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Toward Nanoamphiphiles: Efficient Synthesis of Desymmetrized Polyphenylene Dendrimers

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A new synthetic approach for the desymmetrization of polyphenylene dendrimers (PPDs) is described. Tetrakis(4-ethynylphenyl)methane undergoes facile Diels−Alder cycloaddition with substoichiometric quantities of tetraphenylcyclopentadienones bearing one polar functional group. A single ethynyl group is thereby converted to a rigid, selectively functionalized polyphenylene moiety, which serves as a focal point for further transformations or interfacial anchoring. This is the key feature for the design of desymmetrized monodisperse macromolecules with a spherical shape. The remaining unreacted ethynyl groups provide a trifold core for the stepwise elaboration of first- and second-generation polyphenylene dendrons, which may, in turn, bear specific numbers of different peripheral functional groups at their terminae. Moreover, the resulting macromolecules exhibit the characteristic shape-persistence and monodispersity of PPDs. This approach is an important achievement in nanosciences, especially for tailoring new nanoamphiphiles. It is also of synthetic importance, as it enables the separation of two regioisomeric polyphenylene dendrimers for the first time.

Introduction

Development of new functional materials is an area of current interest.[1] There are already many reported examples of peripherally functionalized latices[2] and semiconductor particles[3,4] but control over the number of surface functionalities is not typically achieved. However, for many applications, e.g. biosensors, diagnosis, or drug-delivery, monodispersity and strictly defined structure are critical requirements. Moreover, the placement of different moieties in a specific environment is often desired. For these purposes dendrimers offer a convenient solution, because they combine efficient fabrication of nanosized objects with exact control of surface functionalization on a molecular level.[5−7]

Three-dimensional polyphenylene dendrimers (PPDs) are shape-persistent, spherical molecules,[8] whose structural properties allow spatial definition and topological isolation of functional groups in the center, in the dendritic scaffold, and at the periphery. These features are important for a large number of applications such as surface functionalization,[9] gene transfection,[10] diagnosis,[11] and supramolecular assembly. PPDs are also essentially monodisperse, an important prerequisite for their application as organic templates.[12−14]

Constitutional desymmetrization of polyphenylene dendrimers is of great importance for tailoring the functional properties of these molecules[15,16] but so far only a few examples for the spatial separation of different functional groups are reported.[17] The basic idea of this work is to introduce a single functional group on the periphery that differs from the other surface groups. The resulting compound will possess two different segments, e.g. one for binding a substrate, the others for sensing or further transformations. A desymmetrized dendrimer could thereby be attached to a cell membrane, an electrode, a

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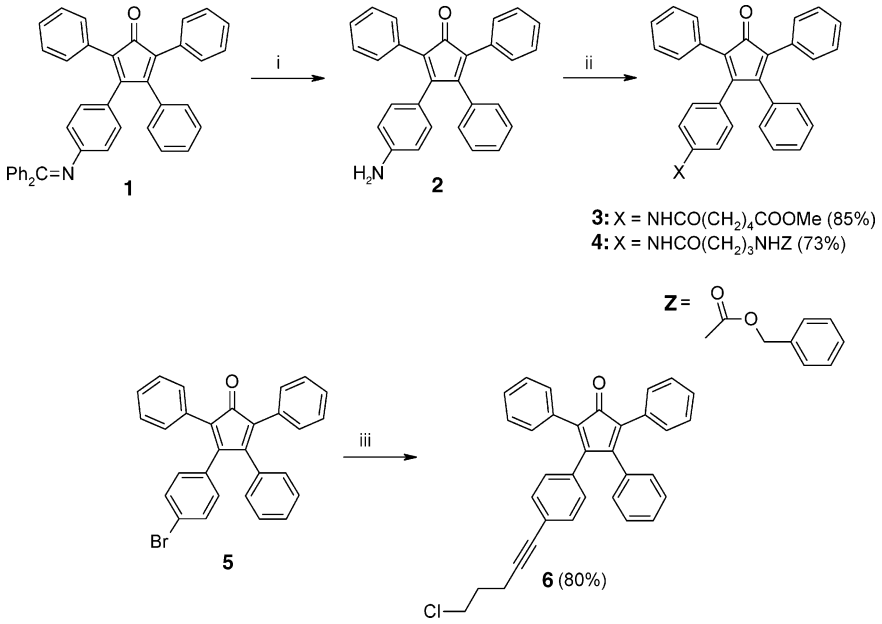
SCHEME 1. Synthesis of Monofunctionalized Tetraphenylcyclopentadienones[a]



[a] Reagents and conditions: (i) HCl, 25 °C, THF; (ii) for **3**—hexanedioic acid monomethyl ester EDC, DMAP, DMF, rt; for **4**—4-benzyloxycarbonylaminobutyric acid, *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, DMAP, DMF, rt; (iii) 5-chloropentyne, bis(triphenylphosphine)palladium(II) dichloride, CuI, triethylamine, 80 °C.

photoactive or solubilizing moiety, or a solid support by using the unique functional group, while the other groups are arranged in a shape-defined manner toward other chemical or physical targets.

The only known route to desymmetrized PPDs proceeds via several protection and deprotection steps of the ethynyl groups of tetrakis(4-ethynylphenyl)methane and subsequent stepwise Diels–Alder cycloaddition and has the disadvantages of low yields and laborious purification.[18] We now show that the preparation of desymmetrized PPDs from the symmetric tetrakis(4-ethynylphenyl)-methane core with substoichiometric amounts of functionalized cyclopentadienones circumvents these problems. This method allows the preparation of dendrimers possessing two types of functionalities in only two steps. Our strategy is particularly applicable to the design of functional nanoparticles possessing a single anchor group. One goal in this context is the design of a new class of precisely tailored nanoamphiphiles. Furthermore, the shape-persistence of PPDs ensures a topological isolation of the functionalities on the periphery, demonstrated here by the unprecedented separation of two regioisomeric PPDs.

Results and Discussion

Synthesis of Functionalized Tetraphenylcyclopentadienones. The synthesis of monofunctional core molecules begins with the preparation of the corresponding monofunctionalized tetraphenylcyclopentadienones (Scheme 1). The preparation of tetracyclones bearing pendant carboxyl or amino groups as in **3** and **4** was described separately.[19] The chloropentynyl-functionalized cyclopentadienone **6** was synthesized via a Hagihara coupling of the monobrominated precursor **5** with 5-chloro-1-pentyne in 80% yield.

Desymmetrization of the Tetrakis(4-ethynylphenyl)methane Core. A statistical Diels–Alder cycloaddition of the symmetric core **7** with the monosubstituted tetraphenylcyclopentadienone **3** (Scheme 2) resulted in a mixture of mono-, di-, tri-, and tetradendronized core molecules (**8**–**11**).

