Synthesis and Antibacterial Activity of Dendritic Architectures

Perumal Rajakumar,*[a] Kilivelu Ganesan,[a] S. Jayavelu,[b] K. Murugesan[b]

[a] Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600025, India
Fax +91(44)22352494; E-mail: perumalrajakumar@hotmail.com

[b] Center for Advanced Studies in Botany, University of Madras, Guindy Campus, Chennai 600025, India

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Abstract: Synthesis of dendrimers with pentanone as core unit and *m*-terphenyl as surface end group has been achieved. The inhibitory activity of pentanone and its dendrimers against human pathogenic bacteria is well-documented.

Key words: pentanone, *m*-terphenyl, bactericidal screening, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*

Dendrimers are used as carrier macromolecules for drug delivery, gene transfer, and as catalyst in homogeneous as well as heterogeneous catalysis.[1] Dendrimers offer innumerable applications in pharmaceutical, biological and biomedical fields. Due to the presence of suitable functional group at the core and surface, dendrimers find application as multivalent bioconjugates, antibacterial and antiviral agents.[2–4] Hybrid dendrimers such as glycodendrimers exhibits potential application in medical field.[5] Covalent attachment of drugs through various degradable linkers such as lactosaminylated and galactosylated human serum albumin has allowed the targeted delivery of antiinflammatory agents such as Naproxen.[6,7] Synthesis of permanent fluorescence sensing hyperbranched dendritic architectures[8] as well as bactericidal efficacy of novel dendrimers[9] and axially chiral enantiopure dendrimers[10] were reported from our laboratory recently. The pentanone nucleus is present in various natural products[11,12] and is known to be a very important precursor to many potentially bioactive compounds.[13] However the synthesis and biological activity of pentanone core based *m*-terphenyl hyperbranched dendritic architecture are yet to be investigated. We report herein the synthesis of pentanone core based dendritic architecture (**1a**–**3a**, **1b**–**3b**, Figure 1) and their antibacterial activity against *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Escherichia coli* bacteria.

