Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Second-Generation Dendrons with an Orthogonal Functional Group at the Focal Point

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Published online: 27 Apr 2009.

To cite this article: Ravi Kumar Cheedarala, Vijaya Sunkara & Joon Won Park (2009) Facile Synthesis of Second-Generation Dendrons with an Orthogonal Functional Group at the Focal Point, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:11, 1966-1980, DOI: 10.1080/00397910802627076

To link to this article: http://dx.doi.org/10.1080/00397910802627076

Synthetic Communications®, 39: 1966–1980, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802627076

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Facile Synthesis of Second-Generation Dendrons with an Orthogonal Functional Group at the Focal Point

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Abstract: Facile synthesis of second-generation dendrons with an aldehyde, epoxy, or t-Boc group at the focal point and nine carboxylic acid groups at the periphery is reported. The scheme includes a coupling of the first-generation dendrons and a two-step, one-pot reaction that proceeds through a Boc deprotection and in situ conjugation at the focal point.

Keywords: Dendrons, deprotection, divergent, epoxy

INTRODUCTION

Dendrimers are monodispersed, repeatedly branched, and highly symmetric macromolecules and are objects of increasing interest because of their unique molecular architecture. They contain multiple functional groups that can be efficiently tailored to control their chemical and physical properties. Dendrons consist of a subgroup of dendrimers and feature multiple functional groups at the periphery and a single reactive group at the focal point. Their unique structures make it possible to graft dendrons to a surface, to another dendron,[1] or to another macromolecule.[2] The first dendrimers were synthesized divergently by

Received September 18, 2008.
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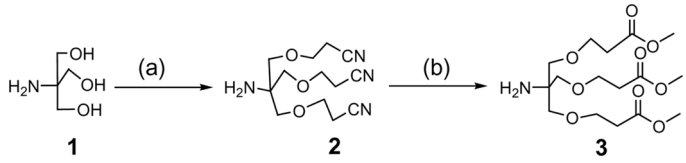
Buhleier et al.,[3] and a convergent synthesis was introduced by Hawker and Fréchet,[4] Divergent[5] and convergent[4,6] approaches have been explored actively since then. Repetitive protection–deprotection and purification processes are involved at each generation level.[7] Several strategies have been devised to expedite the stepwise activation/coupling sequences employed in both methods. Double-stage convergent,[8] double exponential growth,[9] and use of AB_n (usually $n \geq 4$) building blocks termed "hypermonomers"[10] have had success. Use of the orthogonal approach reduces the number of synthetic steps and allows high-generation dendrimers with a few transformations.[11]

During the past two decades, many types of dendrimers and dendrons have been designed, synthesized, and utilized in various fields.[12] They have been used for a wide range of biomedical and industrial applications, such as drug delivery,[13] gene therapy,[14] tissue repair,[15] and solubility enhancers.[16] Recently, applications of dendrons as surface functionalizing agents for silica,[17] glass,[18] gold,[19] poly(dimethylsilaxoane),[20] and carbon nanotubes[21] have been investigated by our group[17,21] and others.[22] In particular, (polyether) amide dendrimers[23] have demonstrated great promise for a variety of biomedical applications. Interestingly, this class of dendrons shows a great number of favorable properties.

Our goal is to establish a facile divergent route leading to molecular building components that will provide a nanoscale-controlled structure on a surface upon self-assembly. Previously, we utilized certain dendrons for the surface modification and successfully applied the modified surface for fabricating DNA microarrays.[24] With this background, the research has been extended to prepare dendrons with a new class of focal point. Herein, we describe a one-pot synthesis of a series of second-generation dendrons with an aldehyde, epoxy, or t-Boc functional group at the focal point and nine carboxylic acid groups at the periphery, which can be assembled on the hydroxylated surface, while biomolecule attachment at the focal point is amenable.[25]

RESULTS AND DISCUSSION

We started our work with monomer **3** [tris(2-methoxycarbonylethoxymethyl)aminomethane], widely known as Lin's amine.[26] The trimethyl ester **3** was prepared in two steps as shown in Scheme 1. The first step was Michael addition of acrylonitrile to tris(hydroxymethyl)amino methane (**1**), affording the desired trinitrile **2** as a pale yellow oil. Trinitrile **2**, when being refluxed in anhydrous methanol saturated with dry HCl, gave the corresponding trimethyl ester as the hydrochloride salt,

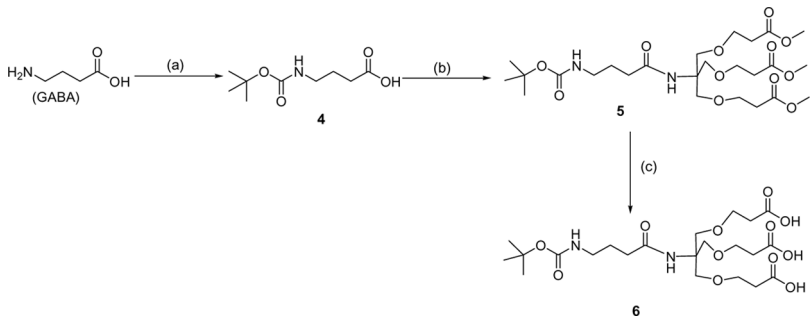


Scheme 1. Reagents and conditions: (a) acrylonitrile, aq. KOH, 1,4-dioxane, rt, 24 h; and (b) dry HCl, methanol, 4 h, reflux.

which was neutralized by treatment with $NaHCO_3$ to produce free amine **3** in 80% yield.

