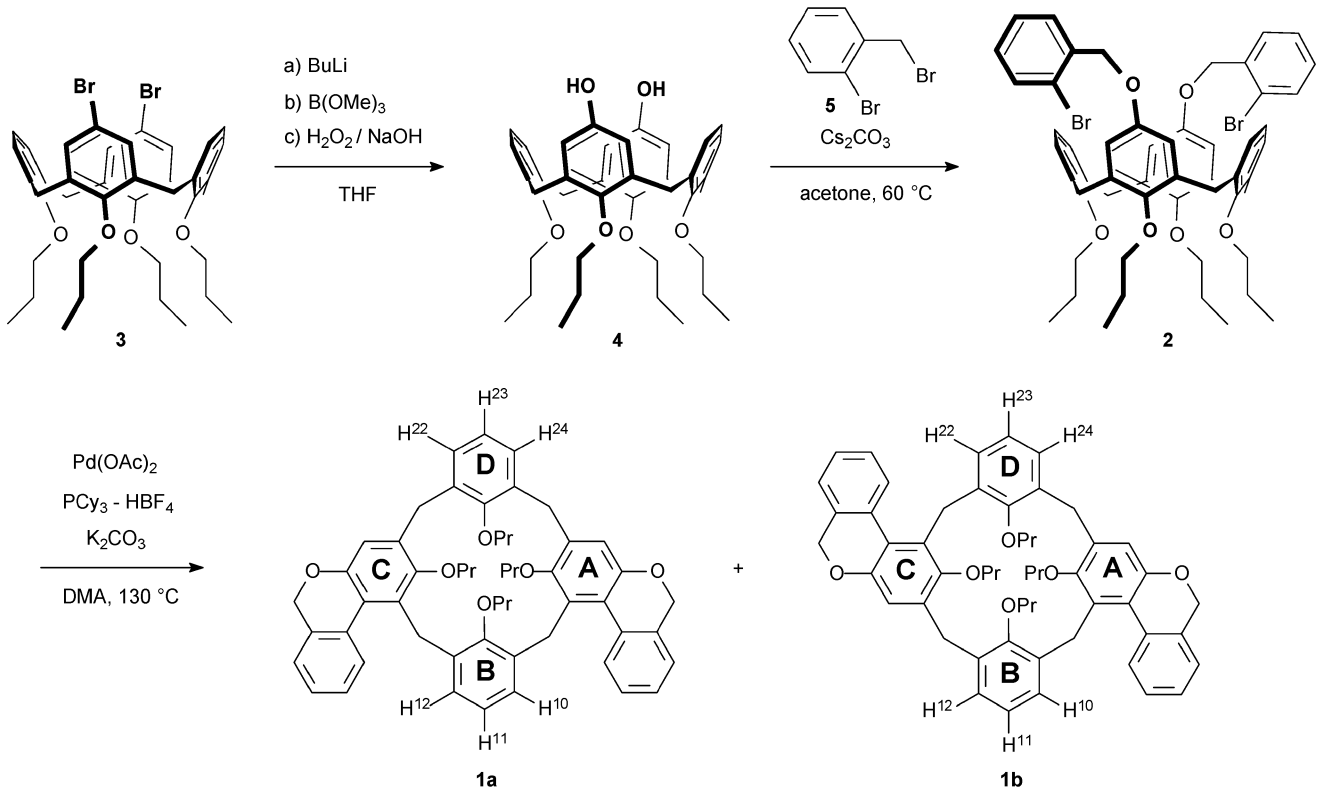


Scheme 1 Synthesis of **1a** and **1b**; indices of protons according to calixarene nomenclature are given in the experimental section.

that its C_2 symmetry generates two sets of signals for two sets of propoxy groups in a 1 : 1 ratio. In the ^{1}H NMR spectrum two well separated triplet signals at 1.17 ppm and 0.94 ppm caused by protons of the terminal methyl groups are easily recognized (Fig. 1b). In contrast the C_s symmetric isomer **1a** gives rise to three sets of signals for the three sets of propoxy groups in a 1 : 1 : 2 ratio. Again the proton signals of the terminal methyl groups at 1.15 ppm, 1.08 ppm, and 0.89 ppm can be found easily (Fig. 1a). Complete assignment of all proton and carbon signals is done on the basis of ^{1}H–^{1}H COSY, ROESY, HMQC and HMBC experiments. The assignment is facilitated by the fact that the signals of the two types of methylene bridges, close to the fused rings and at a distance from the fused rings, are different from each other. The latter ones show shifts which are common for calix[4]arenes in the *cone* conformation. In the ^{1}H NMR spectrum of each isomer, two pairs of AB doublets ($|^2J| = 13$–14 Hz) appear. In each case, one pair of doublets lies in the common region, whereas the other pair is noticeably shifted downfield with