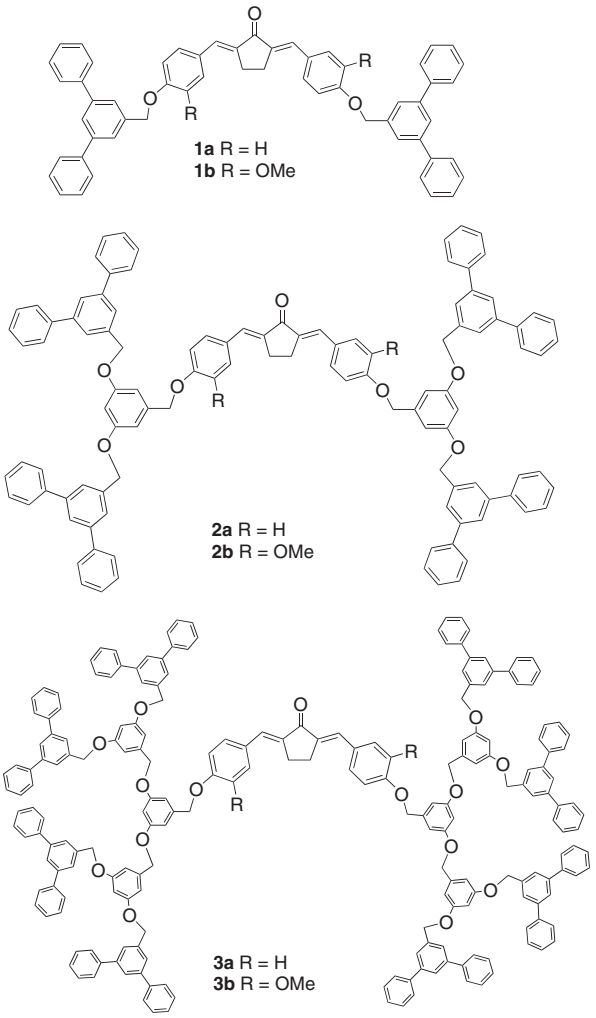

Figure 1

5′-Methyl-1,1′:3′,1″-terphenyl (**4**) was prepared by the application of the Hart reaction[14] from 3,5-dibromo-4-iodotoluene. Radical bromination of **4** with *N*-bromosuccinimide in tetracholoromethane in the presence of Bz_2O_2 afforded 5′-bromomethyl-1,1′:3′,1″-terphenyl (**5**) in 84% yield.[15] Reaction of the pentanone core unit **6a/6b**[16] derived from cyclopentanone and 4-hydroxybenzaldehyde/3-methoxy 4-hydroxybenzaldehyde with 2.1 equivalents of 5′-bromomethyl-1,1′:3′,1″-terphenyl in DMF in the presence of K_2CO_3 gave the dendrimers **1a/1b** in 73% and 70% yields, respectively (Scheme 1). The pentanone core unit **6a/6b** could be also obtained using iodotrimethylsilane[17] or $Yb(OTf)_3$[18] as catalyst for cross-aldol condensation.

The ^{1}H NMR spectrum of dendrimer **1a** displayed a singlet at δ = 3.04 for the methylene protons of cyclopentanone moiety and another sharp singlet at δ = 5.20 for OCH_2 protons in addition to olefinic and aromatic protons. In ^{13}C NMR spectrum CH_2, OCH_2 and C=O carbon appeared at δ = 36.5, 70.2 and δ = 196.4 in addition to ten aromatic carbons. The appearance of a molecular ion peak

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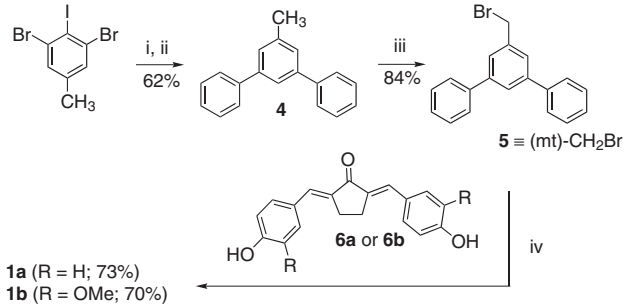
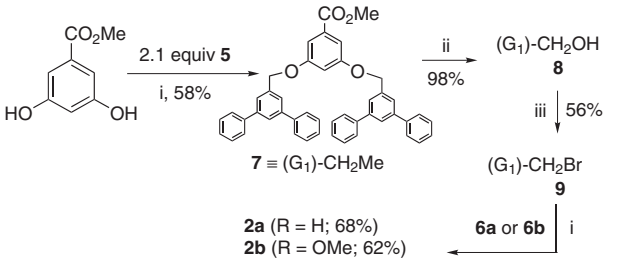


Scheme 1 *Reagent and conditions*: i) PhMgBr (3.1 equiv), THF, reflux, 12 h; ii) H_3O^+; iii) NBS, Bz_2O_2, CCl_4, reflux; iv) K_2CO_3, DMF, 60 °C, 48 h.

at *m*/*z* = 808 in the FAB mass spectrum also confirmed the structure of the dendrimer **1a**. The structure of the dendrimers **1b** was also confirmed based on the spectral and analytical data.

In order to synthesize the first-generation dendrimer **2a**, methyl 3,5-dihydroxybenzoate was reacted with the 5′-bromomethyl-1,1′:3′,1″-terphenyl (**5**) to give compound **7** and was followed by the conventional functional-group transformation[19] which afforded the corresponding dendritic bromide **9**[20] (G_1)-CH_2Br in 56% yield. Reaction of 2.1 equivalents of the dendritic bromide **9** (G_1)-CH_2Br with one equivalent of the pentanone core unit **6a/6b** in the presence of K_2CO_3 in DMF gave dendrimer **2a/2b** in 68% and 62% yields, respectively (Scheme 2).