Monomer **3** is a useful building block for the growth of higher-generation dendrons via an iterative repeat of EDC (or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) and HOBt (or 1-hydroxybenzotriazole) mediated coupling and subsequent saponification. The EDC/HOBt coupling reaction was employed because the reaction condition did not adversely affect the functionalities present within both the precursors and the product and the side reactions were minimal.

On the other hand, another precursor, triacid **6**, was prepared in three steps (Scheme 2), starting from 4-aminobutyric acid (GABA). Protection of the amine group of GABA with di-tert-butyl dicarbonate [$(Boc)_2O$] in the presence of NaOH in 1,4-dioxane produced Boc-GABA **4**.[27] Coupling of the resulting acid **4** with trimethyl ester **3** in the presence of EDC and HOBt in methylene chloride afforded t-Boc-GABA-trimethylester **5** in 86% yield. Hydrolysis of the methyl ester in aq. NaOH/acetone at room temperature afforded the t-Boc-blocked triacid **6** as a stable white solid in 94% yield.

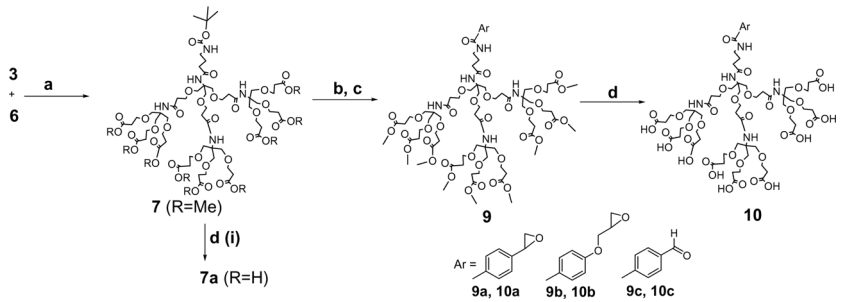


Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, 1,4-dioxane, 1 N NaOH, 12 h; (b) 3 (1.2 equiv.), EDC, HOBt, methylene chloride, rt, 24 h; and (c) aq. Acetone, NaOH, rt, 12 h.

In the next step, trimethyl ester **3** was coupled with triacid **6** under the same coupling condition to produce t-Boc protected methyl ester **7** as a colorless oil in 80% yield. Subsequently, hydrolysis of **7** in aq. NaOH/acetone at room temperature and under controlled acidification gave the t-Boc-blocked nona-acid **7a** in 77% yield. It was observed that t-Boc group was deprotected when conc. HCl was used for the acidification. The unwanted side reaction can be avoided by adding chilled aq. HCl (5% v/v) at a temperature lower than 5°C. The progress of the reaction was monitored with thin-layer chromatography (TLC), and the structure of compound **7** was confirmed by ^{1}H, ^{13}C NMR, and infrared (IR) spectroscopy as well as matrix-assisted laser desorption ionization–mass spectrometry (MALDI-MS).

The second-generation dendrons with an epoxy functional group at the focal point were prepared through the deprotection and the coupling reaction with the relevant benzoic acids (Scheme 3). For this end, the Boc nona-methyl ester **7** was deprotected by treatment with trifluoroacetic acid (TFA) at 0°C in methylene chloride, resulting in the reactive primary amine group. Addition of 4-(oxiran-2-yl)benzoic acid (**8a**) and the coupling reagents (i.e., EDC and HOBt) dissolved in methylene chloride to the reaction solution gave the second-generation dendron **9a**[28] in 75% yield. The approach proved to be efficient and applicable to other cases. Therefore, two analogous benzoic acids [i.e., 4-(oxiran-2-ylmethoxy)benzoic acid (**8b**) and 4-formylbenzoic acid (**8c**)] were used to obtain the corresponding dendrons **9b** and **9c** in 80% and 78% yields, respectively. The employed benzoic acids **8a** and **8b** were prepared from their corresponding methyl esters.[28,29]

When the saponification of the ester groups of **9a** and **9b** was carried out in 50% aq. acetone at room temperature for 12 h in the presence of 3