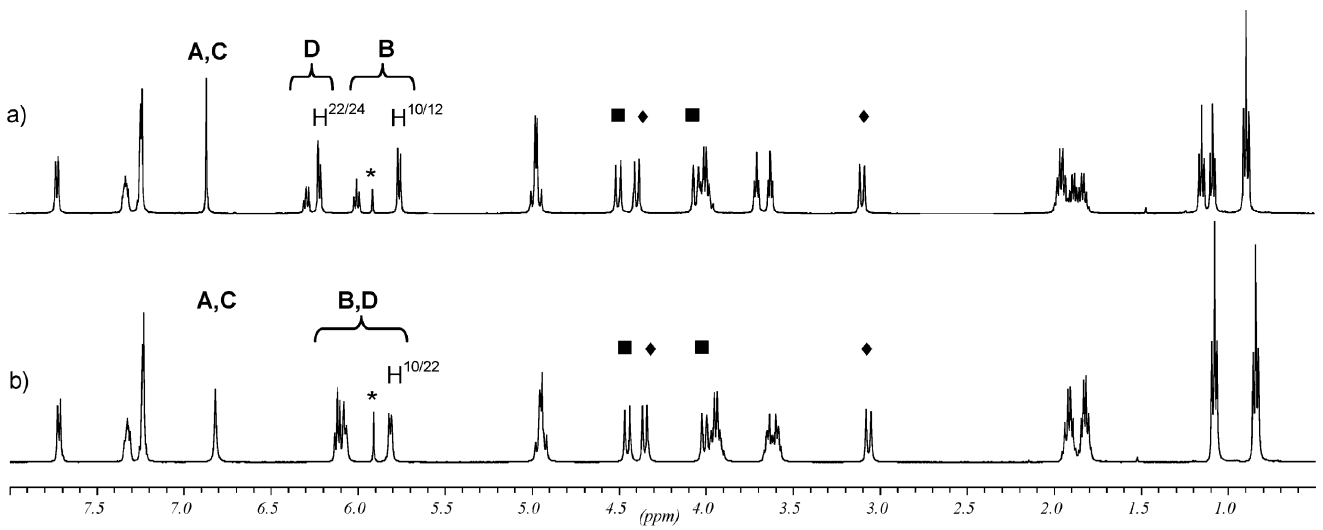


Fig. 1 ^{1}H NMR spectra of (a) **1a** in $C_2D_2Cl_4$ at 55 °C and (b) **1b** in $C_2D_2Cl_4$ at rt, residual solvent signals are marked with an asterisk, signals for the two pairs of diastereomeric protons of the methylene bridges are marked with symbols (■: close to the annealed rings, ◆: distant to the annealed rings).

an extreme shift of the doublet for the equatorial protons. This is explained by the ring current effect of the closely fused aromatics. The corresponding ^{13}C NMR signals are also shifted unusually and appear at a higher field (27.91 ppm for **1b** and 27.38 ppm for **1a**) than the signals of the bridges remote to the fused rings (31.33 ppm for **1b** and 30.88 ppm for **1a**), which again fall in the common region for calix[4]arenes adopting the *cone* conformation (Fig. 2).[10] These tentative assignments are confirmed by HMBC experiments, which show coupling between the bridging carbons and the correct *meta* protons of the phenolic rings. Further support is a NOE contact between the strongly shifted equatorial protons and the bay region proton of the fused ring in each isomer.

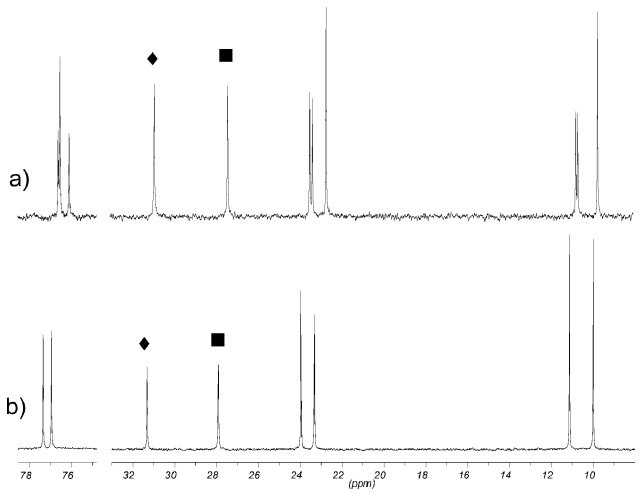


Fig. 2 Partial ^{13}C NMR spectra of (a) **1a** in $C_2D_2Cl_4$ at 55 °C and (b) **1b** in CD_2Cl_2 at rt showing the signals for the propoxy groups. The symbols ◆ and ■ indicate signals from the methylene bridge carbons distant and close to the annealed rings, respectively.

Due to the ring current effect of the fused benzene rings, the proton signals of the unfunctionalized aromatics which lie in proximity to the fused benzene rings are shifted upfield. In the case of the C_2 symmetric isomer **1b**, a highfield shifted doublet at 5.77 ppm can be assigned to the *meta* protons $H^{10/22}$ near the fused benzene rings, whereas the signals of the other *meta* protons $H^{12/24}$ overlap with resonances for the *para* protons $H^{11/23}$ at 6.20–6.15 ppm. In the C_s symmetric isomer **1a** signals for the protons of ring B, which is framed by the fused rings, emerge at higher field than the signals for the protons of ring D. The *meta* protons $H^{10/12}$ on ring B resonate at 5.76 ppm compared to 6.22 ppm for the *meta* protons $H^{22/24}$ on ring D.

^1H NMR experiments at low and high temperatures were carried out to examine the conformational dynamics of both isomers. In the range of −80 °C to room temperature, CD_2Cl_2 was used as the solvent and experiments from room temperature to 120 °C were conducted in $C_2D_2Cl_4$. Surprisingly the spectra were basically unchanged from −80 °C to 120 °C. This means that the conformation of the calix[4]arene skeleton is fixed over the whole temperature range. A possible equilibrium between two *flattened cone* conformations can be ruled out. In that case, resonances for the protons experiencing ring current effects should be shifted markedly, because the shielding and deshielding is sensitive to geometrical changes. In fact all relevant signals stayed the same. A minor change regarding the *meta* protons $H^{12/24}$ of rings B and D of the C_2 symmetric isomer **1b** should not be taken as a hint for any conformational dynamics. Their resonances at low temperature shifted by $\Delta = 0.11$ ppm slightly more downfield than the signals did on average ($\Delta = 0.05$ ppm). This led to a separation from the signals for the *para* protons $H^{11/23}$. However, a separation was also seen at room temperature when $C_2D_2Cl_4$ as solvent was applied (Fig. 3). Another example of small differences caused by the solvent are the resonances of the diastereotopic benzylic methylene protons of isomer **1a**. From −80 °C to room temperature in CD_2Cl_2 they are isochronous, from room temperature to 55 °C in $CDCl_3$ they are slightly split, whereas in $C_2D_2Cl_4$ at room temperature as well as 120 °C they are clearly divided. All minor changes observed in the experiments at low temperature could be attributed to restrictions of local degrees of freedom. The only minor change displayed in the low temperature spectra of the C_s symmetric isomer **1a** concerned the multiplet for the methylene group α to the methyl group of the propoxy chains on rings A and C. This multiplet became broader with new peaks appearing which indicates a splitting of two overlying multiplets consistent with two diastereotopic methylene protons. A similar but more pronounced change is observed in isomer **1b**. Here, both methylene groups of the propoxy chains on rings A and C were affected. The multiplets of the diastereotopic protons became completely separated at −40 °C (Fig. 4). Additionally the signals of the diastereotopic benzylic methylene protons started to split up at low temperature (Fig. 3).

