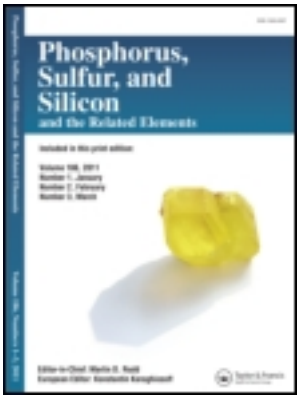

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Synthesis of Poly(amidoamine) Dendrimer with a Diphenyl Diselenide Core

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SYNTHESIS OF POLY(AMIDOAMINE) DENDRIMER WITH A DIPHENYL DISELENIDE CORE

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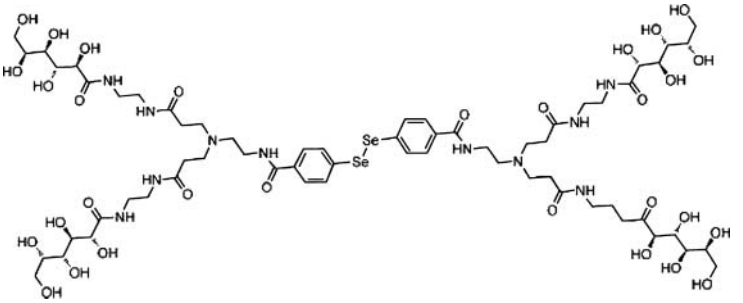
GRAPHICAL ABSTRACT



Abstract *We succeeded in the synthesis of a novel poly(amidoamine) dendrimer having diphenyl diselenide at the core. Modification of the dendrimer diselenide by the reaction with glucono-δ-lactone in methanol gave a water-soluble dendrimer diselenide having chiral terminal groups. The structures of dendrimers were satisfactorily confirmed by MAIDI-TOF MS spectrometry, elemental analysis, and NMR spectroscopy. Interestingly, induced circular dichroism (ICD) of the interaction between the diphenyl diselenide core and D-gluconamide periphery of the dendrimer was observed at 300 nm.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Chiral; diselenide; gluncono-δ-lactone; PAMAM dendrimer

INTRODUCTION

Organoselenium compounds have been employed as very useful reagents in organic synthesis.[1] Selenium is an essential trace element that plays an important role in the pro- and eukaryotic cells. It constitutes a functional element of selenium-containing enzymes,

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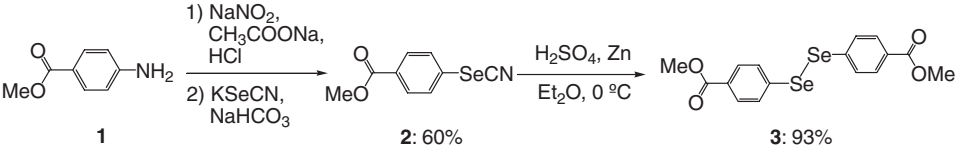
such as glutathione peroxidase (GPx),[2] iodethyronine deiodinase (ID),[3] and thioredoxin reductase (TrxR),[4] which have been implicated in antioxidative defense, iodine homeostasis, and regulation of gene expression. Based on the recognized GPx-like activity of ebselen, several articles have appeared describing simple synthetic organoselenium compounds[5] with this property (e.g., benzoselenazinones,[6] benzoselenazolinones,[7] camphor-devived selenamide,[8] and diaryl diselenides[9]). Mugesh et al. reported that diselenides derived from enantiomerically pure *R*-(+)- and *S*-(−)-*N*,*N*-dimethyl(1-ferrocenylethyl)amine show excellent peroxidase activity.[10] Therefore, the chemistry of chiral organo selenium compounds has recently gained more and more attention.