Scheme 3. Reagents and conditions: (a) EDC, HOBt, methylene chloride, rt, 24 h; (b) i, TFA, methylene chloride, 0°C, 1.5 h; ii, Et_3N; (c) **8**, EDC, HOBt, methylene chloride, rt, 24 h, and (d), i, aq. acetone, NaOH, rt, 12 h; ii, degassed methanol, NaOH, rt, 4 h.

equiv. of NaOH, **9a** and **9b** afforded the corresponding acids **10a** and **10b** in 86% and 84% yields, respectively. Under these conditions, by-products were not observable with TLC analysis. In the case of **9c**, it was thought that hydrolysis of methyl ester in the presence of the aldehyde could result in the formation of Cannizaro products. As a control reaction, hydrolysis of 4-formylmethylbenzoate was carried out under these reaction conditions, and a mixture of 4-formylbenzoic acid (10%), terepthalic acid (41%), and 4-hydroxymethyl benzoic acid (40%) was obtained. In degassed methanol, the hydrolysis resulted in the same mixture, but the formation of 4-formylbenzoic acid was dominant, and the isolation yield was 80%. The last condition was employed for the hydrolysis of **9c** with 3 equiv. of NaOH at room temperature for 4 h, and the aldehyde-9-acid **10c** was isolated in 65% yield.

The structure of the final dendrons was confirmed by IR, NMR, and MALDI-MS spectroscopy. The IR spectra of **10** showed strong absorption peaks at 3300 cm^{-1} for OH, 1728 cm^{-1} for CO of the carboxylic acid, and 1650–1630 cm^{-1} for CO of the amide group.

In ^1H NMR spectra, the assignment of the epoxy, aldehyde, amide, and carboxylic acid functional group was straightforward. In all second generation dendron (**10**) cases, the amide proton was observed between 5.0 ppm and 7.5 ppm as a broad resonance, and the amide proton attached with the aryl ring appeared from 7.7 ppm to 8.5 ppm. For **10a**, the resonances as two doublets of the doublet (dd) at 2.9 ppm and 3.2 ppm for epoxy CH_2 and as a quartet at 3.9 ppm for epoxy CH were observed. In the case of **10b**, signals were recorded as two dds at 3.93 ppm and 4.3 ppm for the exocyclic methylene group, and the signals for the epoxy ring appeared as two dds at 2.6 ppm and 2.7 ppm for CH_2 and a multiplet at 3.1 ppm for CH. O- and *m*-protons on the phenyl ring were observed at 7.3–7.9 ppm as two doublets. In the case of **10c**, a signal at 9.96 ppm as a singlet for the aldehyde proton, a broad signal at 7.75–7.72 ppm for the amide proton attached to the aryl ring, and the signals at 8.1–7.89 ppm as doublet for the aromatic ring protons were observed.

MALDI-TOF-MS was used to confirm the molecular weight of the target dendrons. The spectra showed the expected molecular ion peaks ($[M + Na]^+$) at 1548 for **10a**, 1578 for **10b**, and 1534 for **10c**.

EXPERIMENTAL

General

^1H NMR spectra were recorded on a 300-MHz Bruker NMR spectrometer. Chemical shifts are reported in parts per million

(ppm) using tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were proton decoupled and recorded on a 300-MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. IR spectra were recorded on a Perkin-Elmer Fourier transform–infrared (FT-IR) system and MALDI MS spectra were obtained from Applied Biosystems 4700 proteomics analyzer with TOF/TOF^{TM} optics. TLC was performed on silica plates with F-254 indicator, and the visualization was accomplished by ultraviolet (UV) lamp or an iodine chamber. All reagents and chemicals were obtained from commercial sources and used as received, unless otherwise mentioned.

Synthesis of Boc-GABA-trimethylester (5)

A solution of tris[((methoxycarbonyl)ethoxy)methyl]-aminomethane (**3**, 2.2 g, 5.8 mmol) in MC (10 ml) was added to a solution of 4-(*tert*-butyloxycarbonylamino)-butyric acid (**4**, 1.0 g, 4.9 mM), EDC (1.4 g, 7.3 mmol), and HOBt (0.67 g, 4.9 mmol) dissolved in methylene chloride (MC) (20 mL), and stirred at rt for 24 h. After removal of the solvent at reduced pressure, the residue was dissolved in ethyl acetate (50 mL), washed with water (2×25 mL), chilled 5% HCl (2×25 mL), water (1×25 mL), sat. $NaHCO_3$ solution (3×25 mL), water (2×25 mL), and brine (25 mL). The organic layer was then dried over $MgSO_4$, and the solvent was evaporated to get **5** (2.4 g, 86%).