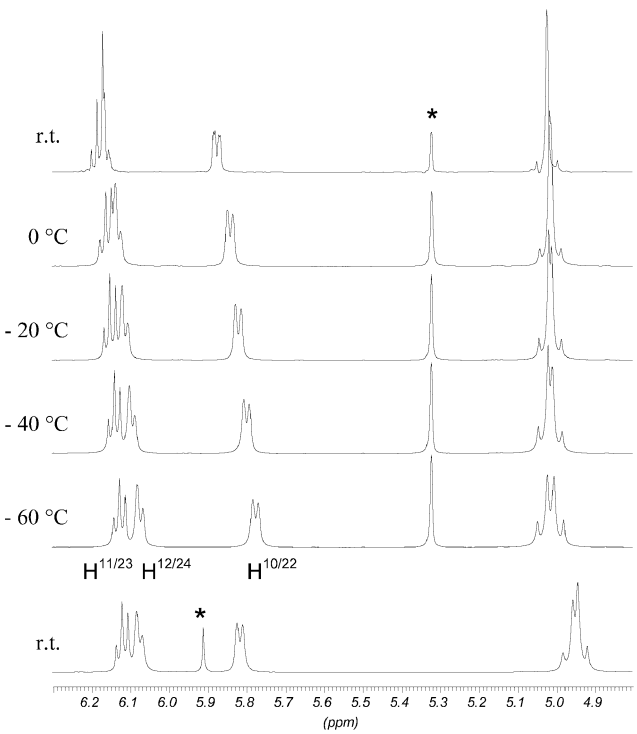


Fig. 3 Partial ^1H NMR spectra of **1b** at variable temperatures in CD_2Cl_2 (top) and at rt in $C_2D_2Cl_4$ (bottom), residual solvent signals are marked with asterisks.

X-Ray analysis

Crystals of isomers **1a** and **1b** suitable for single crystal X-ray structural analysis were grown from chloroform–ethanol and

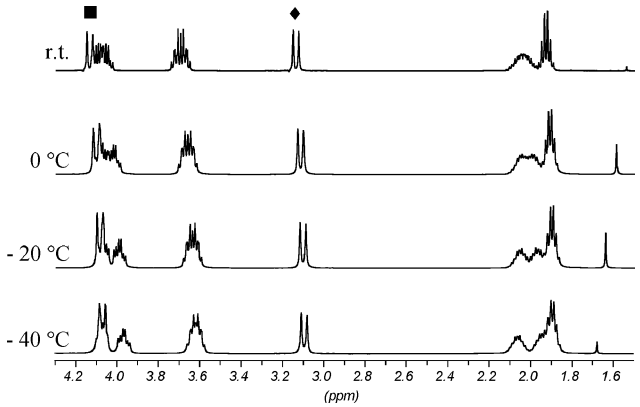


Fig. 4 Partial ^{1}H NMR spectra of **1b** at variable temperatures in CD_2Cl_2; marked signals indicate equatorial methylene bridge protons close to (■) and remote from (◆) the annealed rings.

chloroform–dichloromethane–methanol. Fig. 5 shows the molecular structures in the solid state. No solvent molecules are included. The most prominent feature of both compounds is their *flattened cone* conformation in which the unsubstituted aromatic rings B and D are bent towards each other whereas the *meta* substituted phenolic rings A and C are directed away from each other. In case of isomer **1a**, the unsubstituted ring D, which is most removed from the fused rings, is almost perpendicular to the plane defined by the four oxygen atoms of the propoxy groups (O_4 plane) with a dihedral angle of 89.2°. The unsubstituted ring B lying between the fused rings is tilted towards ring D, its dihedral angle to the O_4 plane is 76.1°. The substituent bearing phenolic rings A and C are flattened with dihedral angles of 136.1° and 151.3° to the O_4 plane. In isomer **1b**, both unsubstituted rings B and D are clearly tilted. The dihedral angles for rings A, B, C and D to the O_4 plane are 127.9°, 77.7°, 149.8° and 77.3°, respectively. The phenolic rings A and C together with their substituents can be regarded as bridged biphenyl moieties to which axial chirality can be ascribed. For isomer **1a**, the descriptor is S_a for ring A with an inter-ring torsion angle of 28.9° and R_a for ring C with an interplanar angle of 30.5°. The aromatic rings, which were attached to the calix[4]arene scaffold, are turned so that they stand steeper on the O_4 plane than the phenolic rings. As a consequence, the bay region carbon atom lies under the plane of the corresponding phenolic ring and the carbon atom of the bridging methylene group is the upmost atom of the calixarene. In contrast, the attached aromatic rings of isomer **1b** are arranged more flat to the O_4 plane than the phenolic rings. Thus, the bay region carbon atom lies above the plane of the corresponding phenolic ring and the bridging methylene group points sidewards. The descriptor of axial chirality for the enantiomer shown in Fig. 5c and d is R_a for rings A and C with inter-ring torsion angles of 23.1° and 28.0°. An important result of the geometry of both isomers **1a** and **1b** in the solid state is the fact that there is no cavity large enough to include guest molecules. This can be illustrated by the short distance between the *para* carbon atoms of the upstanding rings A and C of 4.07 Å and 4.52 Å, respectively.