By controlling the amount of the added tetracyclone, the mixture was selectively enriched with the most desired component. For example, using 0.75 mol of **3** per mol of **7** gave 55% of **8**, 35% of **9**, and negligible quantities of **10** and **11**; unreacted **7** (30%) was also recovered. The reaction proceeded up to the complete consumption of **3**, which was conveniently verified by the complete bleaching of the characteristic red color of the tetracyclone.

We extended this synthetic approach to the protected amino-functionalized cyclopentadienone **4** and the chloro-functionalized cyclopentadienone **6** to obtain the desymmetrized core molecules **8**, **12**, and **13** in isolated yields of 50–55% (Scheme 3). The polar moieties led in all cases to facile product separation of the different products of the Diels–Alder reaction by column chromatography. These core molecules show broad versatility as they exhibit different routinely used anchor groups. The

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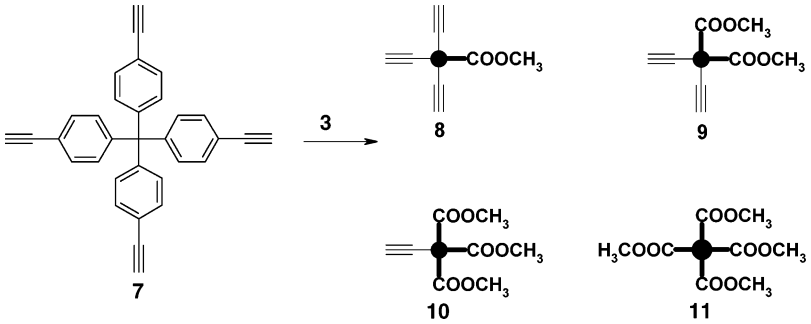
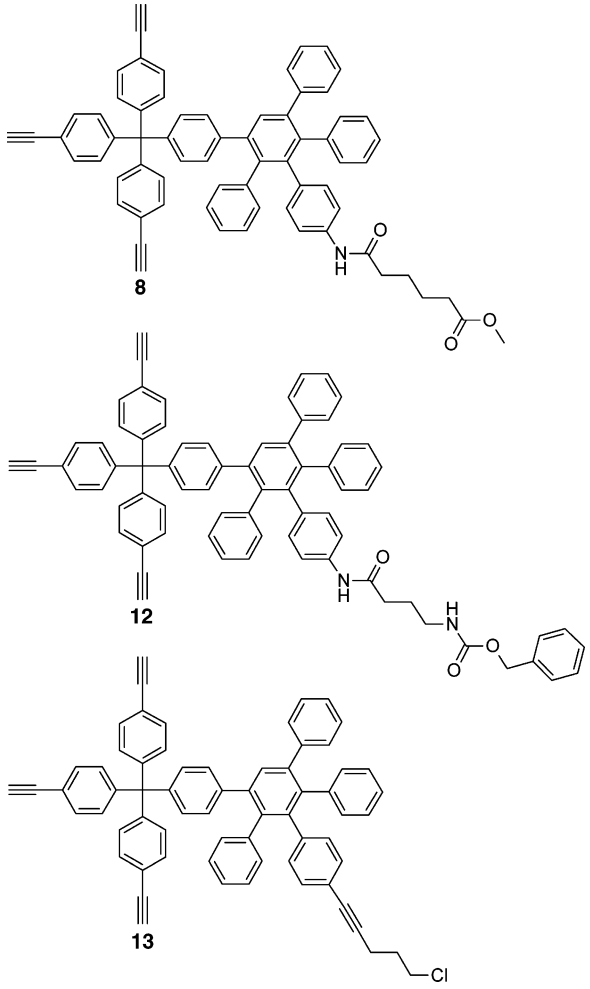
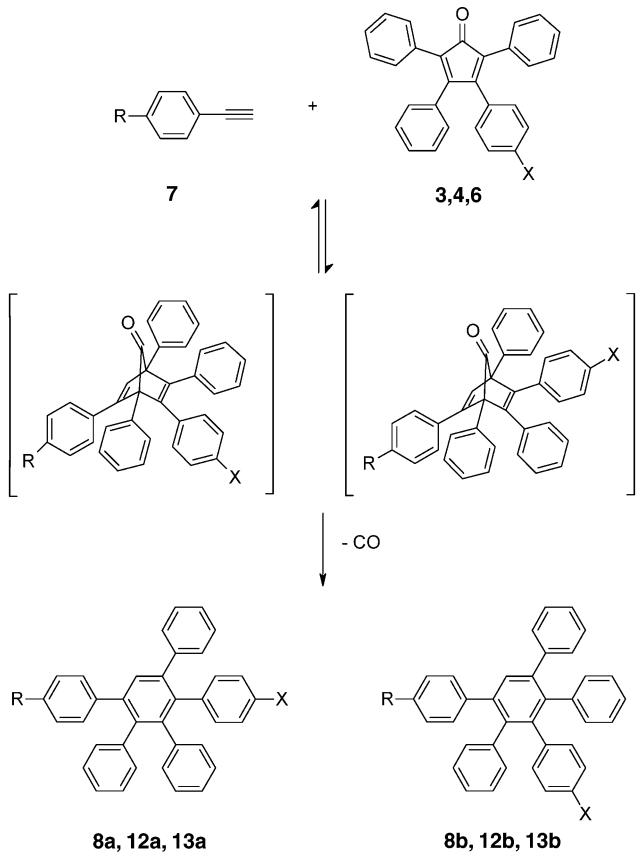
SCHEME 2. Desymmetrization of Tetrakis(4-ethynylphenyl)methane Core



SCHEME 3. Desymmetrized Core Molecules



SCHEME 4. Formation of Regioisomers during Diels–Alder Reaction of 7 with Monofunctionalized Cyclopentadienones



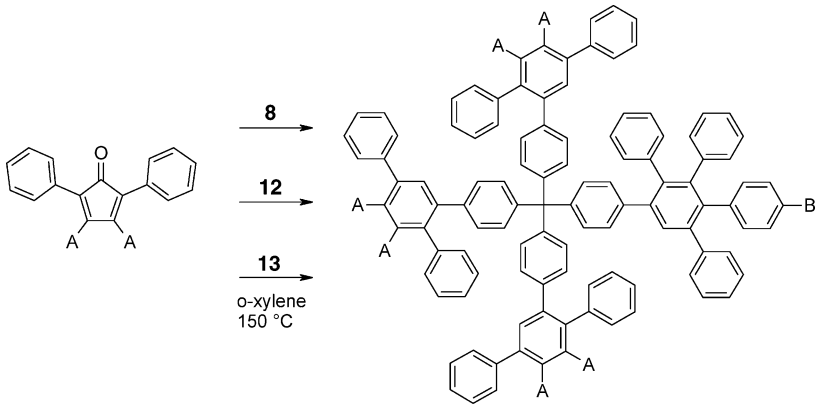
desymmetrization approach contains only one reaction step, including a straightforward purification, so there are no limits for up scaling.