^1H NMR ($CDCl_3$, 300 MHz), **5**: δ 6.36 (s, CON*H*C, 1H), 4.98 (t, Boc-N*H*, 1H), 3.71–3.69 (m, NHCCH_2OCH_2CH$_2$CO, OCH_3, 21H), 3.16–3.14 (q, NHCH_2, 2H), 2.62–2.53 (t, OCH$_2$CH_2CO, 6H), 2.22–2.18 (t, CH$_2$CH$_2$CH_2CONH, 2H), 1.83–1.78 (m, CH$_2$CH_2CH$_2$, 2H), 1.43 (s, Boc, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz), **5**: δ 173 (CH$_2$*C*ONH), 172 (CH$_2$*C*OO), 156 (*C*ONH), 79.0 [(CH$_3$)$_3$*C*OCONH], 69.1 (NHC*C*H$_2$O), 66.7 (NHCCH$_2$O*C*H$_2$), 51.7 (CH$_2$COO*C*H$_3$), 39.8 (CONH*C*H$_2$), 34.8 (OCH$_2$*C*H$_2$COOMe), 34.2 (CH$_2$*C*H$_2$CONH), 28.4 [(*C*H$_3$)$_3$COCO], 25.9 (NHCH$_2$*C*H$_2$CH$_2$CO).

Synthesis of Boc-GABA-triacid (6)

Boc-GABA-trimethyl ester **5** (1 g, 1.7 mmol) was dissolved in a mixture of acetone (40 mL) and 0.4 N NaOH (40 mL) and stirred at rt for 12 h. After completion of the reaction, the reaction mixture was concentrated, and the aqueous solution was washed with ethyl acetate (2×50 mL) and cooled in an ice bath. The pH was adjusted to 3.5, and the resultant

product was extracted with ethyl acetate (4×50 mL). The combined organic layer was dried (anh. $MgSO_4$) and evaporated. The crude product thus obtained was recrystallized in an ethyl acetate–hexane mixture to get pure **6** (0.87 g, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz), **6**: δ 8.98 (br s, OH, 3H), 6.92 (s, CONHC, 1H), 6.54–6.46 (t, CONH, 1H), 3.77–3.66 (t, $NHCCH_2OCH_2CH_2CO$, 12H), 3.11 (q, $NHCH_2$, 2H), 2.6–2.5 (t, OCH_2CH_2CO, 6H), 2.24–2.20 (t, $CH_2CH_2CH_2CONH$, 2H), 1.84–1.77 (m, $CH_2CH_2CH_2$, 2H), 1.44 (s, Boc, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz), **6**: δ 178.3 (CH_2CH_2COOH), 174.0 (CH_2CH_2CONH), 156.9 (OCONH), 79.9 [$(CH_3)_3COCONH$], 69.4 ($NHCCH_2O$), 65.7 ($NHCCH_2OCH_2$), 40.2 ($CONHCH_2$), 34.6 (OCH_2CH_2COOH), 31.2 ($NHCH_2CH_2CH_2CO$), 28.3 [$(CH_3)_3COCO$], 26.3 ($NHCH_2CH_2CH_2CO$).

Synthesis of Boc-GABA-nonamethylester (7)

A solution of **3** (1.1 g, 2.9 mmol) in MC (10 mL) was added to a solution of triacid **6** (0.4 g, 0.76 mmol), EDC (0.57 g, 2.9 mmol), and HOBt (0.31 g, 2.3 mmol) dissolved in MC (10 mL) and stirred at rt for 24 h. The previous general procedure was followed for the isolation of compound **7** (0.98 g, 80%).

IR (neat, cm^{-1}), 7: 3300, 2877, 1739, 1673, 1526, 1199, 1113. ^{1}H NMR ($CDCl_3$, 300 MHz), **7**: δ 6.54 (s, CONHC, 1H), 6.1 (br s, OCH_2CH_2CONH, 3H), 5.2 (t, Boc-NH,1H), 3.69–3.66 (m, $CH_2OCH_2CH_2CONH$ $CCH_2OCH_2CH_2COOCH_3$, 75H), 3.15 (q, Boc-$NHCH_2CH_2CH_2$, 2H), 2.56–2.52 (t, $OCH_2CH_2COOCH_3$, 18H), 2.42–2.40 (t, $CONHCCH_2$-OCH_2CH_2, 6H), 2.25 (t, $NHCH_2CH_2CH_2CO$, 2H), 1.78 (m, $NHCH_2CH_2CH_2CO$, 2H), 1.42 (s, Boc, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz), **7**: δ 172 (CH_2CONH), 171 (CH_2COO), 170.4 (CH_2CONHC-CH_2O), 156 (CONH), 69.1 ($NHCCH_2O$), 67.5 ($NHCCH_2OCH_2$), 66.7 ($CONHCCH_2OCH_2$), 59.7 ($CONHCCH_2OCH_2$), 51.6 (CH_2COOCH_3), 37.2 ($CONHCH_2$), 34.7 (OCH_2CH_2COOMe), 28.4 [$(CH_3)_3COCO$]. MALDI-TOF-MS, **7**: $[M + Na]^+ = 1628$.

