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An Improved Synthesis of a Trifurcated Newkome-Type Monomer and Orthogonally Protected Two-Generation Dendrons

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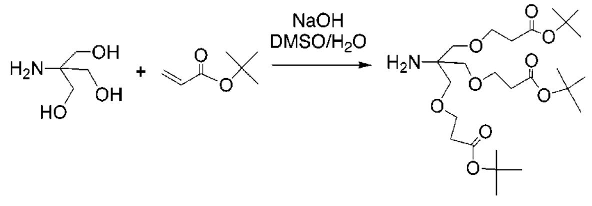
Abstract: The one-step synthesis of amino-polyether tri-*tert*-butyl ester monomer **2**, by condensation of TRIS with *tert*-butyl acrylate, is reported. The nitrogen of the monomer can be protected with a Cbz group; subsequent removal of the *tert*-butyl esters with formic acid affords a triacid that is coupled to three monomers to afford an orthogonally protected two-generation, trifurcated polyether−polyamide dendron. The Cbz protecting group may be removed from the second-generation dendron without disturbing the tert-butyl esters of the periphery.

Dendrimers are highly branched polymers synthesized in an iterative manner that possess interesting physical and topological properties.[1] In the past decade, the study of dendrimers has attracted great interest. These polymers offer the architectural component for the design and the synthesis of functionalized macromolecules, which are capable of interacting with other molecules at specific sites.[2] The relationship of the dendritic periphery with its core is of particular interest since it engulfs and isolates this site, and thus, the polymeric envelope can modulate the properties of molecules located in its interior.

The character of the dendrimer depends on the monomer unit (AB$_n$). Newkome and co-workers have devised trifurcated aliphatic monomers with maximum branching ($n = 3$).[3] Fréchet et al., on the other hand, have developed bifurcated monomers based on poly(aryl) ethers ($n = 2$).[4] These two types of dendritic backbone give rise to molecules with significant differences in internal polarities, which affect the properties of molecules encapsulated in their polymeric envelope.[2a,5] Also, the degree of branching (bifurcation number, *n*) of the monomer can influence the physical isolation of the focal point of a dendrimer.[6] However, there are only a handful of publications[5,6] in which both building block-types have been compared,[2a] and we believe that more researchers will employ these branched monomer units if their synthesis is more convenient.

Scheme 1



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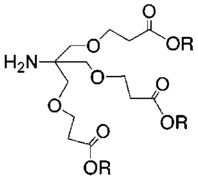
Our own work is aimed at combinatorial design of dendritic hosts for small molecules, and we required an efficient route to a trifurcated dendrimer with bulky end groups to maximize spreading in a two- or three-generation dendrimer. Herein we report a facile method to make a Newkome-type monomer, which can then be employed to synthesize (polyether) amide dendrimers.[7] We also provide the experimental protocol for the synthesis of an orthogonally protected two-generation dendron in high yield.

We wished to begin our work with a (poly-ether) amine monomer such as **1**, known colloquially as Lin's amine.[3a,b]



1

R = Me, Et

However, saponification of ethyl or methyl esters conflicted with our planned protecting group strategy. Therefore, we opted for the *tert*-butyl triester **2** that had been reported by Dupuy and co-workers.[8] This group employed 1,4-addition of tris(hydroxymethyl)aminomethane (TRIS) to *tert*-butyl acrylate, using a phase-transfer catalyst, in 38% yield. In our hands, this yield could not be duplicated, so we sought alternatives. We find that we can get reproducible yields of ≥50% by using 90:10 DMSO/water and sodium hydroxide as base (Scheme 1).

