Design and Synthesis of Novel Janus Dendrimers as Lipophilized Antioxidants

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Abstract: In the search for better antioxidants with more satisfactory lipophilicity, a series of Janus dendrimers that consisted of gallic acid and alkyl chains as the peripheral groups, were designed and synthesized. These dendrimers take advantage of a dendritic display to carry multi-antioxidants and multi-lipophilic moieties simultaneously. Consequently, the resulting dendrimers, which showed satisfactory lipophilicity and better antioxidant activity than the gallic acid monomer, are potential novel lipophilized antioxidant agents.

Key words: Janus dendrimers, gallic acid, antioxidant, lipophilization, polyphenols

Phenols and polyphenols occur widely in natural products and have numerous biological activities.[1] Among them, gallic acid (GA; Figure 1) exhibits antibacterial,[2] antiviral,[3] and antitumor activities.[4] Specifically, the major interest in GA and its derivatives is related to their antioxidant activity, the mechanism of which depends on the tendency of phenolic hydroxyl groups to act as effective free radical scavengers since they may readily donate an electron or hydrogen to intercept and convert free radicals into a more stable compound.[5] Although GA possesses interesting biological properties, its application in oil-based media is limited because of its relatively low solubility in aprotic media, which is also a general problem for most natural phenolic antioxidants. Therefore, a lot of effort has been made to enhance the hydrophobicity of natural phenols by introducing lipophilic moieties.[6] Specifically, different cyclic or chain alkyls were connected to GA by either chemical or enzymatic esterification to obtain a series of amphiphilic derivatives as lipophilic antioxidants.[7]

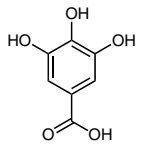

Figure 1 The structure of gallic acid (GA)

Dendrimers are new artificial macromolecules that have monodisperse and highly branched structures with well-defined three-dimensional architecture. Dendrimers are favorable vehicles that can be used to gather multi-bioactive compounds so as to form conjugated macromolecules with improved bioactivities resulting from dendritic effects.[8] To this point, 1st, 2nd, and 3rd generation GA functionalized dendrimers have been synthesized and shown to increase antioxidant activity, collagen cross-linking activity, and chemiluminescence intensity compared with those of the GA monomer.[9]

Janus dendrimers, which are composed of two differently functionalized segments (dendrimeric wedges) on opposite sides, have distinctive features in the dendrimer family.[10] First, most traditional dendrimers have highly symmetrical dendritic skeletons and possess functional groups with statistical numbers and random sites on the surface, whereas Janus dendrimers have two (or more) types of terminal groups precisely situated on each dendron respectively. Second, Janus dendrimers can be used to combine several properties in one single molecule and their applications encompass various fields, such as drug delivery,[11] gene transfection,[12] and fluorescent labeling.[13] Third, Janus dendrimers are frequently designed as amphiphilic structures. The lipophilic-hydrophilic balance, which dramatically affects the biological activity and drug delivery properties of the amphiphilic dendrimers, can be adjusted flexibly by the assembly of different dendrons.[14]

In our previous work, Janus dendrimers were prepared as bone-targeting drug delivery[15] and amphiphilic antibacterial agents.[16] It is also considered that Janus dendrimers can be promising platforms for developing antioxidant agents with highly lipophilized and remarkable antioxidant efficiency. In this paper, we designed and synthesized a series of bifunctionalized Janus dendrimers that consist of multiple GA moieties (antioxidants) and multiple myristic acids (lipophilic molecules). It can be expected that this sort of dendrimer will be a satisfactory amphiphilic antioxidant with not only antioxidant activity but also improved lipophilicity.

