# A Divergent Synthesis of Polyurethane Dendrimers

Richard T. Taylor,* Yuhua Lu and Fahad Alminderej

Department of Chemistry and Biochemistry, Miami University,
Oxford, OH 45056 USA. taylorrt@MiamiOH.edu

**Abstract**:

Utilizing polymer-bound and soluble diphenylphosporyl azide (DPPA) to promote the Curtius reaction, we report a divergent synthesis of several dendrimers. The syntheses involve several diol and triol core molecules. Each generation is propagated through reaction with 3,5-bis(3-acetoxypropoxy)benzoic acid and DPPA. The generations are characterized by HNMR, CNMR and MALDI-TOF MS.

We had previously reported a convergent synthesis of structurally different polyurethane dendrimers and discuss the modification made to facilitate the preparation of these dendrimers.

**Keywords**: Dendrimer, polyurethane, Curtius rearrangement

## Introduction

Dendrimer chemistry has been an area of intense research interest over the past several years in recognition of the role such materials can play in areas as diverse as medicine [1], catalysis [2], photon harvesting [3] and surface/phase behavior [4]. Dendrimers have been constructed using a variety of functional groups for linking the growing generations, including polyamines [5] and polyethers [6] as perhaps the most prominent. Our interest lies in the use of urethanes for the growth steps.

Several strategies for such polyurethane dendrimers have been carried out [7]. We reported [8] a convergent synthesis of aryl-alkyl polyurethane dendrimers using diphenylphosphoryl azide to construct the urethane linkage as well as a polymer supported version of DPPA [9]. We report herein the use of a similar strategy to prepare polyurethane dendrimers in a divergent fashion.

## Experimental

General Methods

Standard workup included washing the reaction mixture with water followed by brine, then the separated organic phase was dried over magnesium sulfate and concentrated in vacuo. Column chromatography was performed over silica gel. Proton and carbon NMR spectra was recorded on Bruker Avance instruments at the

field strength and solvents indicated. MALDI-TOF spectra were recorded on a Bruker Reflex III TOF mass spectrometer equipped with a nitrogen laser (337nm).

*Preparation of 3,5-bis-(3-acetoxypropoxy)benzoic acid (1).* In a 100 mL round bottom flask, methyl 3,5-dihydroxybenzoate (1.68 g, 10 mmol, 1.0 eq), K2CO3 (3.30 g, 24 mmol, 2.4 eq), 3-bromo-1-propanol (2.78 g, 20 mmol, 2.0 eq) and acetone (50 mL) were placed. The reaction mixture was refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry. The slurry was then washed with distilled water (100 mL) and ether (100 mL). Evaporation of the ether layer afforded crude 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester as a white solid:

H NMR (acetone-d, 300 MHz) δ 1.96 (quint, *J* = 6.3 Hz, 4H), 3.71 (m, 4H), 3.85 (s, 3H), 3.87 (br, 2H), 4.12 (t, *J* = 6.3 Hz, 4H), 6.73 (t, *J* = 2.2 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 2H); CNMR (acetone-d, 75 MHz) δ 33.13, 52.41, 58.89, 66.02, 106.71, 108.35, 132.90, 161.23, 167.05.

The crude 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester was dissolved in THF (20 mL) without further purification,. NaOH solution (2.5 M, 30 mL) was added. The mixture was heated to 60 °C and stirred overnight. After cooling to room temperature, the THF and aqueous layers were separated. The aqueous layer was acidified by HCl to pH < 7, and evaporated to afford a white solid with crude product and NaCl. Acetone (50 mL) was then added to the white solid and stirred overnight. After filtration, the white solid was washed carefully with acetone (100 mL). The combined filtrates were evaporated to afford a white solid, which was further vacuum evaporated overnight to remove water completely. The crude 3,5-bis-(3-hydroxypropoxy)benzoic acid was ready for the next step without further purification. H NMR (DMSO-d, 300 MHz) δ 1.84 (quint, *J* = 6.2 Hz, 4H), 3.53 (t, *J* = 5.8 Hz, 4H), 4.04 (t, *J* = 6.3 Hz, 4H), 4.55 (br, 2H), 6.70 (m, 1H), 7.02 (d, *J* = 2.1 Hz, 2H), 12.98 (br, 1H); C NMR (DMSO-d, 75 MHz) δ 32.03, 57.24, 64.98, 105.70, 107.32, 132.79, 159.79, 166.99.