Intramolecular direct arylation in a fourfold functionalized calix[4]arene

The fixed *flattened cone* conformations in **1a** and **1b** raises the question of whether a fourfold arylation would be possible or sterically hindered. Therefore, we synthesised the appropriate probe molecule **6** (Scheme 2). It was treated under the same conditions

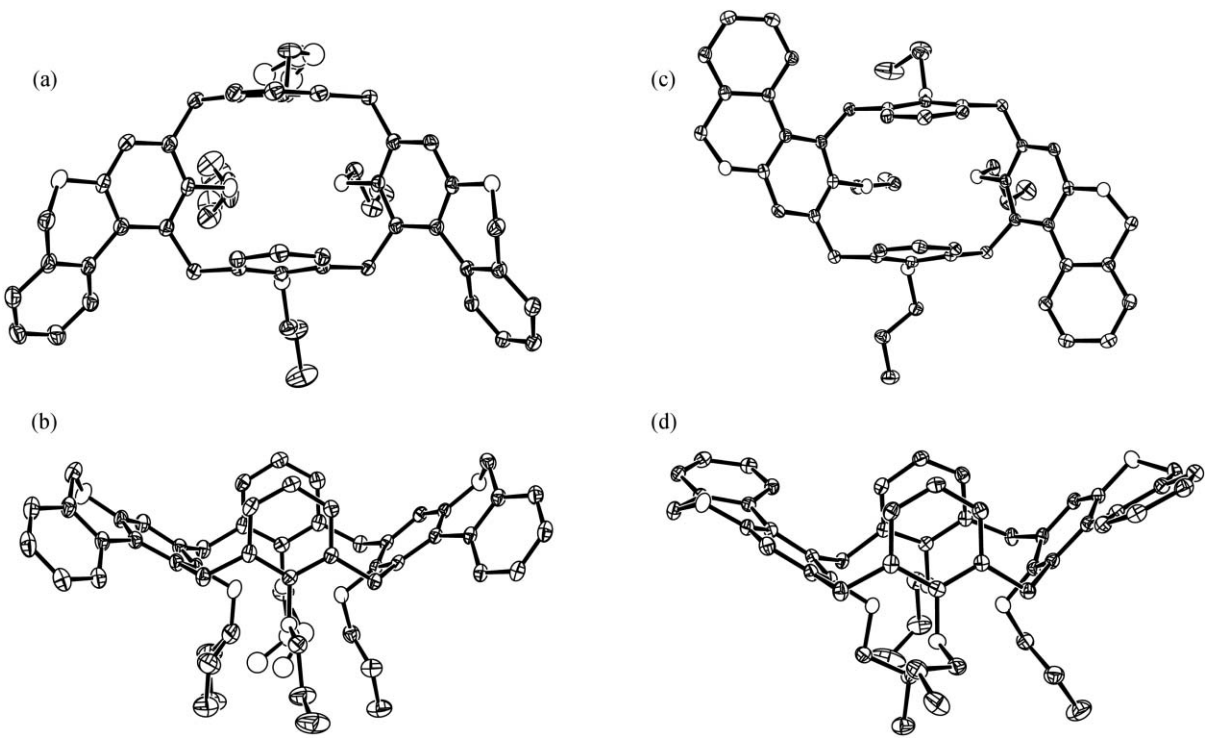
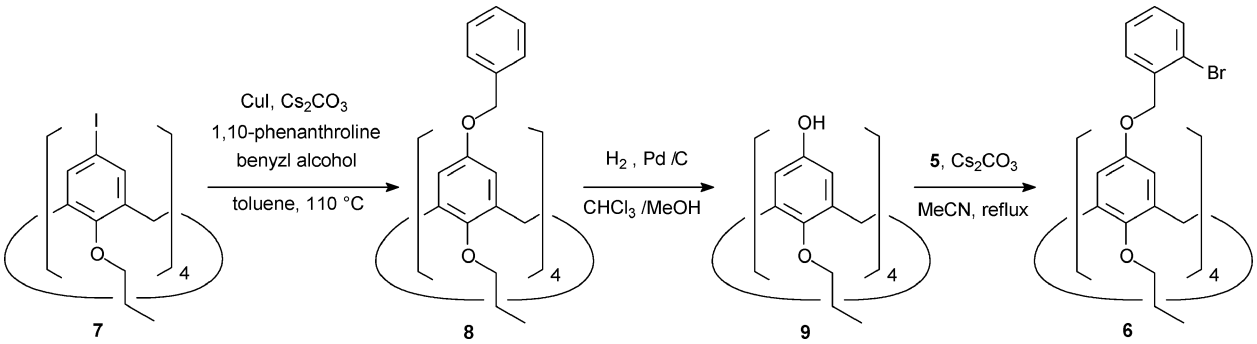


Fig. 5 ORTEP view of **1a**: (a) top view, (b) side view and **1b**: (c) top view, (d) side view. Thermal ellipsoids are drawn at the 50% probability level, disorder in two propoxy groups of **1a** is shown, hydrogen atoms are omitted for clarity.