A typical procedure for the preparation of the Janus dendrimers involves two steps: (1) the synthesis of different dendrons, and (2) the assembly of these two functional dendrons together either directly or through a linker. First, the two types of functional dendrons were prepared by a convergent approach. For the synthesis of dendritic GA (Scheme 1), the core (L-lysine methyl ester) was coupled

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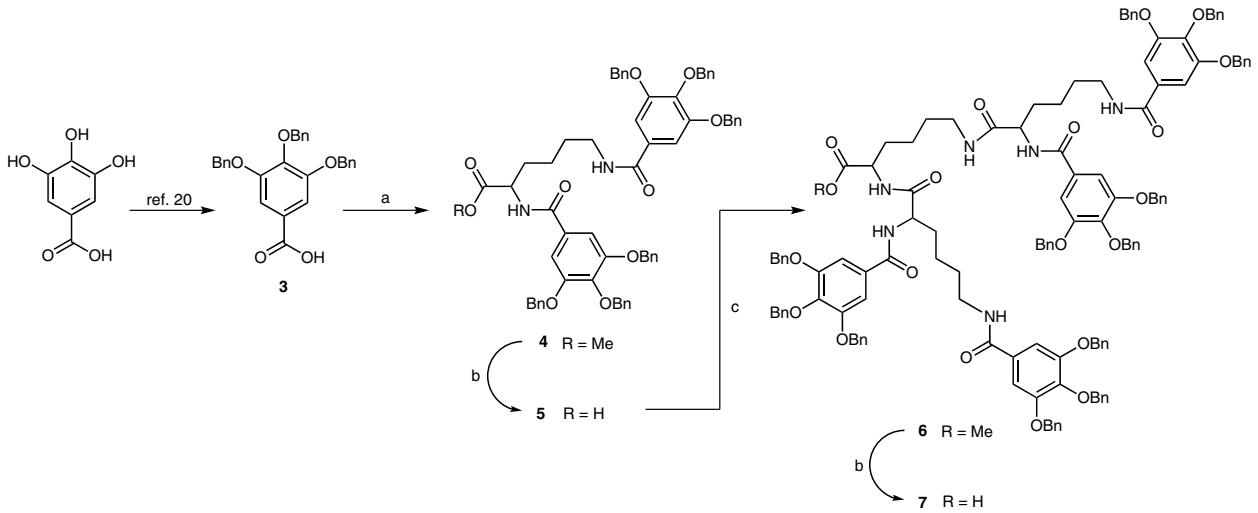
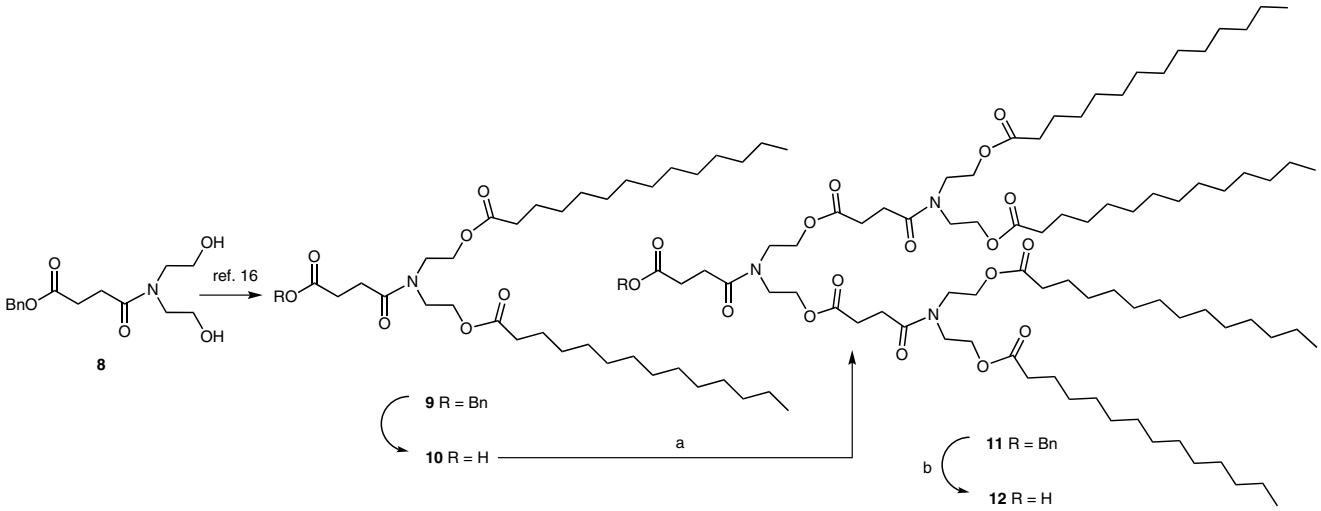