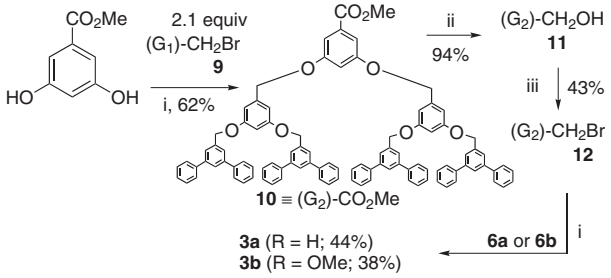


Scheme 2 *Reagent and conditions*: i) K_2CO_3, DMF, 60 °C, 48 h; ii) $LiAlH_4$, THF, reflux, 12 h; iii) CBr_4, PPh_3, THF, r.t.

The ^1H NMR spectrum dendrimer **2a** displayed a singlet at δ = 2.98 for the two identical CH_2 protons of pentanone moiety. Two sharp singlets for 4-H and 8-H were observed at δ = 5.06 and 5.17 for OCH_2 protons in addition to olefinic and aromatic protons. In the ^{13}C NMR spectrum CH_2, OCH_2 and C=O carbon appeared at δ = 36.5, 70.0, 70.2 and at δ = 196.4 in addition to thirteen aromatic carbons. The appearance of molecular ion peak at *m*/*z* = 1504 in the FAB mass spectrum also confirmed the structure **2a**. Similarly structure of the dendrimer **2b** was also confirmed based on the spectral and analytical data.

With a view to synthesize the second-generation dendrimers **3a/3b** methyl 3,5-dihydroxybenzoate was reacted with 2.1 equivalents of dendritic bromide **9** (G_1)-CH_2Br to give the methyl carboxylate **10** (G_2)-CO_2Me, which was converted to the dendritic bromide **12** (G_2)-CH_2Br through dendritic alcohol **11** (G_1)-CH_2OH as described under the synthesis of **2a/2b**.

Reaction of 2.1 equivalents of dendritic bromide **12**[20] (G_2)-CH_2Br with one equivalent of parent compound **6a/6b** gave the dendrimer **3a/3b** in 44% and 38% yields, respectively (Scheme 3).



Scheme 3 *Reagent and conditions*: i) K_2CO_3, DMF, 60 °C, 48 h; ii) $LiAlH_4$, THF, reflux, 12 h; iii) CBr_4, PPh_3, THF, r.t.

Dendrimers **3a** and **3b** were characterized from the spectral and analytical data.

Antibacterial Activity

The bactericidal activity of the parent compounds, dendrimer **1a–3a** and **1b–3b**, were assayed against *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Escherichia coli* by disc diffusion method. Parent compound **6a/6b** exhibited significant activity towards *Enterococcus faecalis* and *Klebsiella pneumoniae* and less significant activity towards *Escherichia coli.* Dendrimers **1a–3a** and **1b–3b** showed good inhibition against the test bacteria when compared with the parent compounds **6a/6b**. Dendrimer **3a/3b** possessed higher inhibitory activity than all other dendrimers and parent compounds. The standard antibiotic disc (*Streptomycin* 10 μg/ disc) inhibited the growth of *Enterococcus faecalis* by 14 mm, *Klebsiella pneumoniae* by 15 mm and *Escherichia coli* by 12 mm, respectively. The diameter of inhibition zone for each concentration against all the test bacteria is depicted in Tables 1–3.

Table 1 Inhibition Effects of Parent and Dendrimers on the Growth of *Enterococcus faecalis*

Compound	Zone of Inhibition (mm)		
	30 μg/mL	50 μg/mL	70 μg/mL
Parent **6b**	3.0	4.0	5.5
Dendrimer **1a**	4.2	5.6	6.8
Dendrimer **1b**	4.8	6.4	7.2
Dendrimer **2a**	5.0	6.5	7.5
Dendrimer **2b**	5.8	7.2	8.4
Dendrimer **3a**	7.2	8.4	10.5
Dendrimer **3b**	7.6	8.8	11.2

Table 2 Inhibition Effects of Parent and Dendrimers on the Growth of *Klebsiella pneumoniae*