Meanwhile, a variety of dendritic molecules have been synthesized so far, and their unique properties have been extensively studied.[11] In particular, their topology enforces a globular shape that offers a unique opportunity to design artificial enzymes. Several studies of dendrimers as enzyme-like catalysts have focused on the combination of catalytic groups at the dendritic core with dendritic branches to modulate catalyst selectivity.[12] Recently, Zhang and coworkers reported the mimic of glutathione peroxidase using hyperbranched polyselenide with multicatalytic sites at the branching units.[13] Zhang et al. also reported the generation-dependent glutathione peroxidase activity of the three generations of Fréchet-type poly(aryl ether)dendrimer with a dibenzyl diselenide core.[14]

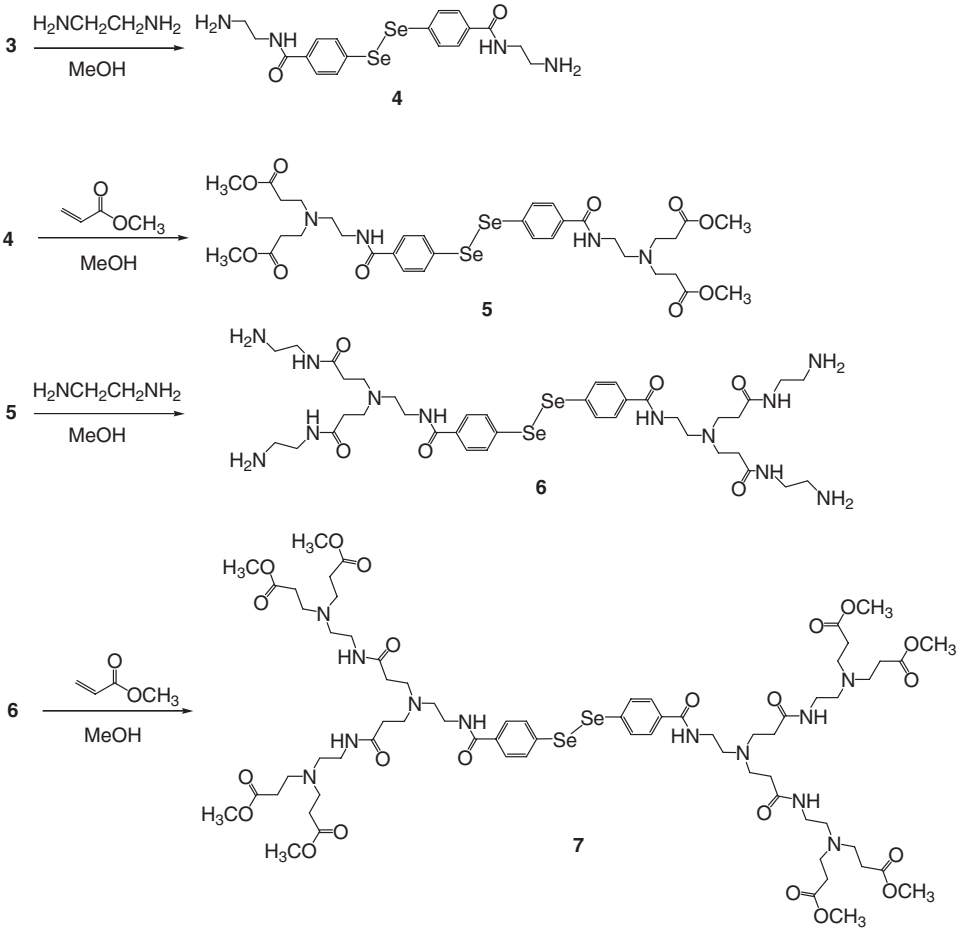
However, we reported the first synthesis of poly(benzyl ether) dendron with a thiol or selenocyanate group at the focal point together with their reversible redox behavior between dendrons and dendrimer dichalcogenides.[15] We also reported the photoinduced isomerization of allyl alcohols to carbonyl compounds using dendrimer disulfide as a catalyst.[16] Because selenium compounds having an aryl group are more stable than dibenzyl diselenides, to investigate some important active species containing selenium atom in catalytic systems, i.e., SeOH, SeH, SeO_2H, radical, and cation, diphenyl diselenide derivatives are considered to be preferred model molecules. Although the synthesis of Fréchet-type poly(aryl ether) dendrimers dibenzyl diselenide has been already reported,[14] there is no report on the synthesis of a dendrimer containing a diphenyl diselenide at the core. In the course of our studies on the investigation of dendrimer or dendron with chalcogen atom(s) at the focal point, we became interested in the poly(amidoamine) dendrimer having a diphenyl diselenide at the core. This article presents the synthesis and characterization of a poly(amidoamine) dendrimer having diphenyl diselenide at the core together with the synthesis of a water-soluble chiral dendrimer diselenide.