As a result of the [4+2] cycloaddition mechanism in the Diels–Alder reaction (Scheme 4), compounds **8**, **12**, and **13** generally are found as pairs of regioisomers. Therefore, a slight splitting of ^{1}H NMR resonances is observed for the polar side chains. However, a separation of reaction products **a** and **b** at this stage is not possible due to their similar physical and chemical properties. We therefore used the mixture of isomers in all further synthetic steps. For clarity, only one of the possible isomers of the desymmetrized molecules is depicted hereafter, even though we will show below an example of the successful separation of the two isomers after growth of a first-generation dendrimer.

Desymmetrized PPDs. With the monofunctionalized core molecules **8**, **12**, and **13** in hand, we next synthesized several desymmetrized first-generation polyphenylene dendrimers bearing well-defined numbers of different groups on the other three dendrons (Scheme 5). The substituents in the **A** and **B** moieties represent both electrophilic and nucleophilic functions and were selected to maximize versatility of subsequent synthetic transformations, including the attachment of functionalized PPDs to surfaces or solubilizing moieties. This opens the way for the design of a new class of nanosized amphiphilic molecules, where a single polymer chain is attached to a desymmetrized dendrimer.

Satisfactory purification of the PPDs is usually achieved by precipitation in hexane or methanol, for the well-

SCHEME 5. Synthesis of First-Generation Desymmetrized Polyphenylene Dendrimers



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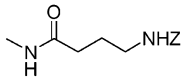
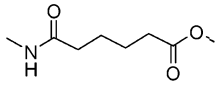
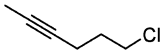
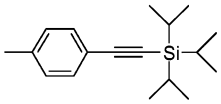
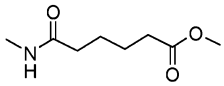
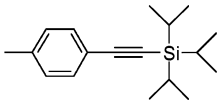
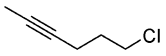
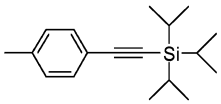
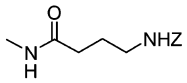
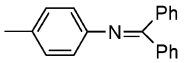
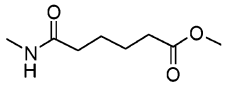
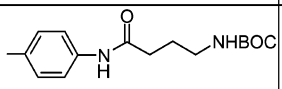
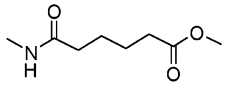
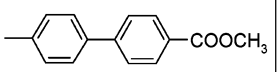
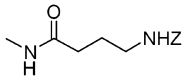
14	20			78
15	21			75
15	22			41
16	23			90
16	24			23
16	25			92
17	26			72
18	27			86
19	28			67

CP = Tetraphenylcyclopentadienone

PPD = Polyphenylene dendrimer

soluble tri(isopropyl)silylethynyl-substituted compounds **23** and **25**, and for the chloro-functionalized PPDs **22** and **24** purification by flash chromatography is required. In the latter case the yield after purification is lower than that for all other compounds, which may be explained with irreversible adsorption onto the column. All other compounds are obtained in good yields of 67−92%. The new polyphenylene dendrimers were analyzed by means of ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF-spectrometry.

Applying the branching cyclopentadienone **16** in Diels−Alder reactions with the desymmetrized core molecules **8**, **12**, and **13** resulted in the first-generation PPDs **23**, **24**, and **25**, respectively.

With use of a divergent synthetic approach, the deprotection of the ethynyl groups (Scheme 6) followed by a

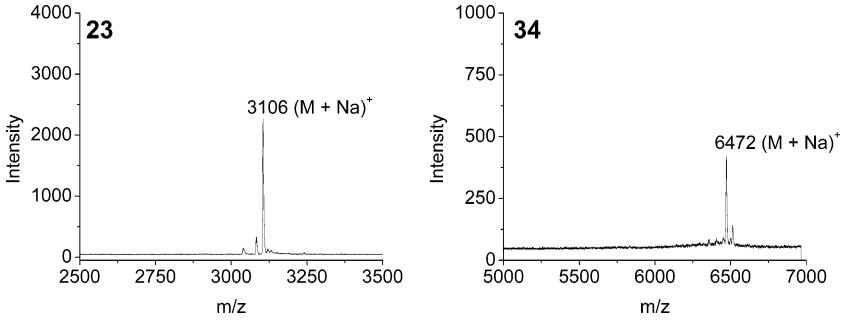
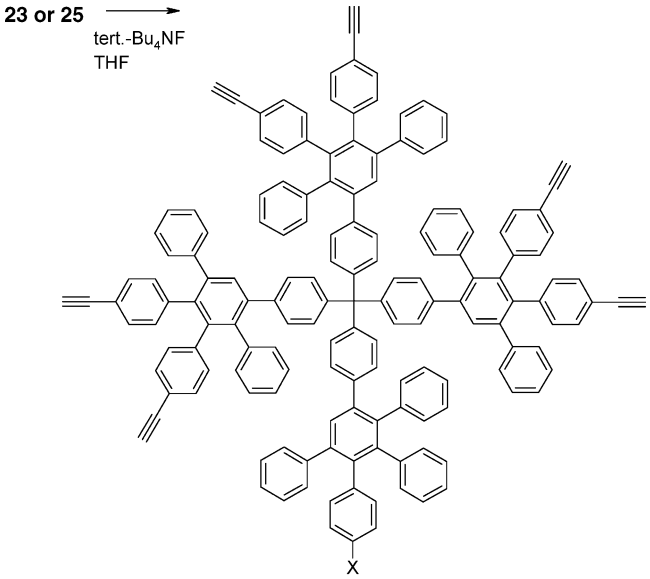


FIGURE 1. MALDI-TOF spectra of **23** and **34**.

SCHEME 6. Deprotection of Ethynyl-Functionalized Desymmetrized Polyphenylene Dendrimers



Diels–Alder cycloaddition with prefunctionalized tetraphenylcyclopentadienones afforded second-generation dendrimers **32**, **33**, **34**, and **35** (Scheme 7).