Compound	Zone of Inhibition (mm)		
	30 μg/mL	50 μg/mL	70 μg/mL
Parent **6b**	3.0	4.0	5.5
Dendrimer **1a**	4.2	5.8	6.6
Dendrimer **1b**	4.6	6.2	7.2
Dendrimer **2a**	4.8	6.4	7.4
Dendrimer **2b**	5.0	6.8	7.8
Dendrimer **3a**	6.2	7.6	10.2
Dendrimer **3b**	7.4	8.4	10.8

Table 3 Inhibition Effects of Parent and Dendrimers on the Growth of *Escherichia coli*

Compound	Zone of inhibition (mm)		
	30 μg/mL	50 μg/mL	70 μg/mL
Parent **6b**	2.5	3.5	5.0
Dendrimer **1a**	3.6	4.4	5.4
Dendrimer **1b**	4.0	5.6	6.6
Dendrimer **2a**	4.4	6.2	7.2
Dendrimer **2b**	5.2	6.6	7.6
Dendrimer **3a**	5.6	7.2	8.2
Dendrimer **3b**	6.8	7.4	8.4

All dendrimers other than the parent compound significantly inhibited the growth of *Enterococcus faecalis, Klebsiella pneumoniae* and *Escherichia coli*. Dendrimers **1a**–**3a** and **1b**–**3b** could be used as potential compounds to ward off diseases caused by the bacteria, especially pneumonia.

Dichloromethane was distilled from P_2O_5 and stored over 4 Å molecular sieves; THF was distilled from sodium prior to use. Materials used were purchased from Lancaster chemicals. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Jeol 500 spectrometer operating at 500 MHz and 125 MHz respectively. The FAB-mass spectral data were recorded on a Jeol SX 102/DA-6000 mass spectrometer using *p*-nitrobenzyl alcohol (NBA) as matrix, MALDI-TOF mass spectra on a Voyager–DE PRO mass spectrometer using α-cyano-4-hydroxycinnamic acid as (CHCA) matrix and EI-mass spectra on a Jeol DX-303 mass spectrometer. Elemental analyses were determined on a Perkin-Elmer 240B elemental analyzer.

Synthesis of Dendritic Esters 7/10; General Procedure

Mixture of methyl 3,5-dihydroxybenzoate (1.0 mmol) and dendritic bromide **5/9** (2.1 mmol) was stirred with K_2CO_3 (5 mmol) in DMF (20 mL) at 60 °C for 48 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of organic layer gave a residue, which was chromatographed over SiO_2 using hexane–$CHCl_3$ as eluent.

Dendritic Ester [G_1]-CO_2Me (7)

Yield: 5.4 g (58%); mp 148 °C; eluent: hexane–$CHCl_3$ (1:1).

^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3 H), 5.11 (s, 4 H), 7.15–7.68 (m, 29 H).

^{13}C NMR: δ = 52.3, 70.3, 107.2, 108.4, 125.3, 125.9, 127.2, 127.5, 128.8, 132.1, 137.4, 140.7, 142.2, 159.7, 166.7.

MS (EI): *m*/*z* = 652.

Anal. Calcd for $C_{46}H_{36}O_4$: C, 84.66; H, 5.52. Found: C, 84.03; H, 5.32.

Dendritic Ester [G_2]-CO_2Me (10)

Yield: 1.30 g (62%); mp 95–98 °C; eluent: hexane–$CHCl_3$ (1:2).

^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H), 4.99 (s, 4 H), 5.12 (s, 8 H), 7.21–7.73 (m, 61 H).

^{13}C NMR: δ = 52.2, 70.1, 101.1, 106.4, 107.1, 108.3, 125.3, 127.2, 127.5, 128.7, 137.7, 138.9, 140.7, 142.1, 159.6, 160.1, 166.6.

MS (FAB): *m*/*z* = 1380.

Anal. Calcd for $C_{98}H_{76}O_8$: C, 85.21; H, 5.51. Found: C, 85.19; H, 5.48.