3,5-Bis-(3-hydroxypropoxy)benzoic acid was dissolved in a mixture of pyridine and acetic anhydride (20 mL, 20 mol% of acetic anhydride). The mixture was stirred at room temperature under nitrogen for 40 hours, then quenched with distilled water (20 mL). Concentrated HCl solution was added to acidify the solution to pH ≈ 2. The solution was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with HCl solution (1 M, 30 mL), distilled water (30 mL ( 3) and brine (30 mL), then evaporated. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether with 0.5 % AcOH) to give pure 3.5-bis-(3-acetoxypropoxy)benzoic acid as a white solid (3.33 g, 94% overall yield from methyl 3,5-dihydroxybenzoate): 1H NMR (CDCl3, 300 MHz) ( 2.03 (s, 6H), 2.08 (quint, J = 6.0 Hz, 4H), 4.03 (t, J = 6.1 Hz, 4H), 4.22 (t, J = 6.2 Hz, 4H), 6.63 (t, J = 2.3 Hz, 1H), 7.19 (d, J = 2.3 Hz, 2H), 10.80 (br, 1H); 13C NMR (DMSO-d6, 75 MHz) 20.82, 28.33, 61.09, 64.54, 107.34, 108.13, 131.07, 159.70, 171.17, 171,19

*Preparation of 1,3,5-tris-(3-hydroxypropoxy)benzene (2)*. Into a 100 mL round bottom flask, benzene-1,3,5-triol (0.63 g, 5 mmol, 1.0 eq), K2CO3(2.50 g, 18 mmol, 3.6 eq), 3-bromo-1-propanol (2.10 g, 15 mmol, 3.0 eq) and acetone (40 mL) were placed. The reaction mixture was refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry which was then partitioned between distilled water and ether. The aqueous layer was then evaporated to get a white solid with crude product, and salts. Acetone (50 mL) was added to the white solid and stirred overnight. After filtration, the white solid was washed carefully with acetone (100mL). The combined filtrates were evaporated to get a white solid, which was further vacuum evaporated overnight to remove water completely. The product (1.16 g, 77% yield), was pure enough for the further reaction: H NMR (DMSO-d, 300 MHz) δ 1.81 (quint, *J* = 6.3 Hz, 6H), 3.51 (t, *J* = 5.8 Hz, 6H), 3.96 (t, *J* = 6.4 Hz, 6H), 4.51 (br, 3H), 6.04 (s, 3H); C NMR (DMSO-d, 75 MHz) δ 32.12, 57.34, 64.59, 93.66, 160.52.

*General Procedure for reaction of (1) with DPPA and alcohols*. 3.5-Bis-(3-acetoxypropoxy)benzoic acid (1), DPPA (either the soluble reagent or the polymer-bound variant) and triethylamine were mixed in a round bottom flask with benzene under a nitrogen atmosphere. The mixture was stirred for 3 hours, and then core compounds or polyurethane dendrimers with hydroxyl groups on the periphery in the previous generation was added. The mixture was further heated to reflux. After cooling to room temperature, the resin was removed by filtration (or the soluble material by aqueous extraction) and washed with EtOAc (60 mL). The combined filtrates were washed with aqueous NaOH solution (1 M, 20 mL × 3), distilled water (20 mL × 3) and brine (20 mL). After drying over MgSO4, solvent was removed under vacuum to afford the crude product. The products were purified by column chromatography (silica gel, hexanes/ethyl acetate).

*General Procedure for saponification of dendritic esters*. The polyurethane dendrimers with acetoxy groups on the periphery obtained above were dissolved in a solution of 5 mol% of K2CO3 in a mixture of MeOH and distilled water (2:1) (50 mL) and stirred for 2 hours. The mixture was vacuum evaporated to afford a white solid. Acetone (50 mL) was added into the round bottom flask with the white solid and stirred overnight. After filtration and washing with more acetone (100 mL), the combined filtrates were vacuum evaporated to afford crude product. After purification and vacuum evaporation overnight, the formed polyurethane dendrimers with hydroxyl groups on the periphery were used as the starting material in the next step.