Compounds **33**–**35** are conveniently obtained in high purity and yield after precipitation in methanol. For pyridyl-functionalized compounds **20** and **32**, reverse-phase HPLC purification was applied, which gave very good separation results. Like the first-generation dendrimers, the second-generation dendrimers were analyzed by means of ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF spectrometry. Figure 1 shows examples for MALDI-TOF spectra of first- and second-generation PPDs. The characteristic monodispersity together with the controlled surface functionalization make these compounds ideal precursors for tailor-made nanoobjects. These attributes are so far unprecedented since functionalized nanosized objects are generally based on dendrimers[20–22] and polymers[2–4] where surface functionalization is under statistical control.

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Separation of Regioisomeric Polyphenylene Dendrimers. As mentioned above, Diels–Alder cycloaddition of monosubstituted tetraphenylcyclopentadienone **3** with an ethynyl group of the core molecule **7** results in two unseparable isomeric reaction products with nearly identical physical and chemical properties (**8a** and 8**b**). However, further growth of the polyphenylene dendrimer leads to localization of the polar ester groups in substantially different surroundings. For example, in the ^{1}H NMR spectrum of **23** the protons of the methoxy group appear as two separate singlets at 3.62 and 3.61 ppm (Figure 2).

Also the polarities of the regioisomers differ, which is evidenced by analytical TLC (R_f 0.66 and 0.73) and ready flash chromatographic separation. This effect is small but important, as it proves that the shape-persistence of the dendritic scaffold *ensures and maintains* the distance between the different functional groups. The possibility of conformational isomerism is ruled out by temperature-dependent ^{1}H NMR studies. Even at temperatures of 403 K the two methoxy resonances do not coalesce.

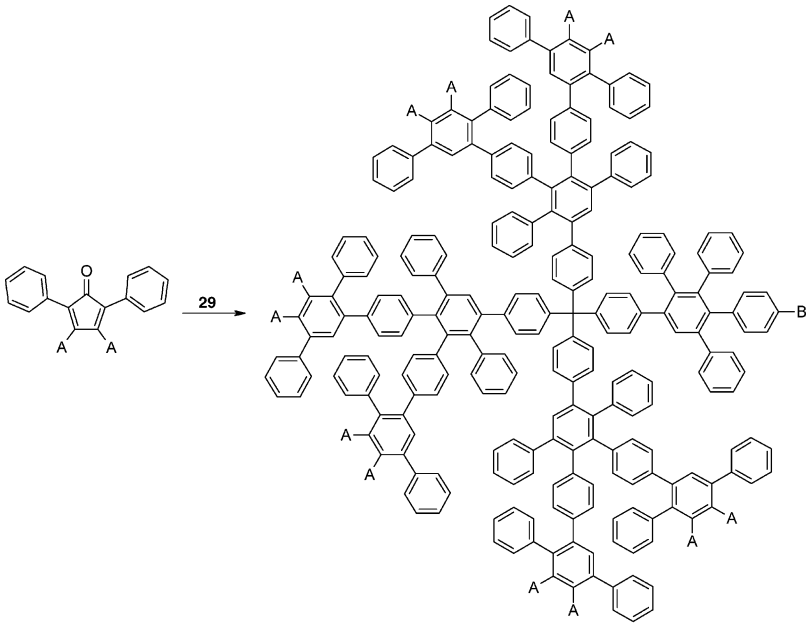
The molecular geometries of the two regioisomers were modeled by using the MM2 (MM+) force field as implemented in HyperChem 6.0 (Hypercube Inc.) (Figure 3). FD and MALDI-TOF mass spectrometry confirmed the identical molecular weight of the isomers. The isomer with lower retention volume in flash chromatography revealed a peak at higher field (3.61 ppm) in ^{1}H NMR spectra (in $C_2D_2Cl_4$). Clearly the ester group of the first eluted isomer is more effectively screened by the proximate functionalities than the ester group of the other. One can hypothesize that compound **23a** (Figure 3) should be assigned to the isomer with lower retention volume.

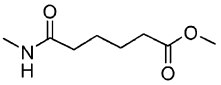
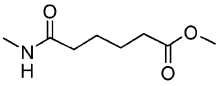
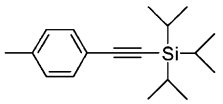
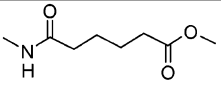
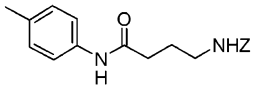
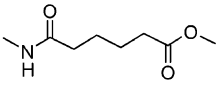
In the case of compound **23** we succeeded for the first time in separating the two regioisomers formed in a Diels–Alder reaction with a monofunctionalized cyclopentadienone. This separation was only possible because the defined spatial structure of the dendrimer leads to substantial differences of their physical properties, further evidence of the shape-persistence of the dendritic PPD structure.

Conclusions

Several first- and second-generation PPDs, each possessing one anchor group and a defined number of surface functionalities, were synthesized by a selective core desymmetrization followed by divergent dendrimer growth. This approach is a convenient, general, and controllable synthetic route to monodisperse macromolecules exhibit-

SCHEME 7. Synthesis of Second-Generation Desymmetrized Polyphenylene Dendrimers



CP	PPD	A (12x)	B(1x)	Yield (%)
14	32			75
15	33			72
16	34			83
31	35			70

CP = Tetraphenylcyclopentadienone

PPD = Polyphenylene dendrimer

ing both a defined number and a determined spatial arrangement of different functionalities. In this regard also the first separation of regioisomeric polyphenylene dendrimers is an important technical achievement made possible by the shape-persistence of the PPD structure.

The single anchor group and the functional groups implemented at the periphery of the desymmetrized PPDs provide opportunities for further applications. In the preparation of nanoamphiphiles,[23] the single functional group in **20**, **21**, **22**, and **28** could serve as the junction point for a polymeric moiety, yielding a well-defined arrangement of a shape-persistent dendrimer headgroup and a polymeric tail. Compounds such as **26** and **27**, which possess an anchor carboxyl group and six amino groups distributed on the periphery, can be readily fixed to a solid support for further solid-phase functionalization or labeled with a chromophore, still offering a defined number of reactive centers for further transformation. These avenues are under exploration in our laboratories.

Experimental Section

Compounds **1**,[9] **2**,[9] **3**,[19] **4**,[19] **5**,[15] **7**,[18] **14**,[24] **16**,[14] **17**,[19] **18**,[19] **19**,[25] and **31**[19] were synthesized according to published procedures.