Synthesis of Dendritic Alcohol 8/11; General Procedure

To a solution of dendritic ester **7/10** (1.0 mmol) in anhyd THF (100 mL) was added $LiAlH_4$ (5.0 mmol) portionwise at r.t. The reaction mixture was stirred at reflux for 12 h and slowly poured into $Na_2SO_4 \cdot 10H_2O$ (10 g) and stirred. It was then digested on a steam bath for 20 min and filtered. The inorganic residue was further extracted (Soxhlet) with THF (100 mL). The combined organic layer on evaporation gave the corresponding alcohol.

Dendritic Alcohol [G_1]-CH_2OH (8)

Yield: 5.10 g (98%); mp 62–65 °C; eluent: $CHCl_3$.

^{1}H NMR ($CDCl_3$): δ = 4.42 (s, 2 H), 4.92 (s, 4 H), 7.18–7.58 (m, 29 H).

^{13}C NMR: δ = 65.5, 70.1, 102.2, 108.2, 125.9, 127.2, 127.5, 128.7, 137.5, 139.8, 140.7, 142.1, 160.0.

MS (FAB): *m*/*z* = 624.

Anal. Calcd for $C_{45}H_{36}O_3$: C, 86.53; H, 5.76. Found: C, 86.43; H, 5.72.

Dendritic Alcohol [G_2]-CH_2OH (11)

Yield: 94%; mp 98–100 °C; eluent: $CHCl_3$.

^{1}H NMR ($CDCl_3$): δ = 4.58 (s, 2 H), 4.98 (s, 4 H), 5.14 (s, 8 H), 7.25–7.77 (m, 61 H).

^{13}C NMR: δ = 65.3, 70.0, 70.2, 101.7, 105.8, 106.5, 128.4, 126.0, 127.4, 127.6, 128.9, 140.2, 160.1 160.2.

MS (FAB): *m*/*z* = 1352.

Anal. Calcd for $C_{97}H_{76}O_7$: C, 71.74; H, 5.62. Found: C, 71.68; H, 5.58.

Synthesis of Dendritic Bromide 9/12; General Procedure

To a solution of the dendritic alcohol **8/11** (1.0 mmol) in THF (30 mL), a solution of CBr_4 (2 × 1.2 mmol) and PPh_3 (2 × 1.2 mmol) in THF (20 mL) was added during 10 min. Upon complete addition, the mixture turned bright yellow and was subsequently quenched by the addition of H_2O, and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to

dryness and the residue was purified by column chromatography (SiO_2).

Dendritic Bromide [G_1]-CH_2Br (9)
Yield: 2.2 g (56%); mp 142–145 °C; eluent: hexane–$CHCl_3$ (2:1).

^{1}H NMR ($CDCl_3$): δ = 4.41 (s, 2 H), 5.12 (s, 4 H), 7.20–7.75 (m, 29 H).

^{13}C NMR: δ = 33.5, 70.1, 102.2, 108.2, 125.9, 127.2, 127.5, 128.7, 137.5, 139.8, 140.7, 142.1, 160.0.

MS (FAB): *m*/*z* = 687.

Anal. Calcd for $C_{46}H_{35}O_2Br$: C, 78.60; H, 5.09. Found: C, 78.58; H, 5.02.

Dendritic Bromide [G_2]-CH_2Br (12)
Yield: 1.25 g (43%); mp 95–98 °C; eluent: hexane–$CHCl_3$ (2:2).

^{1}H NMR ($CDCl_3$): δ = 4.24 (s, 2 H), 4.85 (s, 4 H), 5.03 (s, 8 H), 6.51–7.64 (m, 61 H).

^{13}C NMR: δ = 69.9, 70.1, 101.7, 106.4, 108.1, 125.3, 125.8, 127.2, 127.5, 128.7, 137.7, 140.7, 142.1, 160.1.

MS (FAB): *m*/*z* = 1419

Anal. Calcd for $C_{91}H_{75}O_6Br$: C, 82.17; H, 5.29. Found: C, 82.10; H, 5.22.