Scheme 2 Synthesis of probe molecule **6**.

that led successfully to the doubly *meta* substituted calix[4]arenes. Synthesis began from the known tetra iodinated calix[4]arene **7**.[11] It was transformed into the benzyl protected phenol derivative **8** under recently reported conditions for Ullmann reactions.[12] The benzyl protecting groups were removed under standard conditions yielding the known tetrahydroxycalix[4]arene **9**.[13] Contrary to dihydroxycalix[4]arene **4**, the subsequent alkylation with benzyl bromide **5** was incomplete in boiling acetone and had to be carried out in boiling acetonitrile to achieve completion. Tetrabenzyl ether **6** was subjected to direct arylation. The end of this reaction was indicated, like in the case of the A,C-functionalized calix[4]arene **2**, by a colour change from yellow to gray. The crude product mixture and its TLC spots were examined by MALDI-ToF spectrometry. Masses corresponding to two, three and four times intramolecular arylation could be detected, as well as signals indicating one and two times hydrodehalogenation. Three different TLC spots include molecules with masses corresponding to fourfold intramolecular arylation. This is a hint that of the four possible isomers at least three were formed. However, none of the isomers could be isolated. Judging roughly from the HPLC trace these isomers constitute at most 5% of the product mixture.

Conclusions

We examined the direct intramolecular arylation of an A,C-functionalized calix[4]arene with respect to the regioselectivity of the reaction. Both possible isomers were formed in a 1 : 1 ratio, with an overall yield of 94%. Therefore, no regioselectivity was observed. From NMR and X-ray analysis, we conclude that both isomers are fixed in a *flattened cone* conformation. This is a hint that an expansion of the calix[4]arene cavity cannot be achieved by annealing four arene rings in the described way. Accordingly, an experiment with the ABCD-functionalized calix[4]arene led to very poor results (<5% yield). We suppose that the steric crowding which is imposed by the first fused rings is the reason for a strongly diminished reactivity in further intramolecular arylations.‡

‡ In a preliminary experiment similar to ref. 5, we conducted oxidative photocyclization under standard diluted conditions with an ABCD styryl functionalized calix[4]arene. Mass analysis of the crude product mixture indicated that the reaction took place on only two positions. This result further supports the assumption that building up rings with a phenanthrene connectivity comprising the calix[4]arene *para* and *meta* positions is strongly sterically hindered.

Experimental

General

Melting points were measured in open capillaries with a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500, chemical shifts were calibrated to the residual proton and carbon resonance of the solvent (CD_2Cl_2: $\delta_H = 5.32$ ppm, $\delta_C = 53.80$ ppm; $CDCl_3$: $\delta_H = 7.24$ ppm, $\delta_C = 77.00$ ppm; $C_2D_2Cl_4$: $\delta_H = 5.91$ ppm, $\delta_C = 73.70$ ppm). *J* values are given in Hz. MALDI-ToF mass spectra were obtained with a PerSeptive Biosystems Voyager-DE spectrometer using 2,5-dihydroxybenzoic acid as the matrix, a Bruker Esquire 3000 was used to record ESI mass spectra and exact masses were measured on a Bruker APEX III (FT-ICR). Elemental analyses were determined with a Perkin Elmer 240 instrument. X-Ray crystal structures were determined from data collected with a Nonius Kappa CCD area detector diffractometer, using graphite monochromatized Mo-Kα radiation. Analytical thin-layer chromatography was performed on silica gel 60 F254 (Merck), flash column chromatography on silica gel MN 60, 40–63 μm (Macherey-Nagel) and HPLC on a Nucleosil 100-7 silica gel column 250-20 mm (CS-Chromatographie). All reagents were reagent grade quality and used as received from commercial suppliers. Calix[4]arenes **3** and **7** were prepared according to the literature.[7,11]

5,17-Dihydroxy-25,26,27,28-tetra(1-propyloxy)calix[4]arene (4)

n-BuLi (1.6 M in hexanes, 2.00 mL, 3.20 mmol, 2.4 eq.) was added dropwise to a stirred solution of di-bromo compound **3** (1.00 g, 1.33 mmol) in THF (50 mL) under argon at −78 °C. The reaction mixture was stirred at that temperature for 20 min and then $B(OMe)_3$ (0.75 mL, 6.7 mmol, 5 eq.) was added. The mixture was allowed to warm to room temperature and stirred for 18 h. Then the reaction flask was placed in an ice-water bath and the reaction mixture was treated with an ice-cold solution of 30% H_2O_2 (2.7 mL, 26 mmol, 20 eq.) in 3 N aqueous NaOH solution (4.4 mL, 13 mmol, 10 eq.). After stirring the mixture at room temperature for 6 h, H_2O (100 mL) was added and the aqueous layer was extracted with a mixture of diethyl ether (100 mL) and dichloromethane (20 mL). The organic layer was washed with H_2O (2 × 100 mL) and brine (100 mL) and dried over $MgSO_4$. Chromatographic purification (flash column, silica gel, $CHCl_3$–3% MeOH) and drying under high vacuum afforded a colourless oil (707 mg, 1.13 mmol, 85%). Found: C, 76.34; H, 7.73. $C_{40}H_{48}O_6$

requires C, 76.89; H, 7.74%; δ_H(500 MHz, $CDCl_3$) 7.02 (4 H, d, *J* 7.5), 6.81 (2 H, t, *J* 7.5), 6.29 (2 H, s), 5.53 (4 H, s), 4.39 (4 H, d, *J* 13.2), 3.96 (4 H, t, *J* 8.2), 3.61 (4 H, t, *J* 6.6), 3.06 (4 H, d, *J* 13.2), 1.94–1.80 (8 H, m), 1.09 (6 H, t, *J* 7.4), 0.84 (6 H, t, *J* 7.5); δ_C(125 MHz, $CDCl_3$) 160.0, 149.8, 149.2, 136.7, 134.6, 128.9, 121.8, 114.2, 76.9, 76.4, 31.1, 23.4, 22.9, 10.8, 9.76; *m/z* (MALDI-ToF) 624 ($M^{\bullet+}$), 647 ($[M + Na]^+$), 663 ($[M + K]^+$); ESI-HRMS: *m/z* calc. for $C_{40}H_{52}NO_6$: 642.37891 ($[M + NH_4]^+$); found: 642.37820; for $C_{40}H_{48}NaO_6$: 647.33431 ($[M + Na]^+$); found: 647.33439.