Protection of the nitrogen with benzyl chloroformate (Cbz) produced **3**, and hydrolysis of the three *tert*-butyl esters afforded triacid **4** in 76% overall yield (Scheme 2). This Cbz derivative had been previously prepared by Diederich from the saponification of the Cbz-protected

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[3] (a) Newkome, G. R.; Lin, X. *Macromolecules* **1991**, *24*, 1443. (b) Newkome, G. R.; Lin, X.; Young, J. K. *Synlett* **1992**, 53. (c) Newkome, G. R.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem.* **1991**, *56*, 7162. (d) Moorefield, C. N.; Newkome, G. R. In *Advances in Dendritic Macromolecules*; Newkome, G. R., Ed.; JAI Press: Greenwich, 1994; Vol. 1.

[4] (a) Hawker, G.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010. (b) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287. (c) Narayanan, V. V.; Newkome, G. R. *Top. Curr. Res.* **1998**, *197*, 19.

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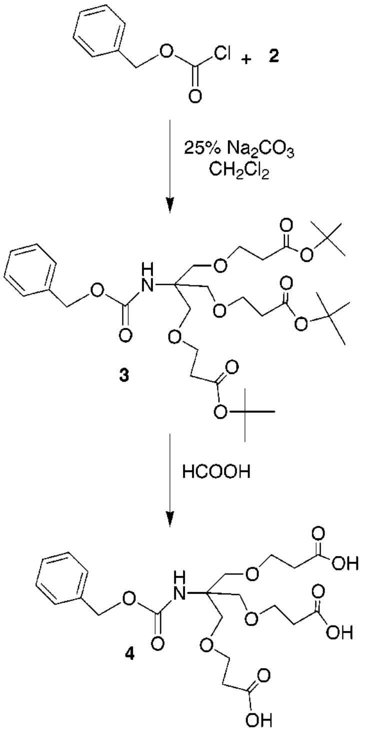
Scheme 2