Synthesis of Boc-GABA-nona-acid (7a)

Boc-GABA-nonamethylester **7** (0.7 g, 0.43 mmol) was dissolved in a mixture of acetone (15 mL) and 0.4 N NaOH (15 mL) and stirred at rt for 12 h. After completion of the reaction, the reaction mixture was concentrated. The aqueous solution was washed with ethyl acetate (2×20 mL) and cooled in an ice bath, and pH was adjusted to 3.5.

The resulting product was extracted with ethyl acetate (2×50 mL). The combined organic layer was dried (anh. $MgSO_4$) and evaporated to dryness. The crude product thus obtained was recrystallized in an ethyl acetate–hexane mixture to get pure **7a** (0.5 g, 77%).

IR (neat, cm^{-1}), **7a**: 3300, 2925, 1716, 1670, 1408, 1179, 1117. ^1H NMR (CD_3OD, 300 MHz), **7a**: δ 7.74–7.71 (t, CON*H*CH_2CH_2, CON*H*C, 1H), 7.49–7.46 (br s, CH_2CONH, 1H), 7.33–7.31 (br s, OCH_2 CH_2CONH, 3H), 3.77–3.67 (m, $CH_2OCH_2CH_2CONHCCH_2OCH_2CH_2$-COOH, 48H), 3.05 (q, Boc-NHC$H_2CH_2CH_2$, 2H), 2.78–2.74 (t, CON-HCC$H_2OCH_2CH_2$, 6H), 2.54–2.51 (t, $OCH_2CH_2COOCH_3$, 18H), 2.25 (t, $NHCH_2CH_2CH_2CO$, 2H), 1.74 (m, $NHCH_2CH_2CH_2CO$, 2H), 1.43 (s, Boc, 9H). MALDI-TOF-MS, **7a**: $[M + Na]^+ = 1502$.

Synthesis of 8

Methyl 4-(oxiran-2-yl) benzoate[28] or methyl 4-(oxiran-2-ylmethoxy)-benzoate[29] (1.0 mmol) were dissolved in mixture of acetone (8 mL) and 0.4 N NaOH (8 mL) and stirred at rt for 2 h. After completion of the reaction, the mixture was concentrated. The aqueous solution was washed with ethyl acetate (2×10 mL) and cooled in an ice bath, and pH was adjusted to 4. The resultant product was extracted with ethyl acetate (3×25 mL). The combined organic layer was dried (anh. $MgSO_4$) and evaporated to dryness. The crude product thus obtained was recrystallized in an ethyl acetate–hexane mixture to get pure **8** (**8a**, 0.138 g, 85%, and **8b**, 0.135 g, 70%).

^1H NMR ($CDCl_3$, 300 MHz), **8a**: δ 10.2 (br s, COO*H*, 1H), 8.1 (d, C_6H_4, 2H), 7.4 (d, C_6H_4, 2H), 3.94–3.92 (q, C*H*CH_2O, 1H, epoxy), 3.22–3.19 (dd, CHCH_2O, 1H, epoxy), 2.81–2.78 (dd, CHCH_2O, 1H, epoxy).

^1H NMR ($CDCl_3$, 300 MHz), **8b**: δ 12.1 (br s, COO*H*, 1H), 8.0 (d, C_6H_4, 2H), 6.9 (d, C_6H_4, 2H), 4.3 (dd, $C_6H_4OCH_2CH$, 1H), 4.0 (dd, $C_6H_4OCH_2CH$, 1H), 3.4 (m, C*H*CH_2O, 1H, epoxy), 2.9 (dd, CHCH_2O, 1H, epoxy), 2.7 (dd, CHCH_2O, 1H, epoxy).

Preparation of 9

Compound **7** (0.24 g, 0.15 mmol) was stirred in a solution of trifluoroacetic acid (1.5 mL) in dry CH_2Cl_2 (1.5 mL) for 1.5 h at 0°C. The reaction mixture was basified with excess Et_3N (pH 12) to generate free amine ester. In another flask, HOBt (20 mg, 0.15 mmol) and EDC (31 mg, 0.16 mmol) were added to the corresponding benzoic acid (**8**, 0.13 mmol)

in 5 mL of dry methylene chloride at room temperature. After activation of carboxylic acid in 20 min, the reagent mixture was added to the reaction flask containing free amine, and the reaction mixture was stirred under N_2 for 24 h. After removal of the solvent at reduced pressure, the residue was dissolved in ethyl acetate (50 mL) washed with water (2×25 mL), chilled 5% HCl (2×25 mL), water (1×25 mL), sat. $NaHCO_3$ solution (3×25 mL), water (2×25 mL), and brine (25 mL). The organic layer was then dried over $MgSO_4$, and the solvent was evaporated to get compound **9**. Yields: **9a**, 0.16 g (75%); **9b**, 0.18 g (80%); **9c**, 0.17 g (78%).