For crystallisation the oil was dissolved in dichloromethane. Under heating, MeOH was added and dichloromethane was allowed to evaporate. After cooling, colourless small needles were collected and dried under high vacuum (217 mg, yield not optimised; according to ^{1}H NMR spectroscopy no solvent molecules included), mp 265 °C.

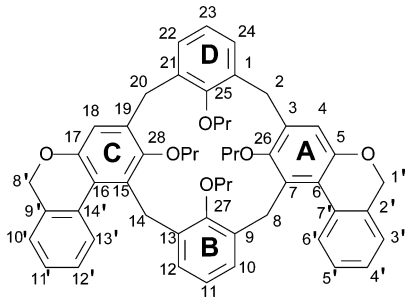
5,17-Di(2-bromo-benzyloxy)-25,26,27,28-tetra(1-propyloxy)calix[4]arene (2)

A mixture of dihydroxy-calixarene **4** (379 mg, 0.606 mmol), 2-bromobenzyl bromide (333 mg, 1.33 mmol) and caesium carbonate (433 mg, 1.33 mmol) in acetone (25 mL) was refluxed for 24 h. After cooling, the mixture was partitioned between water (100 mL) and diethyl ether (100 mL). The organic layer was washed with water (two times 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatographic purification (flash column, silica gel, 50% cyclohexane–50% chloroform) and drying under high vacuum afforded a colourless solid (378 mg, 0.393 mmol, 65%). Mp 58 °C; found: C, 67.32; H, 6.19. $C_{54}H_{58}Br_2O_6$ requires C, 67.36; H, 6.07; Br, 16.60; O, 9.97%; δ_H(500 MHz, $CDCl_3$) 7.47 (2 H, dd, *J* 1.1, 7.9), 7.38 (2 H, dd, *J* 1.2, 7.5), 7.19 (2 H, dt, *J* 1.0, 7.5), 7.06 (2 H, dt, *J* 1.7, 7.6), 6.66 (4 H, d, *J* 7.2), 6.61–6.58 (2 H, m), 6.26 (4 H, s), 4.76 (4 H, s), 4.43 (4 H, d, *J* 13.3), 3.86 (4 H, t, *J* 7.5), 3.78 (4 H, t, *J* 7.44), 3.10 (4 H, d, *J* 13.3), 1.97–1.87 (8 H, m), 1.01–0.97 (12 H, m); δ_C(125 MHz, $CDCl_3$) 156.6, 153.0, 150.9, 137.0, 135.7, 135.0, 132.2, 128.6, 128.2, 127.3, 122.1, 121.8, 114.5, 76.8, 76.7, 69.7, 31.2, 23.21, 23.19, 10.4, 10.3; *m/z* (MALDI-ToF) 983 ($[M + Na]^+$), 999 ($[M + K]^+$), 1093 ($[M + Cs]^+$).

Isomers 1a and 1b

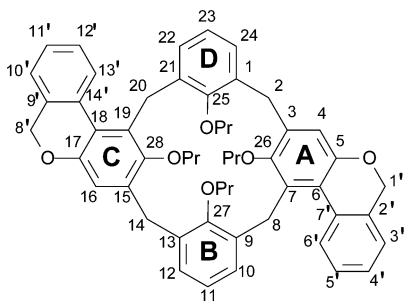
A mixture of calixarene **2** (190 mg, 0.197 mmol) and potassium carbonate (109 mg, 0.789 mmol) in *N*,*N*-dimethylacetamide (DMA, 2 mL) in a screw-cap vial equipped with a magnetic stirrer was carefully degassed and argon-saturated by two freeze-and-pump cycles. After the addition of $Pd(OAc)_2$ (4.4 mg, 0.020 mmol) and PCy_3–HBF_4 (14.5 mg, 0.0394 mmol), two more degassing cycles were carried out. The reaction mixture was heated to 130 °C for 24 h. At the end of the reaction the colour had changed from yellow to grey. After cooling to room temperature, the mixture was partitioned between water (100 mL) and diethyl ether (100 mL)–dichloromethane (20 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The first chromatographic purification (flash column, silica gel, 95% cyclohexane–5% ethyl acetate) gave a mixture of three compounds. Collection of the last band of a second chromatography (flash column, silica gel, 75% chloroform–25% cyclohexane) and drying under high vacuum afforded isomer **1a** as a colourless solid (53.2 mg), crystals suitable for single crystal X-ray structural analysis were grown from chloroform–ethanol. A mixed fraction of **1a** and **1b** was concentrated *in vacuo* and dried under high vacuum, the ratio of isomers was determined from ^{1}H NMR spectroscopy (22.5 mg **1a** and 3.0 mg **1b**). Purification of the residual material by HPLC (88% cyclohexane–6% chloroform–6% diethyl ether) and drying under high vacuum yielded isomer **1b** (70.4 mg), and crystals suitable for single crystal X-ray structural analysis were grown from chloroform–dichloromethane–methanol.