RESULTS AND DISCUSSION

Methyl 4-selenocyanatobenzoate (**2**) was selected as the starting material, which was prepared by the reaction of KSeCN and methyl 4-aminobenzoate (**1**) (Scheme 1).[17] Dendrimer diselenide **7**, which has poly(amidoamine) dendritic wedges at the 4,4′ position of the diphenyl diselenide, was synthesized by the divergent method developed by Tomaria



Scheme 1 Synthesis of bis[4-(methoxycarbonyl)phenyl]diselenide (**3**).



Scheme 2 Synthesis of dendrimer diselenide **7**.

et al. (Scheme 2).[18] Upon treatment of bis[4-(methoxycarbonyl)phenyl]diselenide (**3**) with ethylenediamine in MeOH under a nitrogen atmosphere for 1 d, G0.0 dendrimer **4** was obtained. The dendrimer **4** was immediately used in the next reaction due to its instability. The treatment of G0.0 dendrimer diselenide **4**, the core of dendrimer, with methyl acrylate gave a G0.5 dendrimer **5** in 87% yield. This two-step process could be repeated to prepare the dendrimer **7** in 82% yield. These methyl ester–terminated dendrimers **5** and **7** were found to be stable towards air and light. The structures of G0.5 and G1.5 dendrimer diselenides were satisfactorily confirmed by ^{1}H, ^{13} C and ^{77}Se NMR, UV-vis and IR spectroscopy, MALDI-TOF MS, and elemental analysis. The ^{77}Se NMR spectra of **5** and **7** showed sharp signals at 470 and 467 ppm, respectively. UV-vis spectra of **5** and **7** in $CHCl_3$ showed absorption maxima at 271 and 273 nm, respectively. Those absorptions were assignable to the π–π^* and/or n–σ^* electron transitions for the PhSeSePh chromophore.[19] Although those absorptions show a blue shift compared to that of diphenyl diselenide (340 nm),[19] those absorptions were similar to **3** (275 nm). Hence, the blue shift observed in the UV-vis spectra might not arise from the steric effect of the dendritic wedges, but from the substituent