Scheme 1 Preparation of the dendritic gallic acid. *Reagents and conditions*: (a) L-lysine methyl ester hydrochloride, EDCI/HOBt, CH_2Cl_2, r.t., 24 h (78%); (b) NaOH, MeOH–H_2O, 100 °C, 2 h (98%); (c) L-lysine methyl ester hydrochloride, HOBt/HBTU, DIPEA, CH_2Cl_2, r.t., 24 h (65%).

with benzyl-protected GA **3** in the presence of EDCI/HOBt (1-hydroxybenzotriazole) to afford [G_1]-dendron **4**.[17] The methyl ester on the focal point of **4** was selectively deprotected in the presence of the benzyl group, using 2N NaOH solution, affording dendron **5**. Subsequently, formation of [G_2]-dendron **6** was achieved by utilizing the more powerful coupling system HOBt/HBTU (*o*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) to overcome the increased steric hindrance.[18] Dendron **7** was then obtained through removal of the methyl ester group under the same conditions used for the preparation of **5**. For the synthesis of dendritic myristic acid (Scheme 2), [G_1]-dendrons **9** and **10** were obtained according to our previous work.[16] Subsequently, [G_2]-dendrons were prepared through a similar process that included use of EDCI/DMAP as the coupling reagents for the growth and catalytic hydrogenolysis for focal point activation to give dendrons **11** and **12**, respectively.[19]

The following spectroscopic data for **6** illustrates the characterization of these dendrons. In the ^{1}H NMR spectrum, the structures can be confirmed by calculating the integration of the respective areas of the core protons (-OCH_3 peak at δ = 3.6 ppm) and periphery protons (PhCH_2 peak at δ = 5.0 ppm) to ensure complete coupling. Moreover, the mass spectrum showed molecular ion peaks $[M+Na]^+$ at *m*/*z* 2127.825 (*m*/*z* calcd for $C_{131}H_{128}N_6NaO_{20}^+$: 2127.908), which also confirmed the expected structure.