Isomer 1a (75.7 mg, 0.0944 mmol, 48%)



Mp 282 °C (decomp.); found: C, 80.68; H, 7.09. $C_{54}H_{56}O_6$ requires C, 80.97; H, 7.05%; δ_H(500 MHz, $CDCl_3$) 7.72 (2 H, d, *J* 7.5, H6′/13′), 7.38–7.34 (2 H, m, H5′/12′), 7.31–7.26 (4 H, m, H3′/10′, H4′/11′), 6.88 (2 H, s, H4/18), 6.33–6.31 (1 H, m, H23), 6.26 (2 H, d, *J* 7.5, H22/24), 6.00 (1 H, t, *J* 7.5, H11), 5.73 (2 H, d, *J* 7.5, H10/12), 5.01 (2 H, d, *J* 13.0, H1′/8′), 4.99 (2 H, d, *J* 13.0, H1′/8′), 4.53 (2 H, d, *J* 14.4, $H8_{ax.}/14_{ax.}$), 4.42 (2 H, d, *J* 13.3, $H2_{ax.}/20_{ax.}$), 4.08 (2 H, d, *J* 13.6, $H8_{eq.}/14_{eq.}$), 4.05 (4 H, m, O–CH_2 (A/C)), 3.71 (2 H, t, *J* 6.6, O–CH_2 (B)), 3.64 (2 H, t, *J* 6.6, O–CH_2 (D)), 3.14 (2 H, d, *J* 13.4, $H2_{eq.}/20_{eq.}$), 2.07–1.97 (4 H, m, CH_2 (A/C)), 1.96–1.91 (2 H, m, CH_2 (B)), 1.90–1.84 (2 H, m, CH_2 (D)), 1.19 (3 H, t, *J* 7.5, CH_3 (B)), 1.11 (3 H, t, *J* 7.5, CH_3 (D)), 0.91 (6 H, t, *J* 7.5, CH_3 (A/C)); δ_C(125 MHz, $C_2D_2Cl_4$, 55 °C) 155.0 (C27), 154.9 (C25), 154.3 (C26/28), 150.6 (C5/17), 137.7 (C3/19), 134.3 (C7/15), 133.6 (C9/13, C2′/9′), 132.3 (C1/21), 130.8 (C7′/14′), 127.8 (C5′/12′), 127.1 (C22/24), 126.4 (C4′/11′), 126.3 (C10/12, C6′/13′), 124.9 (C3′/10′), 122.7 (C6/16), 122.4 (C11), 122.2 (C23), 116.5 (C4/18), 76.6 (O–CH_2 (D)), 76.5 (O–CH_2 (A/C)), 76.1 (O–CH_2 (B)), 69.3 (C1′/8′), 30.9 (C2/20), 27.4 (C8/14), 23.5 (CH_2 (B)), 23.3 (CH_2 (D)), 22.7 (CH_2 (A/C)), 10.8 (CH_3 (B)), 10.7 (CH_3 (D)), 9.7 (CH_3 (A/C)); *m/z* (ESI, $CHCl_3$–MeOH) 801.4 ($[M + H]^+$).

Isomer 1b (73.4 mg, 0.0916 mmol, 46%)



Mp 282 °C (decomp.); found: C, 80.86; H, 7.13. $C_{54}H_{56}O_6$ requires C, 80.97; H, 7.05%; δ_H(500 MHz, CD_2Cl_2) 7.77 (2 H, d, *J* 7.8,

H6′/13′), 7.42–7.37 (2 H, m, H5′/12′), 7.31–7.30 (4H, m, H3′/10′, H4′/11′), 6.88 (2 H, s, H4/16), 6.20–6.15 (4 H, m. H11/23, H12/24), 5.87 (2 H, dd, *J* 2.2, 6.9, H10/22), 5.036 (2 H, d, *J* 12.7, H1′/8′), 5.020 (2 H, d, *J* 12.7, H1′/8′), 4.55 (2 H, d, *J* 14.1, $H8_{ax.}/20_{ax.}$), 4.45 (2 H, d, *J* 13.5, $H2_{ax.}/14_{ax.}$), 4.14 (2 H, d, *J* 14.3, $H8_{eq.}/20_{eq.}$), 4.13–4.03 (4 H, m, O–CH_2 (A/C)), 3.74–3.65 (4 H, m, O–CH_2 (B/D)), 3.14 (2 H, d, *J* 13.6, $H2_{eq.}/14_{eq.}$), 2.12–1.98 (4 H, m, CH_2 (A/C)), 1.97–1.90 (4 H, m, CH_2 (B/D)), 1.17 (6 H, t, *J* 7.4, CH_3 (B/D)), 0.94 (6 H, t, *J* 7.5, CH_3 (A/C)); δ_C(125 MHz, $C_2D_2Cl_4$) 155.5 (C25/27), 155.1 (C26/28), 151.3 (C5/17), 138.3 (C3/15), 134.9 (C7/19), 134.33 (C9/21), 134.28 (C2′/9′), 132.9 (C1/13), 131.4 (C7′/14′), 128.2 (C5′/12′), 127.2 (C12/24), 127.0 (C10/22, C4′/11′), 126.9 (C6′/13′), 125.3 (C3′/10′), 123.3 (C6/18), 122.8 (C11/23), 117.0 (C4/16), 77.4 (O–*C*H_2 (A/C)), 77.0 (O–*C*H_2 (B/D)), 69.8 (C1′/8′), 31.3 (C2/14), 27.9 (C8/20), 24.0 (*C*H_2 (B/D)), 23.3 (*C*H_2 (A/C)), 11.1 (*C*H_3 (B/D)), 10.0 (*C*H_3 (A/C)); *m/z* (ESI, $CHCl_3$–MeOH) 801.4 ([M + H]$^+$).