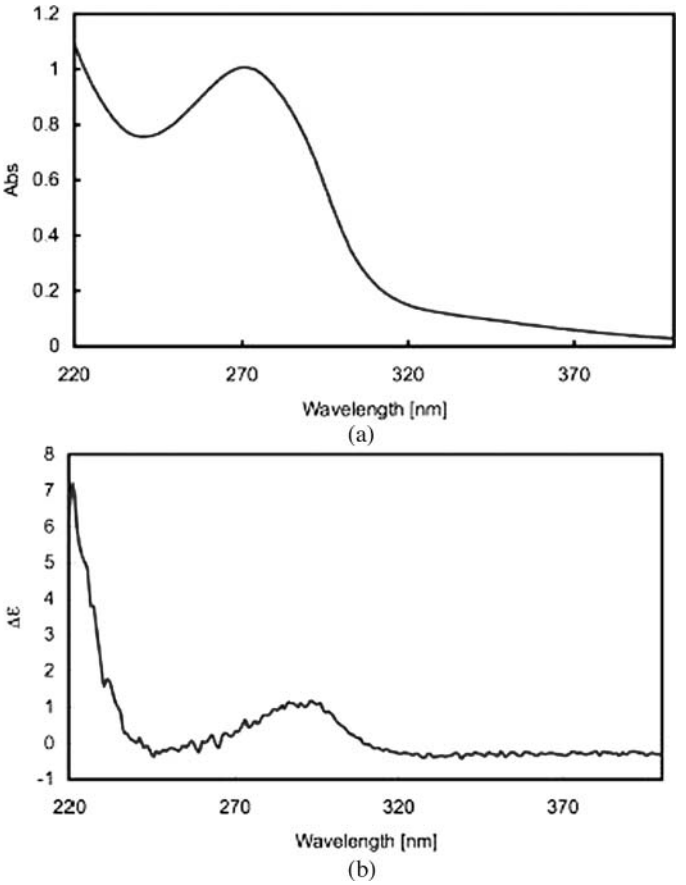
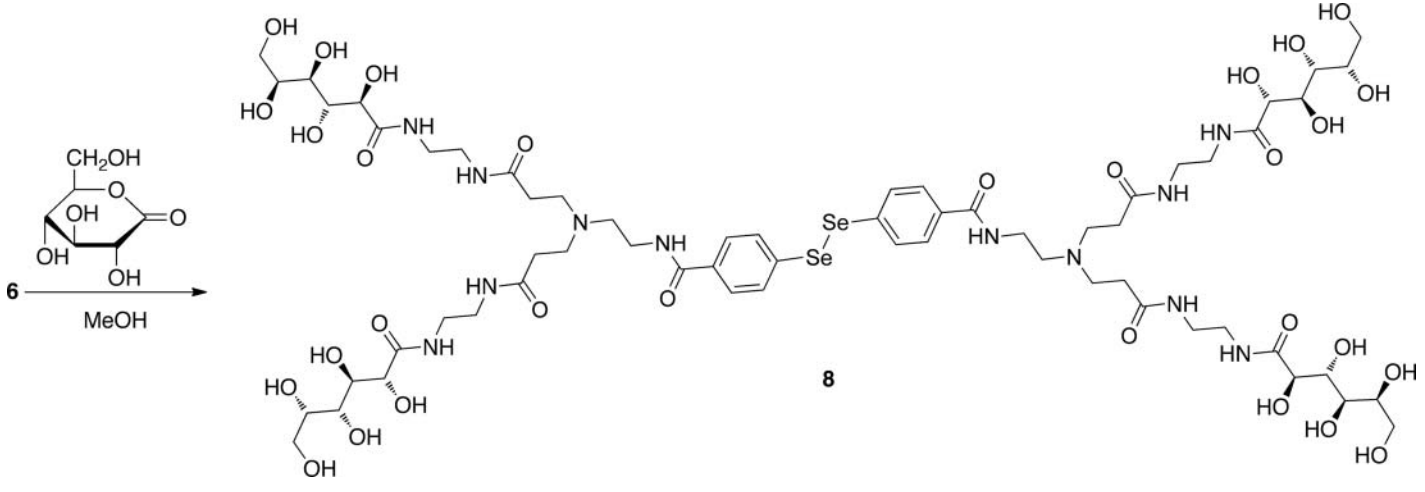


Figure 1 UV (top) and CD (bottom) spectra of 8 in H_2O at 20 °C.

effect of ester groups at the 4,4′-positions of diphenyl diselenide moiety. The MALDI-TOF MS spectra of dendrimers **5** and **7** clearly showed their parent peaks at m/z 832.07 and 1631.62, respectively. Those parent peaks and mass patterns were in good agreement with the calculated one.

The water-soluble dendrimer was prepared from G1.0 dendrimer **6**, which possesses four primary amine groups at the terminals. The linking of the sugars was achieved by amide formation.[20] We selected gluconamide groups as sugar chain moieties of the dendrimer at its terminals since gluconamide was known to form suprastructures, such as fibers[20a] and helices.[21] The thermal reaction of dendrimer **6** with glucono-δ-lactone in MeOH at 50°C for 2 d gave a dendrimer diselenide **8** (Scheme 3). The structure of **8** was determined by NMR spectra and MALDI-TOF MS. The IR spectra of **7** showed two absorptions assignable to the stretching bands of carbonyl groups at 1655 cm^{-1} and 1646 cm^{-1}. The IR spectra for the OH stretching of the sugar group was observed at 3366 cm^{-1}. The MALDI-TOF MS spectra of dendrimer **8** showed a parent peak at m/z 1654.06. It is notable that the dendrimer **8** is soluble in water. Saturated concentrations of **8** in 1 mL of H_2O are 137 mg at 20°C. Diselenide substituted with chiral alkyl groups exhibits Cotton effects within the diselenide chromophore region. The PhSe-SePh unit of the dendrimer **8** is expected



Scheme 3 Synthesis and structure of the chiral dendrimer diselenide **8**.

to be small, and rotatory strength of the 300 nm Cotton effect will contain substantial contributions from the chiral centers of gluconamide groups at the terminals. The circular dichroism (CD) spectrum in aqueous solution showed a positive Cotton effect at around 300 nm, as shown in Figure 1. The specific rotations of the synthesized dendrimer diselenide **7** were as follows: $[\alpha]_D$ +18.0° (c 1.002, H_2O). Although many chiral selenium compounds having chiral alkyl or amide groups have been reported, there is no report of glycoconjugate of chiral diselenide having a sugar as a chiral source.