Compound 6. A solution of 3-(4-bromophenyl)-2,4,5-triphenylcyclopentadienone (**5**) (0.500 g, 1.08 mmol), bis(triphenylphosphine)palladium dichloride (0.117 g 0.17 mmol), triphenylphosphine (0.028 g, 0.11 mmol), and copper(I) iodide (0.020 mg, 0.11 mmol) in triethylamine (20 mL) was heated to 80 °C under argon atmosphere. Then 5-chloro-1-pentyne (0.13 mL, 1.2 mmol) was added dropwise by syringe to the hot solution. After the solution was stirred for 3 h at 80 °C and cooled to room temperature, water (40 mL) and 2 N hydrochloric acid (20 mL) were added. The product was extracted

(23) Velonia, K.; Rowan, A. E.; Nolte, R. J. M. *J. Am Chem. Soc.* **2002**, *124*, 4224−4225.

(24) Arackal, Th. J.; Eistert, B. *Chem. Ber.* **1975**, *108*, 2660−2663.

(25) Weil, T. Ph.D. Thesis, 2002, University of Mainz, Germany.

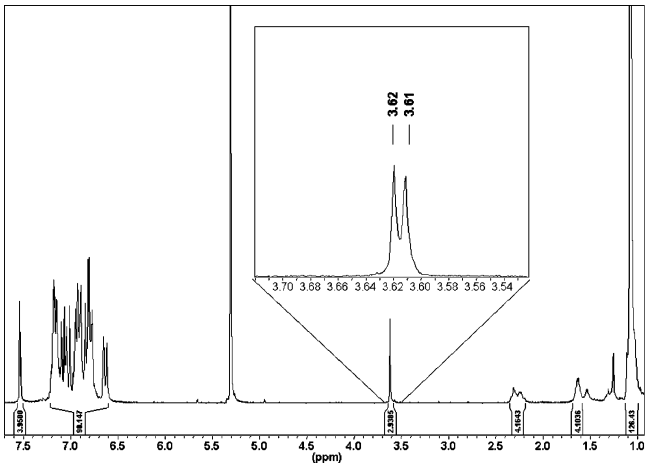


FIGURE 2. ^{1}H NMR spectra of **23** (mixture of regioisomers).

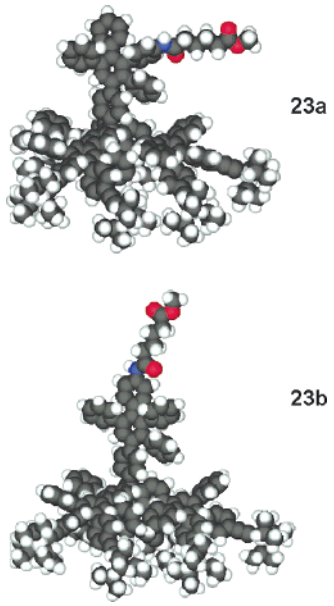


FIGURE 3. Three-dimensional models of the regioisomers of polyphenylene dendrimer **23**.

with dichloromethane (3 × 20 mL) and the combined organic phases were washed with 25 mL of saturated ammonium chloride solution. Then the organic phase was dried over magnesium sulfate, filtered, and evaporated. The product was purified by flash chromatography on silica with dichloromethane as eluent and then by recrystallization from ethanol. Yield 418 mg, 80%. FD (M^+) *m/z* 485.2 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ_H 7.28−7.17 (m, 15H), 6.96 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 3.70 (t, 2H J = 6.3 Hz), 2.55 (t, 2H, J = 6.8 Hz), 2.03 (m, 2H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 200.4, 154.9, 154.3, 133.5, 133.0, 131.4, 131.3, 131.2, 131.0, 129.7, 129.6 128.9, 128.4, 128.3, 128.0, 127.9, 126.1, 125.9, 124.2, 90.1, 81.4, 44.2, 31.8, 17.2.

Compounds 8 and 9. Tetra(4-ethynylphenyl)methane (**7**) (0.1 g, 0.24 mmol) and **3** (0.097 g, 0.18 mmol) in *o*-xylene (50 mL) were heated at 150 °C for 18 h under an argon atmosphere. Next, the solvent was evaporated under reduced pressure and the products were purified by flash chromatography with a CH_2Cl_2/acetone gradient. A mixture of DCM/acetone (40:1) as eluent afforded **8** as a white powder. Yield 0.095 g (56%). FD (M^+) *m/z* 930 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ_H 7.52 (s, 1 H), 7.42−7.29 (d, 6 H), 7.23−6.74 (m, 29 H), 3.62 (s, 3 H), 3.11 (s, 3 H), 2.32−2.20 (m, 4 H), 1.73−1.58 (m, 4 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2, spinecho) δ_C 171.0, 147.3, 143.8, 142.4, 141.5, 141.0, 140.6, 140.2, 139.4, 136.6, 132.5, 131.9, 131.5, 130.5, 129.9, 128.2, 128.1, 127.5, 127.4, 127.2, 126.8, 126.1, 120.6, 118.3, 83.7, 77.9, 65.1, 51.9, 37.7, 34.1, 25.3, 24.9.

A 20:1 mixture of CH_2Cl_2/acetone afforded **9** as a white powder. Yield 0.045 g (35%). FD (M^+) *m/z* 1444 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.53 (s, 2 H), 7.38−7.27 (d, 4 H), 7.20−6.71 (m, 50 H), 3.62 (s, 6 H), 3.11 (s, 2 H), 2.34−2.18 (m, 8 H), 1.71−1.60 (m, 8 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2, spinecho) δ_C 174.2, 170.8, 148.0, 144.4, 142.2, 142.1, 141.3, 141.2, 141.1, 141.0, 140.5, 140.0, 139.1, 136.4, 136.1, 132.4, 132.0, 131.9, 131.8, 131.5, 131.3, 131.1, 130.5, 130.3, 129.2, 128.0, 127.3, 127.2, 127.1, 127.0, 126.6, 126.0, 125.9, 125.8, 120.0, 118.1, 117.8, 86.7, 64.1, 51.7, 37.5, 33.9, 30.1, 24.7.

Compound 12. 12 was prepared analogously to **8** from tetra(4-ethynylphen-1-yl)methane (**7**) (0.1 g, 0.24 mmol) and **4** (0.110 g, 0.18 mmol). The products were purified by flash chromatography with a DCM/acetone mixture (10:1) as eluent to give **12** as a white powder. Yield 0.100 g (55%). FD (M^+) *m/z* 1007 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.52 (s, 1 H), 7.42−6.70 (m, 40 H), 5.07 (s, 2 H), 3.30−3.16 (m, 2 H), 3.12 (s, 3 H), 2.32−2.21 (m, 2 H), 1.87−1.75 (m, 2 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 171.1, 147.3, 145.3, 143.8, 140.6, 132.5, 132.2, 131.9, 131.5, 130.5, 129.9, 129.0, 128.5, 128.2, 127.3, 127.2, 126.8, 126.1, 120.6, 118.3, 83.7, 77.9, 67.2, 65.1, 40.6, 35.1, 27.1.