^{1}H NMR ($CDCl_3$, 300 MHz), **9a**: δ 7.87–7.84 (d, C_6H_4, 2H), 7.79–7.73 (t, CON*H*$CH_2CH_2CH_2$, 1H), 7.33–7.31 (d, C_6H_4, 2H), 6.76 (br s, CON-*H*CCH_2O, 1H), 6.1 (br s, OCH_2CH_2CON*H*, 3H), 3.90 (q, C*H*CH_2O, 1H, epoxy), 3.69–3.67 (m, C*H*$_2$OC*H*$_2$CH$_2$CONHCC*H*$_2$OC*H*$_2$CH$_2$CO-OC*H*$_3$, 75H), 3.5–3.48 (t, CONHC*H*$_2$CH$_2$CH$_2$, 2H), 3.18 (dd, CHC*H*$_2$O, 1H, epoxy), 2.8 (dd, CHC*H*$_2$O, 1H, epoxy), 2.56–2.52 (t, OCH$_2$C*H*$_2$CO, 18H), 2.42–2.40 (t, CONHCCH$_2$OCH$_2$C*H*$_2$, 6H), 2.05–2.04 (t, NHCH$_2$CH$_2$C*H*$_2$CO, 2H), 1.97–1.95 (m, CONH CH$_2$C*H*$_2$CH$_2$, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz), **9a**: δ 173.5 (CH$_2$*CO*NH), 172.1 (CH$_2$*C*OOCH$_3$), 170.4 (CH$_2$*CO*NHCCH$_2$O), 166.9 (*CO*N*H*CH$_2$CH$_2$), 140.8 (C_6H_4), 134.5 (C_6H_4), 127.1 (C_6H_4), 125.5 (C_6H_4), 69 (NHC*C*H$_2$O), 67.4 (CONHCCH$_2$O*C*H$_2$), 66.7 (CONHCCH$_2$O*C*H$_2$), 59.9 (CONH*C*CH$_2$OCH$_2$), 51.9 (*C*HCH$_2$O, epoxy), 51.6 (CH$_2$OCH$_2$CH$_2$COO*C*H$_3$), 51.2 (CH*C*H$_2$O, epoxy), 39.8 (CONH*C*H$_2$CH$_2$CH$_2$), 37.1 (CONHCH$_2$CH$_2$*C*H$_2$CONH), 34.8 (CH$_2$OCH$_2$*C*H$_2$COOCH$_3$), 24.7 (CONHCH$_2$*C*H$_2$CH$_2$CONH).

^{1}H NMR ($CDCl_3$, 300 MHz), **9b**: δ 7.84–7.82 (d, C_6H_4, 2H), 7.54 (t, CON*H*$CH_2CH_2CH_2$, 1H), 6.94–6.92 (d, C_6H_4, 2H), 6.74 (br s, CON-*H*CCH_2O, 1H), 6.15 (br s, OCH_2CH_2CON*H*, 3H), 4.30–4.27 (dd, $C_6H_4OCH_2CH$, 1H), 3.98–3.95 (dd, $C_6H_4OCH_2CH$, 1H), 3.76–3.67 (m, C*H*$_2$OC*H*$_2$CH$_2$CONHCC*H*$_2$OC*H*$_2$CH$_2$COOC*H*$_3$, 75H), 3.5–3.48 (q, CONHC*H*$_2$CH$_2$CH$_2$, 2H), 3.2–3.1 (m, C*H*CH$_2$O, 1H, epoxy), 2.92–2.91 (dd, CHC*H*$_2$O, 1H, epoxy), 2.77 (dd, CHC*H*$_2$O, 1H, epoxy), 2.54 (t, OCH$_2$C*H*$_2$CO, 18H), 2.40 (t, CONHCCH$_2$OCH$_2$C*H*$_2$, 6H), 1.95 (t, NHCH$_2$CH$_2$C*H*$_2$CO, 2H), 1.73 (m, CONH CH$_2$C*H*$_2$CH$_2$, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz), **9b**: δ 173.5 (CH$_2$*CO*NH), 172 (CH$_2$*C*OOCH$_3$), 171 (CH$_2$*CO*NHCCH$_2$O), 166.8 (*CO*N*H*CH$_2$CH$_2$), 160 (C_6H_4, C1), 129 (C_6H_4, C3, C5), 127 (C_6H_4, C4), 114 (C_6H_4, C2, C6), 69 (NHC*C*H$_2$O), 68.8 ($C_6H_4OCH_2CH$), 67 (CONHCCH$_2$O*C*H$_2$), 66.7 (CONHCCH$_2$O*C*H$_2$), 59.9 (CONH*C*CH$_2$OCH$_2$), 51.6 (CH$_2$OCH$_2$CH$_2$COO*C*H$_3$), 49.9 (*C*HCH$_2$O, epoxy), 44.6 (CH*C*H$_2$O, epoxy), 39.7 (CONH*C*H$_2$CH$_2$CH$_2$), 37.1 (CONHCH$_2$CH$_2$*C*H$_2$CONH), 34.6 (CH$_2$OCH$_2$*C*H$_2$COOCH$_3$), 24.8 (CONHCH$_2$*C*H$_2$CH$_2$CONH).