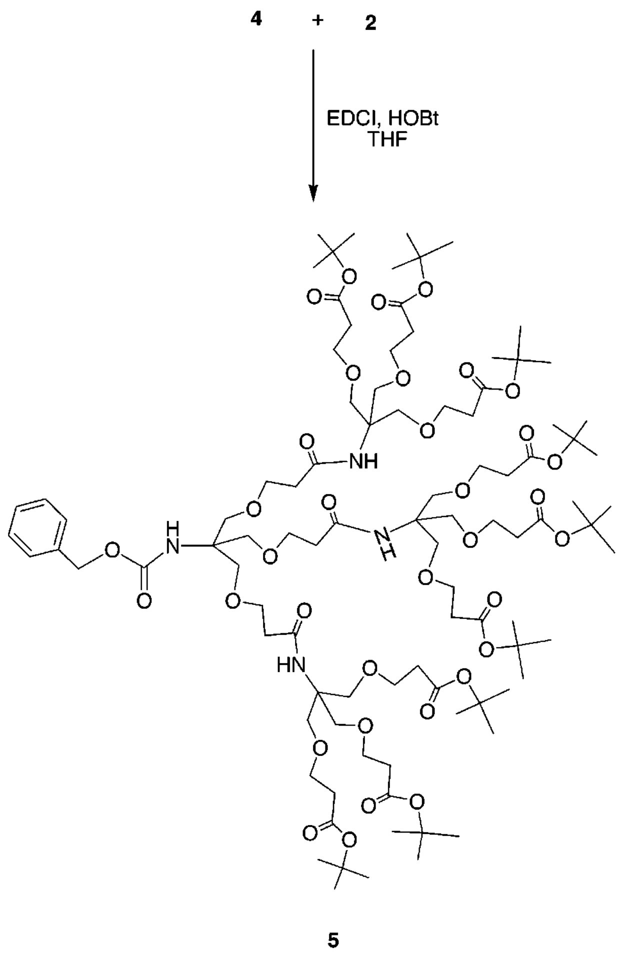


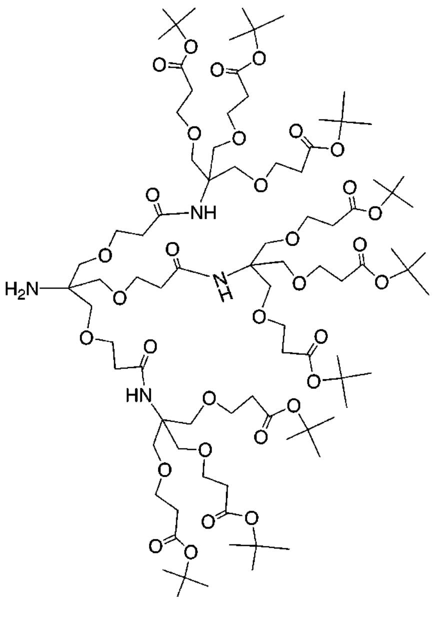
trimethyl ester in about 93% overall yield starting from Lin's amine.[7a] However, synthesis of Lin's amine entails two reactions,[3a] the first of which requires 40 h, and lengthy purification procedures are necessary to produce about a 50% overall yield.

In the next step, we coupled the triacid **4** with amino ester **2** under peptide coupling conditions using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCl) and 1-hydroxybenzotriazole (HOBt) to produce the Cbz-protected dendron **5** in 75% yield in only 24 h (Scheme 3). The progress of the reaction was monitored by ^{1}H NMR and FAB-MS.

The Cbz protecting group was easily removed from **5** by hydrogenation with Pd/C in EtOH, and the second-generation amine (**6**) was recovered in 97% yield, maintaining the integrity of the *tert*-butyl esters at the periphery.

Scheme 3





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In summary, we report a simple, one-step method with a single chromatographic purification to produce a trifurcated amino-polyether polyester monomer, which will be of potential use in dendrimer research. We have also shown that an orthogonally protected second-generation dendron, based on monomer **2,** can be generated simply and expeditiously and that removal of the Cbz protecting group is straightforward.

Experimental Section

General Methods. All reagents were commercially available and used without further purification. THF and CH_2Cl_2 were freshly distilled from sodium−benzophenone ketyl and CaH_2, respectively. Column chromatography was performed on silica gel 60 (230−400 mesh) while TLC was carried out using aluminum-backed plates coated with 0.25 mm silica gel 60 (F-254). FAB mass spectra were recorded on a single-stage quadrupole mass spectrometer. NMR chemical shifts (δ) are reported in ppm using either TMS or residual solvent as internal reference, as noted, and peak assignments were deduced with DEPT as well as 2D NMR experiments such as COSY and HETCOR (Supporting Information).

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Tris{[2-(*tert*-butoxycarbonyl)ethoxy]methyl}methylamine (2). The TRIS (1.21 g, 10.0 mmol) in 2.0 mL of a newly opened bottle of DMSO was cooled to 15.0 °C under N_2. Then, 0.2 mL of 5.0 M NaOH was injected while stirring, followed by the *tert*-butyl acrylate (5.0 mL, 34 mmol), which was injected dropwise. (A solvent mixture of 5−10% water in DMSO is optimal for this reaction.) The reaction mixture was allowed to reach room temperature and left stirring for 24 h. At this point, the excess reagent and solvent were removed under vacuum at room temperature and the residue was purified by column chromatography (SiO_2, 2:1 EtOAc/hexane + 0.05% v/v NH_4OH) to yield a colorless oil (2.70 g, 54%). IR (CH_2Cl_2): 1734 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, $(CH_3)_3C$, 27H); 2.46 (t, CH_2CH_2O, $J = 6.0$ Hz, 6H); 3.32 (s, CCH_2O, 6H); 3.65 (t, OCH_2CH_2, $J = 6.0$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.01 ($(CH_3)_3C$); 36.29 (CH_2CH_2O); 55.95 (CCH_2O); 67.11 (OCH_2CH_2); 72.80 (CCH_2O); 80.37 ($C(CH_3)_3$); 170.91 (*C*OO*t*-Bu). FAB-MS (*m*/*z*): 506 (80, MH^+), 450 (16, $MH^+ - CH_2C(CH_3)_2$), 394 (11, $MH^+ - 2CH_2C(CH_3)_2$), 338 (50, $MH^+ - 3CH_2C(CH_3)_2$), 57 (100, $(CH_3)_3C^+$). This compound has been previously prepared, with no analytical data reported.[8]