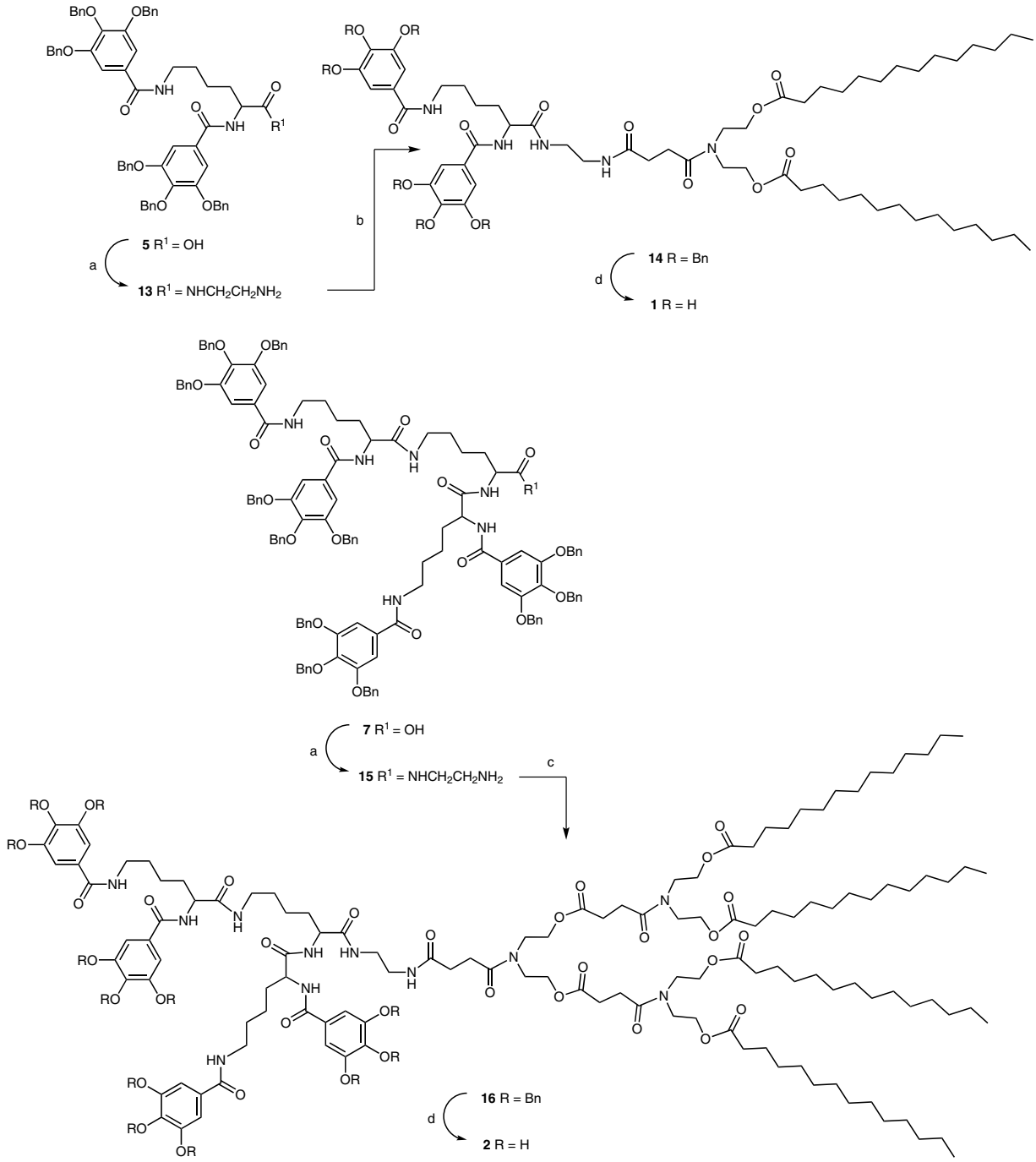
The key point of the synthesis of Janus dendrimers is the coupling of two different dendrons. This process involves the reaction of one dendron in a controlled manner with a difunctional core, then a second dendron is grafted onto the remaining functional group of the core.[10] In this work (Scheme 3), dendritic GA **5**/**7** (1.0 equiv) and EDCI/HOBt (1.1 equiv) were added to a large excess (50 equiv) of eth-



Scheme 2 Preparation of the lipophilic dendrons. *Reagents and conditions*: (a) **8**, EDCI /DMAP, CH_2Cl_2, r.t., 24 h, (70%). (b) H_2, Pd/C (10 wt%), CH_2Cl_2–MeOH, r.t., 8 h (99%).

ylenediamine (the difunctional core) in CH_2Cl_2 dropwise to make sure only one of the amino groups of ethylenediamine was connected with the GA dendron while the second amino group was available for the next dendron (excess ethylenediamine can be removed easily by extraction without further purification). Dendrons **10** and **12** were introduced into the difunctional core by coupling **13** and **15** with HBTU/HOBt to obtain Janus dendrimers **14** and **16**, respectively. Finally, after removal of the benzyl protecting groups by catalytic hydrogenolysis, the target molecules **1** and **2** were obtained.

Quantitative coupling was demonstrated by ^{1}H NMR spectroscopy, with the characteristic resonance signals being assigned to the two opposite sides. For dendrimers **1** and **2**, the peaks at δ = 6.80–6.88 ppm (Ph*H* of GA) were used to compare with the peaks at δ = 0.86 ppm (CH_3 of myristic acid), which confirmed the perfect joining. Moreover, the well-defined nature of the dendrimers were further verified by ESI MS, which showed the molecular ion peak $[M+H]^+$ at *m*/*z* 1100.6746 (**1**; *m*/*z* calcd for $C_{58}H_{94}N_5O_{15}^+$: 1100.6741) and $[M+Na]^+$ at *m*/*z* 2477.4323 (**2**; *m*/*z* calcd for $C_{128}H_{203}N_{11}NaO_{35}^+$: 2477.4335), respec-