CONCLUSION

In conclusion, we have successfully synthesized a novel poly(amidoamine) dendrimer having a diselenide unit at the core. The dendrimer bearing chiral units at the periphery was also synthesized from achiral poly(amidoamine) dendrimer diselenide. In the viewpoint of the wide utility and important role of selenium compounds in biochemical science and organic synthesis, further investigation on the reactivity and catalytic activity of newly obtained poly(amidoamine) dendrimer diselenides is currently in progress.

EXPERIMENTAL

All experiments were performed under a N_2 atmosphere unless otherwise noted. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{77}Se NMR (57 MHz) spectra were measured in $CDCl_3$ or DMSO-d_6 with JEOL JNM AL-300 spectrometer. ^{1}H and ^{13}C NMR chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta = 0$ ppm) and the ^{13}C resonance of the solvent ($CDCl_3$: $\delta = 77.2$ ppm, DMSO-d_6: $\delta = 39.5$ ppm). ^{77}Se NMR chemical shifts were referenced with diphenyldiselenide ($\delta = 470$ ppm) as an external standard. MALDI-TOF MS spectral data were obtained on a Bruker Daltonics AutoFLEX spectrometer. Electronic spectra were recorded on a Shimadzu UV-3150 spectrometer. Circular dichroism (CD) experiments were performed at 20°C on a Jasco J-720 spectropolarimeter (Jasco Spectroscopic Co. Ltd., Japan). All melting points were determined on a MEL-TEMP micro melting point apparatus and are uncorrected. Elemental analyses were carried out at the Parkin Elmer 2400II. The reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co. Ltd., or Aldrich Chemical Co. The reagents used as reaction solvents were further purified by general methods.

Synthesis of Methyl 4-Selenocyanatobenzoate (2)

A mixture of water (14 mL), methyl 4-aminobenzoate (1) (0.73 g, 4.8 mmol), and concentrated hydrochloric acid (12.0 N in H_2O, 0.86 mL, 27.6 mmol) was cooled to 0°C with NaCl/ice bath. An aqueous solution (2 mL) of $NaNO_2$ (0.33 g, 4.8 mmol) was added to the mixture at 0°C. After the solution was stirred for a few min, sodium acetate (1.33 g, 16.2 mmol) was added at 0°C. KSeCN (0.58 g, 4.00 mmol), and $NaHCO_3$ (0.10 g, 1.19 mmol) in water (2 mL) was added to the mixture at 0°C, then stirred for 30 min at this temperature. After the mixture was stirred at 55°C for 30 min, the mixture was extracted several times with $CHCl_3$. The organic layers were combined, washed with water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography (SiO_2, eluent: $CHCl_3$:hexane = 1:1) followed by recrystallization from hexane to give methyl 4-selenocyanatobenzoate (2) (571 mg, 2.38 mmol) as pale pink crystals in 60% yield.

Mp: 92–93°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.66 (d, 4H, $J = 6.5$ Hz), 8.04 (d, 4H, $J = 6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3 (q), 100.3 (s), 130.3 (d), 130.9 (d), 131.0 (s), 132.3 (s), 165.7 (s); Anal. Calcd for $C_9H_7NO_2Se$: C, 45.02; H, 2.94; N, 5.87 Found,; C, 45.32; H, 2.85; N, 5.65.

Synthesis of Bis[4-(methoxycarbonyl)phenyl]diselenide (3)[17]

A suspension of Et_2O (14 mL), an aqueous solution of 20% H_2SO_4, Zn powder (689 mg, 10.5 mmol), and methyl 4-selenocyanatobenzoate (2) (682 mg, 2.84 mmol) was stirred at 40°C for 50 min. The unconsumed Zn powder was removed by filtration, and the residue was evaporated. After extraction with $CHCl_3$ several times, and the organic layers were combined, washed with water, and then dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was recrystallized from MeOH to afford bis[4-(methoxycarbonyl)phenyl]diselenide (3) (565 mg, 1.32 mmol, 93% yield) as yellow crystals.