Benzyl *N*-Tris{[2-(*tert*-Butoxycarbonyl)ethoxy]methyl}methylcarbamate (3). The amine **2** (1.37 g, 2.72 mmol) was dissolved in 20.0 mL of CH_2Cl_2 and 10.0 mL of 25% aqueous Na_2CO_3 was added while stirring. Then, the benzyl chloroformate (1.2 mL, 8.4 mmol) was added dropwise and the reaction mixture was stirred for 24 h. The product was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, 2:1 hexane/EtOAc) to yield a colorless oil (1.33 g, 76%). IR (CH_2Cl_2): 1726 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.43 (s, $(CH_3)_3C$, 27H); 2.44 (t, CH_2CH_2O, $J = 6.4$ Hz, 6H); 3.64 (t, OCH_2CH_2, $J = 6.4$ Hz, 6H); 3.66 (s, CCH_2O, 6H); 5.03 (s, CH_2 benzylic, 2H); 5.30 (bs, NH, 1H); 7.27−7.40 (m, CH aromatic, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, solvent peak as reference): δ 28.06 ($(CH_3)_3C$); 36.20 (CH_2CH_2O); 58.70 (CCH_2O); 66.08 (CH_2 benzylic); 67.07 (CH_2CH_2O); 69.36 (CCH_2O); 80.43 ($C(CH_3)_3$); 127.85, 127.94, 128.36, 136.73 (CH aromatic); 155.07 (CONH); 170.79 (*C*OO*t*-Bu). FAB-MS: 640 *m*/*z* (MH^+). Anal. Calcd for $C_{33}H_{53}NO_{11}$ (639.4): C 61.95, H 8.35. Found: C 62.12, H 8.50.

Benzyl *N*-Tris[(2-carboxyethoxy)methyl]methylcarbamate (4). Tri-*tert*-butyl ester **3** (0.64 g, 1.0 mmol) was stirred in 10.0 mL of 96% formic acid for 18 h. Then, the formic acid was removed at reduced pressure at 50 °C to produce a colorless oil in quantitative yield. ^1H NMR (CD_3COCD_3, 300 MHz, solvent as reference): δ 2.52 (t, CH_2CH_2O, $J = 6.3$ Hz, 6H); 3.67 (s, CCH_2O, 6H); 3.67 (t, CH_2CH_2O, $J = 6.3$ Hz, 6H); 5.01 (s, CH_2 benzylic, 2H); 5.75 (bs, NH, 1H); 7.27−7.35 (m, CH aromatic, 5H). ^{13}C NMR: (CD_3COCD_3, 75 MHz, solvent as reference): δ 35.06 (CH_2CH_2O); 59.76 (CCH_3O); 66.07 (CH_2 benzylic); 67.63 (CH_2CH_2O); 69.87 (CCH_2O); 128.46, 128.50, 129.12, 138.36 (CH aromatic); 155.71 (CONH); 172.94 (COOH). FAB-MS: 472 *m*/*z* (MH^+). This compound has been previously reported with complete characterization.[7d]