^{1}H NMR ($CDCl_3$, 300 MHz), **9c**: δ 10.1 (s, C_6H_4CHO, 1H), 8.13 (br s, $CONHCH_2CH_2CH_2$, 1H), 8.07–8.05 (d, C_6H_4, 2H), 7.95–7.92 (d, C_6H_4, 2H), 6.8 (br s, $CONHCCH_2O$, 1H), 6.1 (br s, OCH_2CH_2CONH, 3H), 3.68–3.65 (m, $CH_2OCH_2CH_2CONHCCH_2OCH_2CH_2COOCH_3$, 75H), 3.55–3.51 (q, $CONHCH_2CH_2CH_2$, 2H), 2.56–2.52 (t, OCH_2-CH_2CO, 18H), 2.42–2.32 (t, $CONHCCH_2OCH_2CH_2$, 6H), 2.0–1.88 (t, $CONHCH_2CH_2CH_2$, 2H), 1.68 (m, CONH $CH_2CH_2CH_2$, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz), **9c**: δ 191 (C_6H_4CHO), 173.7 (CH_2CONH), 172 (CH_2COOCH_3), 171.1 ($CH_2CONHCCH_2O$), 166.2 ($CONHCH_2CH_2$), 139.9 (C_6H_4), 137.9 (C_6H_4), 129.5 (C_6H_4), 127.9 (C_6H_4), 69.09 ($NHCCH_2O$), 67.5 ($CONHCCH_2OCH_2$), 66.7 ($CONHCCH_2OCH_2$), 59.9 ($CONHCCH_2OCH_2$), 51.6 ($CH_2OCH_2CH_2COOCH_3$), 40.0 ($CONHCH_2CH_2CH_2$), 37.0 ($CONHCH_2CH_2CH_2CONH$), 34.6 ($CH_2OCH_2CH_2COOCH_3$), 24.5 ($CONHCH_2CH_2CH_2CONH$).

Preparation of 10

The nona-ester **9** (0.09 mmol) was stirred in 20 mL of acetone and 20 mL 0.4 N NaOH mixture (1:1, 3 equiv.) for 12 h at room temperature. After removal of acetone at reduced pressure, the aqueous layer was acidified with 1 N HCl until pH reached 3.5. The resultant nona-acid **10** was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and the solvent was removed by evaporation. The crude product was purified by recrystallization in methanol and ethyl acetate to obtain a pale yellow solid, **10**. Yields: **10a**, 0.12 g (86%); **10b**, 0.12 g (84%).

FT-IR (neat, cm^{-1}), **10a**: 2944, 2910, 1727, 1654, 1634, 1631, 1544, 1192, 1111. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.2 (br s, $COOH$, 9H), 8.45–8.42 (t, $CONHCH_2CH_2CH_2$, 1H), 7.87–7.84 (d, C_6H_4, 2H), 7.37–7.34 (d, C_6H_4, 2H), 7.1 (br s, $CONHCCH_2OCH_2CH_2CONH$, 4H), 3.98 (q, $CHCH_2O$, 1H, epoxy), 3.57–3.54 (m, $CH_2OCH_2CH_2CONHC$-CH_2OCH_2-CH_2, 48H), 3.48 (q, $CONHCH_2CH_2CH_2$, 2H), 3.14 (dd, $CHCH_2O$, 1H, epoxy), 2.8 (dd, $CHCH_2O$, 1H, epoxy), 2.43–2.39 (t, $CONHCCH_2OCH_2CH_2COOH$, 18H), 2.43–2.39 (t, $CONHCCH_2O$-CH_2CH_2, 6H), 2.19–2.17 (t, CONH $CH_2CH_2CH_2$, 2H), 2.1 (m, CONH $CH_2CH_2CH_2$, 2H). ^{13}C NMR (CD_3OD, 300 MHz): δ 175.8 (CH_2COOH), 174 ($CONH$), 158.6 ($CONHCH_2CH_2$), 132 (C_6H_4), 130 (C_6H_4), 129 (C_6H_4), 70, 68.8 ($NHCCH_2O$), 68.3, 68 ($CONHCCH_2OCH_2$), 64 ($CHCH_2O$, epoxy), 61.5 ($CONHCCH_2CH_2O$), 46.8 ($CHCH_2O$, epoxy), 41.3 ($CONHCH_2CH_2CH_2$), 38 (OCH_2CH_2CONH), 36 ($CH_2OCH_2CH_2$-$COOH$), 35 ($CONHCH_2CH_2CH_2CO$), 27 ($CONHCH_2CH_2CH_2CO$). MALDI-TOF-MS: $[M + Na]^+ = 1548$.