Scheme 3 Preparation of the Janus dendrimers. *Reagents and conditions*: (a) ethylenediamine, EDCI/HOBt, DIPEA, CH_2Cl_2, r.t., 24 h (92% for **13**, 86% for **15**); (b) **10**, HBTU/HOBt, DIPEA, CH_2Cl_2, r.t., 24 h (83%); (c) **12**, HBTU/HOBt, DIPEA, CH_2Cl_2, r.t., 24 h (72%); (d) H_2, Pd/C (10 wt%), CH_2Cl_2–MeOH, r.t., 5 h (92% for **1**, 90% for **2**).

tively. The polydispersity values (Mn/Mw) of dendrimers **1** and **2** were measured to be 1.01 and 1.02, respectively, which indicated high purity.[21]

Table 1 LogP Values and Antioxidant Activity of GA and the Janus Dendrimers

Compound	LogP[a]	DPPH EC_{50} (μM)
GA	0.733	1.952±0.049
1	10.608	1.177±0.034
2	21.445	0.727±0.038

[a] Determined by using the atom-based method published by Ghose and Crippen[22] to calculate the *n*-octanol/water partition coefficient (LogP).

Lipophilization is the method of introducing a lipophilic moiety on hydrophilic substrates, resulting in new molecules with a modified hydrophilic/lipophilic balance. Generally, logP values, which represent the partitioning of a compound in an *n*-octanol/water system, is an appropriate parameter to describe the hydrophilicity/hydrophobicity of compounds. In this work, the logP values of both GA and the Janus dendrimers were determined by using Discovery Studio 3.1 software (Accelrys Inc., San Diego; Table 1). First, whereas GA was a typical hydrophilic molecule, Janus dendrimers **1** and **2** showed remarkably hydrophobic properties. With logP values of 10.608 and 21.445, respectively, the logP value of [G_2] dendrimer **2** was about two times as much as that of [G_1] dendrimer **1**, which is presumably because the [G_2] molecules have more and condensed lipophilic groups at the surface area.

The synthesized dendrimers were allowed to react with 1,1-diphenyl-2-picrylhydrazyl (DPPH), with GA being included as a control.[23] For phenolic antioxidants, the phenolic hydroxyl worked as the hydrogen donor, so the number of Ph-OH groups affected the antioxidant activity prominently. Therefore, it is an effective approach to attach several GA moieties to a multivalent scaffold, such as a dendrimer,[9a] gelatin,[24] or chitosan,[25] to obtain conjugates as more powerful antioxidants. In this work, the results showed the following radical scavenging efficiency: dendrimer **2** > dendrimer **1** > GA (Table 1). As a result, the Janus dendrimers showed better antioxidant activity than the GA monomer, and [G_2] dendrimer **2**, with more GA moieties on the surface, exhibited better antioxidant activity than [G_1] **1**, as expected. However, the antioxidant activities of **1** and **2** were not 2- and 4-fold higher than that of the GA monomer, respectively, presumably because extensive steric crowding suppressed the valency effect of the surface units.[8b]

In summary, a series of Janus dendrimers consisting of GA and alkyl chains as the peripheral groups, were synthesized by a convergent approach and well characterized. The structure of these Janus dendrimers had the distinctive feature that both multi-bioactive and multi-lipophilic moieties were attached to the dendrimer, with the two kinds of functional groups placed precisely on opposite dendrons. Consequently, the resulting dendrimers showed simultaneously satisfactory lipophilicity and improved antioxidant activity. The result indicates that Janus dendrimers are promising molecular scaffolds for the design of more potent and lipophilized antioxidants. Further biological evaluations, such as on the antioxidant activity of the Janus dendrimers in oils or oil-in-water emulsions, are ongoing.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Convergent Synthesis of Dendrons; Typical Procedure for 4:** L-Lysine methyl ester hydrochloride (0.91 g, 5 mmol), **3** (4.62 g, 10.5 mmol), EDCI (10.5 mmol), and HOBt (10.5 mmol) were dissolved in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 24 h, then the