Compound 13. 13 was prepared analogously to **8** from tetra(4-ethynylphen-1-yl)methane (**7**) (0.150 g, 0.37 mmol) and **6** (0.135 g, 0.28 mmol). The products were purified by flash chromatography with a DCM/hexane mixture (1:2) as eluent to give **13** as a white powder. Yield 0.104 g (43%). FD (M^+) *m/z* 873 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.54 (s, 1H), 7.38−7.35 (m, 6H), 7.21−6.75 (m, 30H), 3.69−3.64 (m, 2H), 3.12 (s,3H), 2.53−2.50 (m, 2H), 2.00−1.96 (m, 2H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 147.3, 141.2, 140.5, 131.9, 131.5, 130.6, 130.5, 130.4, 129.9, 128.2, 127.3, 127.2, 126.1, 120.5, 88.6, 83.8, 77.9, 44.5, 32.0, 30.3.

Compound 20. Compounds **12** (0.050 g, 0.050 mmol) and **14** (0.087 g, 0.225 mmol) in *o*-xylene (15 mL) were heated at 150 °C for 24 h under argon atmosphere. The solvent was evaporated, and the dry rest was dissolved in 0.1 M aqueous trifluoroacetic acid (3 mL). The final purification was performed by reverse-phase HPLC with a linear AB gradient from A to B over 21 min, with eluent A consisting of a mixture of 98% water/2% acetonitrile (plus 0.1% TFA) and eluent B consisting of a mixture of 50% acetonitrile/50% 2-propanol (plus 0.05% TFA). The flow rate was 3 mL/min. Yield 0.080 g (78%). MALDI TOF MS *m/z* 1965 g/mol (M^+); ^{1}H NMR (250 MHz, acetone-d_6) δ_H 8.87−8.76 (m, 1 H, NH), 8.42−8.15 (m, 12 H), 7.81−7.67 (m, 6H), 7.58 (s, 3H), 7.38−6.53 (m, 77 H), 5.06 (s, 2H), 3.11−2.97 (m, 2H), 2.25−2.12 (m, 2 H), 1.76−1.62 (m, 2H); ^{13}C NMR (175 MHz, acetone-d_6) δ_C 171.3, 159.9, 159.7, 149.2, 145.9, 145.1, 143.1, 142.9, 142.6, 141.9, 141.7, 141.6, 141.5, 141.4, 141.3, 141.2, 141.1, 140.8, 140.6, 140.1, 139.7, 138.6, 138.1, 137.7, 135.9, 132.6, 132.4, 131.3, 131.1, 130.9, 130.8, 129.8, 129.7, 129.2, 129.0, 128.6, 128.5, 128.4, 128.0, 127.8, 127.5, 127.4, 126.3, 124.8, 124.5, 118.3, 118.1, 117.7, 116.0, 66.5, 64.4, 41.0, 34.8, 26.6; RP-HPLC: retention time = 15 min.

Compound 21. Compounds **8** (0.050 g, 0.054 mmol) and **15** (0.123 g, 0.322 mmol) in *o*-xylene (15 mL) were heated at 150 °C for 24 h under argon atmosphere. The reaction mixture was concentrated to one-fourth of the initial volume and precipitated from hexane to afford **21** as a white powder. Yield 0.80 g (75%). FD (M^+) *m/z* 2000 g/mol; ^{1}H NMR (250 MHz, CD_2Cl_2) δ_H 7.55 and 7.54 (s, s, 4 H), 7.20−6.60 (m, 95H), 3.67 (s, 3H), 2.40−2.20 (m, 4H), 1.87−1.75 (m, 4H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 176.6, 145.0, 142.4, 141.1, 140.8, 140.7, 140.1, 132.6, 132.1, 131.0, 130.8, 130.5, 129.3, 128.1, 127.4, 127.3, 127.1, 126.8, 126.1, 126.0, 125.9, 118.3, 64.0, 37.6, 33.6, 30.3, 24.7.

Compound 22. 22 was prepared analogously to **21** from **13** (0.035 g, 0.041 mmol) and **15** (0.094 g, 0.244 mmol). The

product was purified by precipitation from methanol to give **22** as a white powder. Yield 0.032 g (41%). MALDI TOF MS *m/z* 1965 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.54 (s, 4H), 7.25−6.60 ppm (m, 95H), 3.74−3.59 (m, 2H), 2.57−2.45 (m, 2H), 2.05−1.91 (m, 2H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 173.9, 144.8, 142.2, 141.9, 141.3, 141.1, 140.9, 140.6, 140.5, 139.9, 139.7, 131.9, 130.8, 130.6, 130.3, 129.1, 127.9, 127.2, 127.1, 126.9, 126.6, 125.9, 125.8, 125.7, 81.5, 63.8, 44.3, 31.9, 17.1.

Compound 23. 23 was prepared analogously to **21** from **8** (0.100 g, 0.108 mmol). The products were purified by flash chromatography with a mixture od DCM/acetone (40:1) as eluent to give **23** as a white powder. Yield 0.300 g (90%). MALDI TOF MS *m/z* 3106 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.54 (s, 4 H), 7.21−6.59 (m, 92 H), 3.620 and 3.614 (s, s, 3 H), 2.35−2.19 (m, 4H), 1.72−1.58 (m, 4H), 1.09 (s, 126 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C 173.6, 147.4, 144.5, 144.1, 143.2, 142.7, 142.5, 142.1, 141.2, 134.6, 134.0, 133.7, 133.4, 133.0, 131.7, 130.9, 130.0, 129.8, 123.6, 123.4, 120.9, 120.6, 110.4, 93.3, 93.1, 66.5, 54.8, 36.8, 32.8, 27.8, 27.4, 21.8, 14.4.

Separation of Regioisomers 23a and 23b. The mixture of isomers (0.300 g) was separated by flash chromatography on Silicagel 60 (0.04−0.063 mm) with a mixture of DCM/acetone (100:1) to give **23a** (R_f 0.73, yield 0.115 g), **23b** (R_f 0.66, yield 0.115 g) and an unseparated mixture of **23a** and **23b** (yield 0.065 g).

Compound 24. 24 was synthesized analogously to **21** from **13** (0.072 g, 0.084 mmol) and **16** (0.374 g, 0.502 mmol). The product was purified by flash chromatography with a DCM/hexane mixture (1:2) as eluent to give **24** as a white solid. Yield 0.56 g (23%). MALDI-TOF MS *m/z* 3047 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.58−6.62 (m, 93H), 3.74−3.59 (m, 2H), 2.57−2.45 (m, 2H), 2.03−1.90 (m, 2H), 1.26 (s, 18H), 1.09 (s, 108H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 144.9, 141.9, 141.5, 141.2, 141.1, 140.9, 140.7, 140.1, 140.0, 138.7, 133.7, 131.8, 131.1, 130.8, 130.6, 130.2, 129.9, 129.0, 128.1, 127.9, 126.9, 126.1, 121.2, 121.0, 107.3, 91.0, 90.9, 44.3, 31.8, 30.1, 18.8, 17.1, 11.7.