Synthesis of Enone Based Dendrimers; General Procedure
A mixture of pentanone **6a/6b** (1.0 mmol) and the bromide **5/9/12** (2.1 mmol) was stirred with K_2CO_3 (5.0 mmol) in DMF (20 mL) at 60 °C for 48 h. The reaction mixture was then poured into H_2O and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extract was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue, which was chromatographed over SiO_2 using hexane–$CHCl_3$ to give the corresponding dendrimers.

Dendrimer 1a
Yield: 176 mg (73%); mp 88–90 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 4 H), 5.20 (s, 4 H), 7.02–8.01 (m, 36 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 70.2, 115.2, 125.3, 126.1, 127.4, 127.7, 128.9, 132.6, 140.8, 142.3, 159.7, 196.4.

MS (FAB): *m*/*z* = 808.

Anal. Calcd for $C_{57}H_{44}O_5$: C, 84.65; H, 5.44. Found: C, 84.60; H, 5.40.

Dendrimer 1b
Yield: 250 mg (70%); mp 74–78 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.05 (s, 4 H), 3.91 (s, 6 H), 5.31 (s, 4 H), 7.02–8.01 (m, 34 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 56.0, 71.1, 113.7, 114.1, 124.4, 125.1, 126.0, 127.4, 127.7, 128.9, 140.9, 142.3, 149.5, 196.1.

MS (FAB): *m*/*z* = 868.

Anal. Calcd for $C_{59}H_{48}O_7$: C, 81.56; H, 5.52. Found: C, 81.50; H, 5.48.

Dendrimer 2a
Yield: 128 mg (68%); mp 94–98 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.98 (s, 4 H), 5.06 (s, 4 H), 5.17 (s, 8 H), 6.97–8.04 (m, 68 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 70.0, 70.2, 101.8, 106.4, 115.2, 125.4, 126.0, 127.4, 127.7, 128.9, 137.8, 140.9, 142.3, 159.6, 160.3, 196.4.

MS (FAB): *m*/*z* = 1504.

Anal. Calcd for $C_{99}H_{84}O_7$: C, 85.83; H, 6.06. Found: C, 85.80; H, 6.62.

Dendrimer 2b
Yield: 110 mg (62%); mp 114–116 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.98 (s, 4 H), 3.89 (s, 6 H), 5.16 (s, 4 H), 5.18 (s, 8 H), 6.88–8.02 (m, 66 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 56.0, 70.2, 70.8, 101.7, 106.1, 115.2, 125.4, 126.0, 127.4, 127.6, 128.9, 137.8, 139.4, 140.9, 142.2, 149.4, 160.3, 196.4.

MS (FAB): *m*/*z* = 1384.

Anal. Calcd for $C_{101}H_{88}O_9$: C, 83.93; H, 6.09. Found: C, 83.88; H, 6.64.

Dendrimer 3a
Yield: 90 mg (44%); mp 126–130 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (s, 4 H), 4.98 (s, 4 H), 5.06 (s, 8 H), 5.17 (s, 16 H), 6.97–8.04 (m, 132 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 68.1, 70.0, 70.2, 101.8, 106.4, 115.2, 125.4, 126.0, 127.4, 127.7, 128.9, 137.8, 140.9, 142.3, 159.6, 160.3, 196.4.

MS (MAL–TOF): *m*/*z* = 2960.

Anal. Calcd for $C_{213}H_{164}O_{15}$: C, 86.35; H, 5.54. Found: C, 86.30; H, 5.40.

Dendrimer 3b
Yield: 130 mg (38%); mp 136–140 °C; eluent: $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.93 (s, 4 H), 3.87 (s, 6 H), 4.96 (s, 4 H), 5.06 (s, 8 H), 5.17 (s, 16 H), 6.97–8.04 (m, 130 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.5, 56.0, 68.1, 70.1, 70.2, 101.7, 106.5, 114.8, 125.4, 126.0, 127.4, 127.6, 128.9, 137.8, 139.4, 140.9, 142.2, 160.2, 160.3, 196.4.

MS (MAL–TOF): *m*/*z* = 3020.

Anal. Calcd for $C_{215}H_{168}O_{17}$: C, 85.43; H, 5.56. Found: C, 85.38; H, 5.42.

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