solution was washed with 1 M HCl (10 mL), 1 M $NaHCO_3$ (10 mL), and brine (10 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration, the crude product was recrystallized by EtOAc to obtain **4** (78%) as a white solid; mp 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.54 (m, 2 H, Lys-γ-CH_2), 1.61–1.70 (m, 2 H, Lys-β-CH_2), 1.83–2.00 (m, 2 H, Lys-δ-CH_2), 3.42–3.46 (m, 2 H, Lys-ω-CH_2), 3.78 (s, 3 H, OCH_3), 4.75–4.78 (m, 1 H, Lys-α-*H*), 5.01–5.07 (m, 12 H, 6 × Ph-CH_2), 6.27 (br s, 1 H, CON*H*), 6.83 (br s, 1 H, CON*H*), 7.10 (s, 2 H, GA-Ph-*H*), 7.17 (s, 2 H, GA-Ph-*H*), 7.20–7.37 (m, 30 H, OBn-Ph-*H*). MS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{63}H_{60}N_2NaO_{10}^+$: 1027.41; found: 1027.36. Anal. Calcd for $C_{63}H_{60}N_2O_{10}$: C, 75.28; H, 6.02; N, 2.79; O, 15.92. Found: C, 75.14; H, 5.97; N, 2.69; O, 15.88.

(18) Data of dendron **6**: Yield: 65%; white solid; mp 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.77 (m, 18 H, 3 × Lys-γ-CH_2+3 × Lys-β-CH_2+3 × Lys-δ-CH_2), 3.33–3.41 (m, 6 H, 3 × Lys-ω-CH_2), 3.60 (s, 3 H, OCH_3), 4.67–4.69 (m, 3 H, 3 × Lys-α-*H*), 4.89–5.02 (m, 24 H, 12 × Ph-CH_2), 6.80–7.50 (m, 68 H, Ph-*H*). ESI-TOF-MS: *m*/*z* [M+Na]$^+$ calcd for $C_{131}H_{128}N_6NaO_{20}^+$: 2127.908; found: 2127.825. Anal. Calcd for $C_{131}H_{128}N_6O_{20}$: C, 74.69; H, 6.12; N, 3.99; O, 15.19. Found: C, 74.58; H, 6.07; N, 3.93; O, 15.11.

(19) Data of dendron **11**: Yield: 70%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.90 (t, *J* = 6.4 Hz, 12 H, 4 × CH_3), 1.25 (br s, 80 H, 40 × myristic acid CH_2), 1.58–1.60 (m, 8 H, 4 × myristic acid-β-CH_2), 2.27–2.34 (m, 8 H, 4 × myristic acid-α-CH_2), 2.63–2.72 (m, 12 H, 6 × succinic acid CH_2), 3.60–3.69 (m, 12 H, 6 × NCH_2), 4.17–4.23 (m, 12 H, 6 × NCH$_2$CH_2), 5.12 (s, 2 H, Ph-CH_2), 7.35–7.36 (m, 5 H, Ph-*H*). ESI-TOF-MS: *m*/*z* [M+Na]$^+$ calcd for $C_{87}H_{151}N_3NaO_{17}^+$: 1533.094; found: 1533.074. Anal. Calcd for $C_{87}H_{151}N_3O_{17}$: C, 69.15; H, 10.07; N, 2.78; O, 18.00. Found: C, 69.08; H, 10.02; N, 2.71; O, 17.93.