Compound 25. 25 was prepared analogously to **21** from **12** (0.130 g, 0.129 mmol) and **16** (0.350 g, 0.470 mmol). The product was purified by flash chromatography with a mixture of DCM/acetone (40:1) as eluent to give **25** as a white powder. Yield 0.377 g (92%). MALDI-TOF MS *m/z* 3181 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.54 and 7.53 (s, s, 4H), 7.33−7.31 (m, 4 H), 7.20−6.61 (m, 92 H), 3.65−3.62 (m, 2 H), 2.37−2.31 (m, 2H), 2.28−2.22 (m, 2H), 1.07 (s, 126 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 170.9, 157.6, 153.9, 145.0, 144.8, 142.3, 142.1, 141.9, 141.5, 141.3, 141.1, 141.0, 140.8, 140.6, 140.1, 140.0, 139.7, 138.8, 133.4, 132.4, 131.9, 131.6, 131.1, 130.9, 130.7, 130.5, 130.3, 129.7, 129.1, 128.8, 128.5, 128.4, 128.3, 128.1, 127.3, 127.1, 126.9, 126.7, 126.1, 125.8, 124.1, 121.3, 121.0, 118.2, 107.3, 91.0, 90.9, 67.0, 63.8, 40.4, 34.9, 26.9, 18.8, 11.7.

Compound 26. 26 was prepared analogously to **21** from **8** (0.050 g, 0.054 mmol) and **17** (0.180 g, 0.243 mmol). The product was purified by precipitation from methanol to give a yellow powder. Yield 0.120 g (72%). MALDI TOF MS *m/z* 3076 g/mol (M^+); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.72−7.61 (m, 8 H), 7.50−6.50 (m, 132 H), 6.33−6.17 (m, 12 H), 3.63 and 3.62 (s, s, 3 H), 2.35−2.19 (m, 4H), 1.70−1.58 (m, 4H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 170.8, 167.9, 167.8, 149.2, 148.8, 144.7, 144.4, 142.7, 142.3, 141.8, 141.3, 141.1, 140.9, 140.5, 140.2, 140.0, 139.8, 139.5, 139.1, 136.3, 136.1, 135.7, 135.4, 132.7,132.4, 132.1, 132.0, 130.6, 130.3, 129.9, 129.5, 129.0, 128.4, 128.3, 128.2, 128.0, 127.2, 126.5, 125.8, 120.0, 119.8, 118.1, 117.8, 114.0, 113.7, 63.7, 51.7, 37.4, 33.9, 25.1, 24.7.

Compound 27. 27 was synthesized analogously to **21** from **8** (0.050 g, 0.054 mmol) and **17** (0.190 g, 0.243 mmol). The product was purified by precipitation from methanol to afford a yellow powder. Yield 0.150 g (86%). MALDI TOF MS *m/z* 3221 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.51 (s, 4 H), 7.20−6.55 (m, 89 H), 3.61 (s, 3 H), 3.17−3.03 (m, 12 H), 2.35−2.17 (m, 16 H), 1.88−1.58 (m, 16 H), 1.4 (s, 54 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 174.2, 171.5, 157.1, 144.8, 142.3, 141.5, 141.3, 141.1, 140.5, 140.2, 139.9, 139.3, 136.6, 136.3, 132.3, 132.0, 130.6, 130.3, 129.1, 128.0, 127.2, 127.0, 126.5, 125.9, 118.4, 118.2, 79.6, 63.7, 51.7, 41.3, 39.9, 34.9, 33.9, 30.0, 28.5, 26.9, 25.1, 24.7.

Compound 28. 28 was prepared analogously to **21** from **12** (0.042 g, 0.042 mmol) and **19** (0.150 g, 0.25 mmol). The product was purified by precipitation from hexane to give a white powder. Yield 0.81 g (67%). MALDI-TOF MS *m/z* 2904 ($M(Na)^+$); ^1H NMR (250 MHz, CD_2Cl_2) δ 8.03−7.87 (m, 12 H), 7.65−6.69 (m, 110 H), 5.07 (s, 2 H), 3.84 (s, 18 H), 3.28−3.15 (m, 2 H), 2.35−2.21 (m, 2H), 1.89−1.75 (m, 2H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 170.9, 167.0, 157.6, 154.3, 145.1, 145.0, 142.0, 141.4, 141.3, 141.2, 140.9, 140.6, 140.3, 140.0, 139.8, 139.0, 137.2, 136.9, 132.5, 132.0, 130.1, 129.2, 128.1, 127.3, 126.9, 126.1, 125.8, 118.2, 117.9, 67.0, 63.8, 52.3, 40.4, 34.9, 26.8.

Compound 29. To a solution of **23** (0.240 g, 0.076 mmol) in THF (20 mL) was added $(t\text{-Bu})_4NF{\cdot}3H_2O$ (0.280 g, 0.92 mmol). The reaction mixture was stirred for 5 h at room temperature. Subsequently, water (20 mL) was added and the product was extracted with DCM (3 × 15 mL). The organic phase was isolated, dried on magnesium sulfate, filtered, and concentrated to 5 mL. The product was purified by precipitation from methanol to give a yellow powder. Yield 0.150 g (94%). MALDI-TOF MS *m/z* 2167 g/mol ($M(Na^+)$); ^1H NMR (250 MHz, CD_2Cl_2) δ_H 7.57 (s, 3 H), 7.53 (s, 1 H), 7.19−6.64 (m, 89 H), 3.62 (s, 3 H), 3.03 and 3.01 (s, s, 6 H), 2.38−2.20 (m, 4 H), 1.72−1.57 (m, 4 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 174.2, 173.5, 145.0, 141.6, 141.5, 141.5, 141.2, 141.1, 140.9, 140.5, 140.3, 140.0, 139.8, 139.6, 138.6, 131.9, 131.5, 131.2, 130.9, 130.7, 130.2, 129.0, 128.1, 127.3, 126.9, 126.1, 119.8, 119.5, 83.8, 77.3, 63.8, 51.7, 35.9, 34.0, 30.3, 24.4.