Mp: 114–115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 6H), 7.64 (d, 4H, $J = 8.0$ Hz), 7.91 (d, 4H, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1 (q), 129.3 (d), 130.2 (d), 130.1 (s) 136.4 (s), 166.4 (s); UV/Vis ($CHCl_3$) λ_{max} 275 nm ($\varepsilon = 5.0 \times 10^4$), Anal. Calcd for $C_{16}H_{14}O_4Se_2$: C, 44.88; H, 3.30; N, 0.00 Found; C, 44.97; H, 3.18; N, 0.08.

Synthesis of G0.5 Dendrimer Diselenide 5

A solution of bis(4-methoxycarbonyl phenyl) diselenides (3) (302 mg, 0.706 mmol) in methanol (16.9 mL) was added dropwise to ethylenediamine (16.9 mL, 281 mmol) at 0°C. The mixture was stirred at room temperature for 3 d. After the removal of the solvent and the reagent in vacuo, the residue was reprecipitated from a methanol/diethyl ether (2 mL/120 mL) solution to afford the dendrimer 4 (0.377 mg, 0.779 mmol), which was used for the following reaction without further purification. A mixture of 4 (0.377 mg, 0.779 mmol), methyl acrylate (2.82 mL, 31.2 mmol), and methanol (113 mL) was stirred at 45°C for 5 d. After removal of the solvent, the mixture was separated by column chromatography (SiO_2, eluent, ethyl acetate:methanol = 30:1) to afford the dendrimer 5 (560 mg, 0.676 mmol) as a yellow thick oil in 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (t, $J = 6.3$ Hz, 8H), 2.62 (t, $J = 5.4$ Hz, 4H), 2.74 (t, $J = 6.3$ Hz, 8H), 3.49–3.57 (m, 4H), 3.52 (s, 12 H), 7.29 (t, $J = 4.8$ Hz, 2H), 7.63 (d, $J = 8.1$ Hz, 4H), 7.79 (d, $J = 8.1$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5 (t), 37.3 (t), 48.8 (t), 51.5 (s), 52.8 (t), 128.0 (d), 130.6 (d), 134.1 (s), 134.2 (s), 166.4 (s), 173.1 (s); ^{77}Se NMR (57 MHz, $CDCl_3$) δ 470; IR (KBr) 1733 (C=O), 1647 (NHCO), 1533 (C=C, phenyl), 1436 (CH_2) cm^{-1}; UV/Vis ($CHCl_3$) λ_{max} 271 nm ($\varepsilon = 2.3 \times 10^4$), MALDI-TOF MS (matrix, dithranol) *m/z*: calcd for $C_{34}H_{46}N_4O_{10}{}^{80}Se_2$ 831.23 [MH$^+$], found 832.070 [MH$^+$]; Anal. Calcd for $C_{34}H_{46}N_4O_{10}Se_2$: C, 49.28; H, 5.60; N, 6.76 Found; C, 49.07, H, 5.70; N, 6.67.

Synthesis of G1.5 Dendrimer Diselenide 7

A solution of 5 (220 mg, 0.265 mmol) in methanol (28.7 mL) was added dropwise to ethylenediamine (14.4 mL, 212 mmol) at 0°C. The mixture was stirred at room temperature for 2 d. After removal of the solvent and the reagent in vacuo, the residue was reprecipitated from a methanol/diethyl ether (2 mL/120 mL) solution to afford the dendrimer 6 (249 mg,