Benzyl *N*-Tris[(2-{[(tris{[2-(*tert*-butoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methylcarbamate (5). The HOBt (0.11 g, 0.81 mmol), Et_3N (0.40 mL, 2.9 mmol), and EDCl (0.55 g, 2.9 mmol) were added to **4** (0.39 g, 0.83 mmol) in 5.0 mL of dry THF. Then, the amine **2** (1.51 g, 2.99 mmol) dissolved in 5.0 mL of dry THF was added, 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 diethyl ether and washed with 0.5 M HCl and brine. The ether layer was then dried over $MgSO_4$, the solvent was removed in vacuo, and column chromatography (SiO_2, 2:1 EtOAc/Hexane) yielded a colorless oil (1.2 g, 75%). IR (CH_2Cl_2): 1729 cm^{-1} (C═O ester), 1675 (C═O amide). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, $(CH_3)_3C$, 81H); 2.40 (t, CH_2CH_2O generation (gen.) 1, $J = 6.9$ Hz, 6H); 2.43 (t, CH_2CH_2O gen. 2, $J = 6.3$ Hz, 18H); 3.59−3.72 (m, CH_2CH_2O gen. 1 & 2, CCH_2O gen. 1 & 2, 48H); 5.04 (s, CH_2 benzylic, 2H); 5.55 (bs, NH, 1H); 6.21 (bs, NH amide, 3H); 7.28−7.39 (m, CH aromatic, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): 28.11 ($(CH_3)_3C$); 36.11 (CH_2CH_2O gen. 2); 37.32 (CH_2CH_2O gen. 1); 58.83 (CCH_2O gen. 1); 59.74 (CCH_2O gen. 2); 66.01 (CH_2 benzylic); 67.01 (CH_2CH_2O gen. 2); 67.55 (CH_2CH_2O gen. 1); 69.10 (CCH_2O gen. 2); 69.33 (CCH_2O gen. 1); 80.40 ($(CH_3)_3C$); 127.87, 128.01, 128.39, 136.84 (CH aromatic); 155.10 (CONH carbamate); 170.81 (CONH amides); 170.88 (COO*t*-Bu). MALDI-MS: 1956.13 (MNa^+), 1972.13 (MK^+), 1900.07 ($MNa^+ - t$Bu), 1801.12 ($M^+ -$ Cbz). Anal. Calcd for $C_{96}H_{164}N_4O_{35}$ (1933.12): C 59.61, H 8.55. Found: C 59.43, H 8.46.

***N*-Tris[(2-{[(tris{[2-(*tert*-butoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methylamine (6).** Nano-*tert*-butyl ester **5** (0.068 g, 0.035 mmol) was stirred with 10% Pd/C (0.0072 g) in EtOH (5 mL) under H_2 at rt for 7 h. The mixture was then filtered with a 0.2 μm Millipore filter. The filter was rinsed with CH_2Cl_2, which had been dried over basic alumina. The solvent was removed under reduced pressure at 50 °C, and a colorless oil was recovered (0.062 g, 97%). IR (CH_2Cl_2): 1725 cm^{-1} (C═O ester), 1672 (C═O amide). ^1H NMR (CD_3COCD_3, 300 MHz): δ 1.33 (s, $(CH_3)_3C$, 81H); 2.27 (t, CH_2CH_2O gen. 1, $J = 6.0$ Hz, 6H); 2.33 (t, CH_2CH_2O gen. 2, $J = 6.0$ Hz, 18H); 3.20 (s, CCH_2O gen. 1, 6H); 3.50−3.60 (m, CH_2CH_2O gen. 1 & 2, CCH_2O gen. 2, 42H); 6.50 (bs, NH amide, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz, solvent as reference): 28.32 ($(CH_3)_3C$); 36.77 (CH_2CH_2O gen. 2); 37.93 (CH_2CH_2O gen. 1); 56.88 (CCH_2O gen. 1); 60.66 (CCH_2O gen. 2); 67.83 (CH_2CH_2O gen. 2); 68.30 (CH_2CH_2O gen. 1); 69.76 (CCH_2O gen. 2); 73.51 (CCH_2O gen. 1); 80.45 ($(CH_3)_3C$); 171.26 (CONH amides); 171.33 (COO*t*-Bu). FAB-MS: 1800 (MH^+), 1744 ($MH^+ -$ *t*-Bu). Anal. Calcd for $C_{88}H_{158}N_4O_{33}$ (1799.08): C 58.71, H 8.85. Found: C 58.95, H 8.82.

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Supporting Information Available: 1D, 2D, and DEPT NMR spectra of **2**−**6** and FT-IR spectrum of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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