Compound 30. Analogously to **29**, from compound **25** (0.350 g, 0.111 mmol) and $(t\text{-Bu})_4NF{\cdot}3H_2O$ (0.400 g, 1.32 mmol) was obtained **30** as a yellow powder. Yield 0.220 g (88%). MALDI-TOF MS *m/z* 2244 g/mol ($M(Na^+))^+$; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.56 (s, 3 H), 7.52 (s, 1 H), 7.45−7.29 (m, 6 H), 7.18−6.74 (m, 82 H), 6.67−6.60 (m, 6 H), 5.06 (s, 2 H), 3.31−3.13 (m, 2 H), 3.03 and 3.00 (s, s, 6 H), 2.33−2.24 (m, 2 H), 1.87−1.75 (m, 2 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 171.0, 157.6, 145.0, 142.3, 142.2, 142.1, 141.7, 141.6, 141.5, 141.2, 141.1, 141.0, 140.6, 140.0, 139.9, 139.6, 139.2, 138.7, 137.2, 136.6, 136.0, 132.4, 131.9, 131.5, 131.2, 130.9, 130.7, 130.3, 129.1, 128.8, 128.4, 128.3, 128.1, 128.0, 127.9, 127.3, 127.1, 127.0, 126.2, 119.8, 119.6, 118.2, 117.9, 83.8, 77.3, 67.0, 63.8, 40.4, 34.8, 26.8, 23.8.

Compound 32. 32 was prepared and purified analogously to **20** from **29** (0.055 g, 0.025 mmol) and **14** (0.114 g, 0.295 mmol). Yield 0.080 g (75%). MALDI-TOF MS *m/z* 4299 g/mol ($M(4H^+))^+$; ^1H NMR (250 MHz, acetone-d_6) δ 8.87−8.76 (m, 1 H, NH), 8.44−8.27 (m, 24 H), 7.86−7.74 (13 H), 7.50−7.30 (m, 24 H), 7.23−7.07 (m, 48 H), 7.05−6.55 (m, 101 H), 3.57 and 3.56 (s, s, 3 H), 2.35−2.23 (m, 4 H), 1.66−1.57 (m, 4 H)); ^{13}C NMR (175.5 MHz, acetone-d_6) δ_C 174.5, 171.4, 160.2, 159.9, 148.9, 145.4, 142.7, 142.4, 141.8, 141.7, 141.0, 140.8, 140.6, 140.3, 139.7, 138.9, 138.5, 138.3, 137.6, 135.7, 133.0, 132.4, 132.1, 132.0, 131.6, 131.1, 130.8, 129.6, 129.3, 129.0, 128.6, 128.5, 128.3, 128.0, 127.7, 127.5, 127.4, 127.2, 126.5, 124.7, 119.4, 118.3, 117.8, 116.1, 114.5, 64.3, 51.5, 37.3, 33.9, 32.6, 25.6, 25.3; RP-HPLC, retention time = 19 min.

Compound 33. 33 was prepared analogously to **21** from **29** (0.038 g, 0.017 mmol) and **15** (0.106 g, 0.280 mmol). The product was purified by precipitation from hexane to give a yellow powder. Yield 0.055 g (72%). MALDI-TOF MS *m/z* 4307 g/mol ($M(Na^+))^+$; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.53 (s, 1 H), 7.50 (s, 3 H), 7.41 (s, 3 H), 7.36 (s, 3 H), 7.17−7.12 (m, 42 H), 7.09−7.05 (m, 13 H), 6.90−6.84 (m, 86 H), 6.79−6.71 (m, 40 H), 6.67−6.60 (m, 17 H), 6.55−6.47 (m, 12 H), 3.62 (s, 3 H), 1.75−1.58 (m, 4 H), 1.37−1.19 (m, 4 H); ^{13}C NMR (175.5 MHz, CD_2Cl_2) δ_C 174.2, 144.5, 142.1, 141.9, 141.8, 141.1, 140.9, 140.7, 140.5, 140.4, 140.3, 140.2, 139.7, 139.7, 139.6, 139.4, 139.3,

139.2, 139.1, 138.8, 138.4, 138.3, 138.0, 132.4, 132.0, 131.9, 131.8, 131.4, 131.2, 130.6, 130.4, 130.2, 129.9, 128.9, 128.6, 127.9, 127.8, 127.1, 127.0, 126.8, 126.5, 126.4, 126.2, 125.7, 125.6, 125.4, 118.1 52.3, 38.0, 33.9, 30.0, 24.6.

Compound 34. 34 was prepared analogously to **21** from **29** (0.030 g, 0.014 mmol) and **16** (0.124 g, 0.17 mmol). The product was purified by precipitation from methanol to give a yellow powder. Yield 0.075 g (83%). MALDI-TOF MS *m/z* 6473 ($M(Na^+)$); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.53 (s, 1 H), 7.50 (s, 3 H), 7.41 (s, 3 H), 7.36 (s, 3 H), 7.21−6.44 (m, 197 H), 3.63 and 3.62 (s, s, 3 H), 2.36−2.23 (m, 4 H), 1.78−1.58 (m, 4 H), 1.09 (s, 253 H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ_C 142.1, 141.4, 140.9, 140.1, 138.8, 132.0, 131.2, 130.9, 130.4, 128.3, 127.6, 121.4, 121.1, 107.5, 91.1, 91.0, 18.9, 11.9.

Compound 35. 35 was synthesized analogously to **21** from **29** (0.020 g, 0.009 mmol) and **31** (0.92 g, 0.108 mmol). The product was purified by precipitation from methanol to give a yellow powder. Yield 0.045 g (70%). MALDI-TOF MS *m/z* 7118 g/mol ($M(Na^+)$); ^{1}H NMR (250 MHz, DMSO-d_6) δ_H 9.75−9.62 (m, 12 H, NH), 7.40−6.41 (m, 267 H), 4.99 (s, 24 H), 3.55 and 3.54 (s, s, 3 H), 3.16−2.94 (m, 24 H), 2.29−2.13 (m, 28 H), 1.74−1.58 (m, 24 H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ_C 171.5, 171.4, 157.2,145.0, 144.6, 142.6, 142.1, 141.8, 141.6, 141.2, 140.7, 140.6, 140.5, 140.3, 140.2, 140.1, 140.0, 139.5, 139.3, 139.2, 138.8, 138.5, 138.4, 138.3, 138.1, 135.7, 135.3, 132.3, 131.7, 131.4, 131.1, 130.7, 130.4, 129.5, 129.3, 129.0, 128.4, 127.6, 127.0, 126.4, 119.4, 117.9, 117.6, 66.1, 51.5, 41.0, 33.8, 26.3, 25.4, 25.0.

Supporting Information Available: Materials and analytical methods; ^{1}H NMR and ^{13}C NMR data for compounds **6**, **8**, **12**, **13**, **20**−**30**, and **32**−**35**; temperature-dependent ^{1}H NMR of compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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