0.265 mmol), which was used for following reaction without further purification. A mixture of 6 (249 mg, 0.265 mmol), methyl acrylate (2.0 mL, 21.7 mmol), and methanol (78.2 mL) was stirred at 45°C for 4 d. After the removal of the solvent, the residue was purified by silica gel column chromatography (SiO_2, eluent, chloroform:methanol = 18:1) and GPC to give the dendrimer 7 (364 mg, 0.223 mmol) as a yellow thick oil in 82% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36–2.44 (m, 32H), 2.67 (t, $J = 6.5$ Hz, 20H), 2.81 (t, $J = 5.0$ Hz, 8H), 3.20 (q, $J = 6.5$ Hz, 8H), 3.54–3.60 (m, 4H), 3.64 (s, 24H), 6.87 (s, 4H), 7.63 (d, $J = 8.5$ Hz, 4H), 7.86 (brs, 2H), 7.88 (d, $J = 8.5$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6 (t), 33.8 (t), 37.0 (t), 37.7 (t), 49.1 (t × 2), 51.6 (s), 52.5 (t), 52.8 (t), 128.3 (d), 130.3 (d), 131.0 (s), 134.1 (s), 166.3 (s), 172.3 (s), 173.0 (s); ^{77}Se NMR (57 MHz, $CDCl_3$) δ 467; IR (neat) 3407 (N-H), 2947 (C−H), 1735 (C=O), 1647 (C=O), 1637 (C=O), 1560 (C=C, phenyl), 1470 (CH_2), 1200 (O−C−O), 840 (C−H) cm^{-1}; UV/Vis ($CHCl_3$) λ_{max} 273 nm ($\varepsilon = 3.8 \times 10^4$), MALDI-TOF MS (matrix, dithranol) *m/z*: calcd for $C_{70}H_{110}N_{12}O_{22}{}^{80}Se_2$ 1631.62 [MH^+], found 1631.05 [MH^+].

Synthesis of Water-Soluble Dendrimer Diselenide 8

A solution of G1.0 dendrimer diselenide 6 (591 mg, 0.629 mmol) and glucono-δ-lactone (2.241 g, 12.6 mmol) in MeOH (134 mL) was heated at 50°C for 2 d. The mixture was recrystallized from the solution at 2°C to give water-soluble dendrimer diselenide 8 (684 mg, 0.414 mmol) as a yellow powder in 66% yield.

Mp 110°C (decomp); ^{1}H NMR (300 MHz, DMSO) δ 2.13(t, 8H, $J = 7.1$ Hz), 2.42–2.49 (m, 8H), 2.61 (t, 8H, $J = 7.2$ Hz), 3.03 (brs, 8H+4H), 3.09 (brs, 4H), 3.40 (brs, 10H), 3.48–3.55 (m, 6H), 3.84 (brs, 4H), 3.91 (brs, 4H), 4.29- 4.49 (m, 20H), 5.31-5.33 (m, 4H), 7.62-7.74 (m, 8H), 7.82 (brs, 8H), 8.28 (brs, 4H), Signals of amide units are not observed; ^{13}C NMR (75.5 MHz, DMSO) δ 33.5 (t), 37.3 (t), 38.5(t), 49.7(t), 52.3(t), 63.7(t), 70.5(d), 71.8(d), 72.6(d), 73.2(d), 73.8(d), 128.5(d), 130.5 (d), 133.8 (s), 134.1 (s), 165.8 (s), 172.1 (s), 173.2 (s); ^{77}Se NMR (57.3 MHz, DMSO) δ 460.7; IR (KBr) 3366 (NH and OH), 2945 (C−H), 1650 (C=O), 1556 (C=C, phenyl), 1434 (CH_2), 1262 (O−C−O), 1084 (C−O) cm^{-1}; MALDI-TOF MS (matrix, dithranol) *m/z:* calcd for $C_{62}H_{102}N_{12}O_{30}{}^{80}Se_2$ 1655.52 [MH^+], found 1655.07 [MH^+]. $[\alpha]_D^{20} = +17.9640$ (c 1.002. H_2O).

Circular Dichroism

An aqueous solution of the dendrimer diselenide 8 (46.4 μM) was recorded using a Jasco J-720 spectropolarimeter at 20°C. Spectrum was measured between 220 and 400 nm with a data pitch of 1.0 nm. The bandwidth was set to 5.0 nm, with a data scanning speed of 20 nm min^{-1} and a response time of 0.5 s. The path length was 10 mm in a demountable Spectrosil quartz cuvette.

Supplementary Data

Copy of ^{1}H, ^{13}C, and ^{77}Se NMR spectra for some compounds are available online in the Supporting Information.

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