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(21) **Synthesis of Janus Dendrimers; Typical Procedure for 1:** Dendron **5** (0.99 g, 1 mmol), HOBt (1.1 mmol), HBTU (1.1 mmol), DIPEA (2 mmol) were dissolved in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at room temperature for 30 min. The above solution was added dropwise into ethylenediamine (3 g, 50 mmol) in CH_2Cl_2 (30 mL). After stirring at room temperature for 24 h, the solution was washed with 10% citric acid (10 mL), 1 M $NaHCO_3$ (10 mL), and brine (10 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration, **13** (1.01 g, 98%) was obtained for the next step without further purification. Dendron **13** (516 mg, 0.5 mmol), **10** (312 mg, 0.5 mmol), HBTU (0.6 mmol), HOBt (0.6 mmol), and DIPEA (1 mmol) were dissolved in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at room temperature for 24 h. The solution was then concentrated under vacuum and the residue was purified by silica-gel column chromatography to obtain **14** as a white waxy solid. 10% Pd/C (100 mg) was added to a solution of **14** in MeOH–CH_2Cl_2 (3:1 v/v, 30 mL) and the reaction mixture was stirred under a hydrogen atmosphere for 24 h in the dark, filtered through a membrane filter, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **1** (76%, two steps from **13**) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.83–0.86 (m, 6 H, 2 × CH_3), 1.23 (br s, 42 H, 20 × myristic acid CH_2+Lys-γ-CH_2), 1.45–1.49 (m, 6 H, 2 × myristic acid-β-CH_2+Lys-β-CH_2), 1.70 (br s, 2 H, Lys-δ-CH_2), 2.23–2.31 (m, 4 H, 2 × myristic acid-α-CH_2), 2.50–2.57 (m, 4 H, 2 × succinic acid CH_2), 3.08–3.17 (m, 6 H, Lys-ω-CH_2+NHCH_2CH_2NH), 3.47–3.60 (m, 4 H, 2 × NCH_2), 4.04–4.17 (m, 4 H, 2 × NCH$_2$CH_2), 4.26–4.28 (m, 1 H, Lys-α-*H*), 6.80 (s, 2 H, Ph-*H*), 6.88 (s, 2 H, Ph-*H*), 7.84 (br s, 1 H, CON*H*), 7.93 (br s, 1 H, CON*H*), 7.95 (br s, 1 H, CON*H*), 8.06 (br s, 1 H, CON*H*), 8.65 (br s, 2 H, 2 × Ph-O*H*), 8.98 (br s, 2 H, 2 × Ph-O*H*), 9.03 (br s, 2 H, 2 × Ph-O*H*). MS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{58}H_{94}N_5O_{15}^+$: 1100.6741; found: 1100.6746. GPC: PDI(Mw/Mn) = 1.01. Data of dendrimer **2**: Yield: 65% (two steps from **15**). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.76–0.86 (m, 12 H, 4 × CH_3), 1.22 (br s, 86 H, 40 × myristic acid CH_2+3 × Lys-γ-CH_2), 1.36–1.48 (m, 14 H, 4 × myristic acid-β-CH_2+3 × Lys-β-CH_2), 1.69 (br s, 6 H, 3 × Lys-δ-CH_2), 2.22–2.31 (m, 8 H, 2 × myristic acid-α-CH_2), 2.47–2.61 (m, 12 H, 6 × succinic acid CH_2), 3.00–3.13 (m, 10 H, 3 × Lys-ω-CH_2+NHCH_2CH_2NH), 3.48–3.59 (m, 12 H, 6 × NCH_2), 4.05–4.16 (m, 12 H, 6 × NCH$_2$CH_2), 4.28–4.30 (m, 3 × Lys-α-*H*), 6.80–6.89 (m, 8 H, Ph-*H*), 7.81–7.95 (br s, 4 H, CON*H*), 8.07 (br s, 3 H, CON*H*), 8.17 (br s, 1 H, CON*H*), 8.66 (br s, 4 H, 4 × Ph-O*H*), 8.99 (br s, 4 H, 4 × Ph-O*H*), 9.04 (br s, 4 H, 4 × Ph-O*H*). ESI-TOF-MS: *m*/*z* [M+Na]$^+$ calcd for$C_{128}H_{203}N_{11}NaO_{35}^+$: 2477.4335; found: 2477.4323. GPC: PDI(Mw/Mn) = 1.02.

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(23) **Evaluation of the Antioxidant Activity by DPPH Assay:** Briefly, 2,2-diphenyl-1-picrylhydrazyl (DPPH) in ethanol (200 μM, 2 mL) was added to the test compound (2 mL) at different concentrations in ethanol. In the reaction mixtures, the final concentration of DPPH was 100 μM, and the concentrations of the test compounds were 0.1–10 μM. Each mixture was then shaken vigorously and held for 30 min at room temperature in the dark. The decrease in absorbance of DPPH at 517 nm was measured. All tests were performed in triplicate. EC_{50} corresponds to effective concentration of test compounds resulting in 50% decolorization of initial DPPH.

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