IR (neat, cm^{-1}), **10b**: 2944, 2912, 1728, 1654, 1632, 1631, 1544, 1185. ^1H NMR (DMSO-d_6, 300 MHz): δ 12.1 (br s, COO*H*, 9H), 8.32 (t, CON*H*$CH_2CH_2CH_2$, 1H), 7.81–7.78 (d, C_6H_4, 2H), 7.54 (t, CON-*H*$CH_2CH_2CH_2$, 1H), 6.99–6.96 (d, C_6H_4, 2H), 5.1 (br s, OCH_2CH_2-CON*H*, 3H), 4.3 (dd, $C_6H_4OCH_2CH$, 1H), 3.93 (dd, $C_6H_4OCH_2CH$, 1H), 3.54–3.50 (m, $CH_2OCH_2CH_2CONHCCH_2OCH_2CH_2COOH$, 48H), 3.2 (q, $CONHCH_2CH_2CH_2$, 2H), 3.1 (m, $CHCH_2O$, 1H, epoxy), 2.7 (dd, $CHCH_2O$, 1H, epoxy), 2.6 (dd, $CHCH_2O$, 1H, epoxy), 2.50 (t, OCH_2CH_2CO, 18H), 2.40 (t, $CONHCCH_2OCH_2CH_2$, 6H), 2.26 (t, $NHCH_2CH_2CH_2CO$, 2H), 1.97 (m, CONH $CH_2CH_2CH_2$, 2H). MALDI-TOF-MS: $[M + Na]^+ = 1578$.

Preparation of 10c

NaOH (0.067 g, 1.67 mmol, 3.1 equiv.) was added to a solution of **9c** (0.1 g, 0.06 mmol) in 4 mL of degassed methanol and stirred for 4 h at room temperature. After removal of methanol at reduced pressure, water was added to the residue, and the aqueous layer was acidified. The product **10c** was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and then evaporated to get the crude product. The crude product was isolated as a white solid after recrystallization in methanol and ethyl acetate. Yield: 0.059 g (65%).

FT-IR (neat, cm^{-1}), **10c**: 2925, 2912, 1728, 1654, 1632, 1631, 1545, 1185, 1112. ^1H NMR (CD_3OD, 300 MHz): δ 9.96 (s, C_6H_4CHO, 1H), 8.1–7.89 (d, C_6H_4, 4H), 7.75–7.71 (t, NH, 1H), 7.48–7.44 (s, NH, 3H), 5.4 (s, NH, 1H), 3.6–3.5 (m, $CH_2OCH_2CH_2CONHCCH_2OCH_2$-$CH_2COOH$, 48H), 3.4 (q, $CONHCH_2CH_2CH_2$, 2H), 2.45–2.40 (t, OCH_2CH_2CO, 18H), 2.32 (t, $CONHCCH_2OCH_2CH_2$, 6H), 1.8 (t, $CONHCH_2CH_2CH_2$, 2H), 1.7 (m, $CONHCH_2CH_2CH_2$, 2H). ^{13}C NMR (CD_3OD, 300 MHz): δ 193 (C_6H_4CHO), 175 (CH_2COOH), 174 (*C*ONH), 139 (C_6H_4), 130.7 (C_6H_4), 129.6 (C_6H_4), 128 (C_6H_4), 127 (C_6H_4), 70.09 ($NHCCH_2O$), 69.7 ($CONHCCH_2OCH_2$), 68.8 (CON-$HCCH_2OCH_2$), 58.8 ($CONHCCH_2OCH_2$), 40.5 ($CONHCH_2CH_2CH_2$), 38.09 (OCH_2CH_2CONH), 35.9 ($CH_2OCH_2CH_2COOH$), 30.7 (CON-$HCH_2CH_2CH_2CO$), 25.8 ($CONHCH_2CH_2CH_2CO$). MALDI-TOF-MS: $[M + Na]^+ = 1534$.

CONCLUSION

In conclusion, we report a facile method for the preparation of (polyether) amide dendrons by the divergent method. A relatively pure form

of the dendrons was prepared without going through the column chromatography step. The approach is synthetically convenient and saves time. Also, the scheme can be applied for the preparation of dendrons with various functional groups at the focal point in a one-pot, two-step reaction. Exploration of this approach can be utilized to allow facile synthesis of various higher-generation dendrons substituted with various functional groups at the focal point. All the new dendrons will be of potential use in surface modifications and drug delivery.

ACKNOWLEDGMENTS

We are grateful for financial support from the Korea Research Foundation (KRF-2004-005-C00007). We thank Prof. Young Ho Rhee for his valuable suggestions.

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