5,11,17,23-Tetrabenzyloxy-25,26,27,28-tetra(1-propyloxy)calix[4]arene (8)

Tetraiodocalix[4]arene **7** (547 mg, 0.500 mmol) was combined with copper(I) iodide (38 mg, 0.20 mmol), 1,10-phenanthroline (76 mg, 0.42 mmol), caesium carbonate (1.30 g, 4.00 mmol), benzyl alcohol (4.33 g, 40.0 mmol) and toluene (4.1 mL). The reaction tube was sealed and the mixture was stirred at 110 °C for 48 h. The resulting suspension was cooled to room temperature and filtered through a pad of silica gel, eluting with diethyl ether. The filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (silica gel, 95–90% cyclohexane, 5–10% ethyl acetate) and subsequent trituration with dichloromethane–methanol provided a colourless solid (173 mg, 0.170 mmol, 34%). Mp 151 °C; found: C, 80.22; H, 7.25; $C_{68}H_{72}O_8$ requires C, 80.28; H, 7.13%; δ_H(500 MHz, $CDCl_3$) 7.33–7.27 (16 H, m), 7.24–7.21 (4 H, m), 6.30 (8 H, s), 4.74 (8 H, s), 4.41 (4 H, d, *J* 13.2), 3.77 (8 H, t, *J* 7.5), 3.03 (4 H, d, *J* 13.2), 1.94–1.87 (8 H, m), 0.97 (12 H, t, *J* 7.5); δ_C(125 MHz, $CDCl_3$) 153.5, 150.8, 137.8, 135.6, 128.4, 127.6, 127.3, 114.2, 76.8, 70.2, 31.4, 23.1, 10.3; *m/z* (ESI, $CHCl_3$–MeOH) 1017.4 ([M + H]$^+$).

5,11,17,23-Tetra(2-bromo-benzyloxy)-25,26,27,28-tetra(1-propyloxy)calix[4]arene (6)

A solution of calix[4]arene **8** (171 mg, 0.168 mmol) in $CHCl_3$–MeOH (1 : 1, 50 mL) was subjected to hydrogenolysis over 10% palladium (134 mg) on activated carbon and under a high pressure of H_2 (2 bar) for 20 h. The mixture was filtered over celite, the solid was washed with $CHCl_3$–MeOH (1 : 1) and the combined filtrate was concentrated under reduced pressure to afford 5,11,17,23-tetrahydroxy-25,26,27,28-tetra(1-propyloxy)calix[4]arene **9** which was used in the following step without further purification. A mixture of crude tetrahydroxycalix[4]arene **9**, 2-bromobenzyl bromide (253 mg, 1.01 mmol) and caesium carbonate (331 mg, 1.01 mmol) in acetonitrile (25 mL) was refluxed for 24 h. After cooling, the mixture was partitioned between water (100 mL) and diethyl ether (100 mL). The organic layer was washed with water (two times 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 95% cyclohexane–5% ethyl acetate), HPLC (80% chloroform–20% cyclohexane) and drying under high vacuum afforded a colourless oil (138 mg, 0.103 mmol, 61% over two steps). Found: C, 61.27; H, 5.25; $C_{68}H_{68}Br_4O_8$ requires C, 61.28; H, 5.14%; δ_H(500 MHz, $CDCl_3$) 7.45 (4 H, dd, *J* 1.3, 8.0), 7.42 (4 H, dd, *J* 1.5, 7.6), 7.21 (4 H, dt, *J* 1.3, 7.5), 7.04 (4 H, dt, *J* 1.8, 7.7), 6.32 (8 H, s), 4.77 (8 H, s), 4.41 (4 H, d, *J* 13.2), 3.77 (8 H, t, *J* 7.2), 3.05 (4 H, d, *J* 13.2), 1.94–1.87 (8 H, m), 0.97 (12 H, t, *J* 7.5); δ_C(125 MHz, $CDCl_3$) 153.2, 150.9, 137.0, 135.6, 132.2, 128.6, 128.5, 127.3, 121.7, 114.3, 76.9, 69.7, 31.4, 23.2, 10.3; *m/z* (ESI, $CHCl_3$–MeOH) 1333 [M + H]$^+$.

Direct intramolecular arylation of 6

A mixture of calixarene **6** (138 mg, 0.104 mmol) and potassium carbonate (115 mg, 0.828 mmol) in *N*,*N*-dimethylacetamide (DMA, 2.8 mL) in a screw-cap vial equipped with a magnetic stirrer was carefully degassed and argon-saturated by two freeze-and-pump cycles. After the addition of $Pd(OAc)_2$ (4.7 mg, 0.021 mmol) and PCy_3–HBF_4 (15.3 mg, 0.0414 mmol), two more degassing cycles were carried out. The reaction mixture was heated to 130 °C. After 24 h, its colour had changed from yellow to brown and after a further 12 h to black. Subsequently it was cooled to room temperature and the mixture was partitioned between water (100 mL) and diethyl ether (100 mL)–dichloromethane (20 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Crystal structure determination§

Crystal data for 1a. $C_{54}H_{56}O_6$, $M = 800.99$, monoclinic, $a = 17.3668(7)$, $b = 11.4423(3)$, $c = 23.2936(9)$ Å, $\beta = 108.9726(17)°$, $V = 4377.3(3)$ Å^3, $T = 100$ K, space group $P2_1/c$, $Z = 4$, μ(Mo-Kα) = 0.078 mm^{-1}, 41 011 reflections measured, 9820 unique ($R_{int} = 0.056$) which were used in all calculations. The final w$R(F^2)$ was 0.1447 (all data). CCDC 657956.

Crystal data for 1b. $C_{54}H_{56}O_6$, $M = 800.99$, triclinic, $a = 11.5936(2)$, $b = 11.6506(3)$, $c = 17.2247(3)$ Å, $\alpha = 73.0552(11)$, $\beta = 75.3562(13)$ $\gamma = 77.6072(12)°$, $V = 2128.35(8)$ Å^3, $T = 100$ K, space group $P\bar{1}$, $Z = 2$, μ(Mo-Kα) = 0.080 mm^{-1}, 59 242 reflections measured, 12 396 unique ($R_{int} = 0.068$) which were used in all calculations. The final w$R(F^2)$ was 0.1271 (all data). CCDC 657957.

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§ CCDC 657956 and 657957. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b713357j

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