1,4-bis-(3-hydroxypropyloxy)benzene (3). In a 100 mL round bottom flask, benzene-1,4-diol (0.55 g, 5 mmol, 1.0 eq), K2CO3 (1.66 g, 12 mmol, 2.4 eq), 3-bromo-1-propanol (1.53 g, 11 mmol, 2.2 eq) and acetone (40 mL) were placed. The reaction mixture was

refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry which was then partitioned between distilled water and ether. The aqueous layer was then evaporated to get a white solid with crude productand salts. Acetone (50 mL) was added to the white solid and stirred overnight. After filtration, the white solid was washed carefully by acetone (100mL). The combined filtrates were evaporated to get a white solid, which was further vacuum evaporated overnight to remove water completely. The product obtained was pure enough for further reaction: H NMR (acetone-d, 300 MHz) δ 1.91 (quint, *J* = 6.3 Hz, 4H) 3.70 (t, *J* = 6.2 Hz, 4H), 4.01 (t, *J* = 6.4 Hz, 4H), 6.83 (s, 4H); C NMR (acetone-d, 75 MHz) δ 33.40, 59.07, 65.97, 116.03, 154.09.

NMR data on isolated dendrimers (Yields and MALDI-TOF data in results section)

<u>Dendrimers from compound (1) core</u>

Generation one acetate: H NMR (CDCl3, 300 MHz) δ 2.03 (m, 36H), 3.98 (t, *J* = 6.0 Hz, 18H), 4.21 (t, *J* = 6.2 Hz, 12H), 4.31 (t, *J* = 6.0 Hz, 6H), 6.04 (s, 3H), 6.14 (m, 3H), 6.59 (m, 6H), 6.69 (br, 3H); C NMR (CDCl3, 75 MHz) δ 20.93, 28.49, 28.80, 61.21, 62.04, 64.38, 94.10, 96.71, 97.50, 139.65, 153.22, 160.28, 160.60, 171.06
Generation one alcohol: H NMR (acetone-d, 300 MHz) δ 1.92 (quint, *J* = 6.2 Hz, 12H), 2.07 (quint, *J* = 6.0 Hz, 6H), 3.70 (m, 18H), 4.03 (t, *J* = 6.3 Hz, 18H), 4.26 (t, *J* = 6.2 Hz, 6H), 6.10 (s, 3H), 6.18 (t, *J* = 2,1 Hz, 3H), 6.80 (d, *J* = 2.1 Hz, 6H), 8.63 (br, 3H); C NMR (acetone-d, 75 MHz) δ 29.63, 33.26, 58.90, 59.03, 65.23, 65.54, 94.80, 96.39, 98.06, 141.77, 154.22, 161.48, 161.72.

Generation two acetate: H NMR (CDCl3, 300 MHz) δ 2.02 (m, 78H), 3.95 (t, *J* = 6.0 Hz, 42 H), 4.22 (m, 42H), 5.96 (s, 3H), 6.12 (m, 9H), 6.58 (d, *J* = 2.1 Hz, 18H), 7.16 (br, 9H); C NMR (CDCl3, 75 MHz) δ 20.91, 28.49, 28.71, 61.24, 61.73, 64.36, 64.67, 96.62, 97.60, 139.88, 153.43, 160.24, 171.11
Generation two alcohol: H NMR (methanol-d, 300 MHz) δ 1.96 (m, 42H), 3.74 (m, 42H), 4.01 (t, *J* = 6.2 Hz, 24H), 4.10 (t, *J* = 6.3 Hz, 18 H), 6.08 (s, 3H), 6.14 (m, 9H), 6.65 (m, 18) 7.89 (s, 9H).

<u>Dendrimers from diethylene glycol</u>

Generation one acetate: H NMR (CDCl3, 300 MHz) δ 2.02 (m, 20H), 3.71 (t, *J* = 4.2 Hz, 4H), 3.94 (t, *J* = 6.1 Hz, 8H), 4.18 (t, *J* = 6.3 Hz, 8H), 4.27 (t, *J* = 4.5 Hz, 4H), 6.11 (t, *J* = 2.0 Hz, 2H), 6.56 (d, *J* = 2.0 Hz, 4H), 7.08 (br, 2H); C NMR (CDCl3, 75 MHz) δ 20.82, 28.37, 61.12, 63.97, 64.24, 69.23, 96.58, 97.46, 139.57, 153.18, 160.13, 171.01
Generation one alcohol: H NMR (acetone-d, 300 MHz) δ 1.93 (quint, *J* = 6.2 Hz, 8H), 3.71 (m, *J* = 5.0 Hz, 16H), 4.04 (t, *J* = 6.3 Hz, 8H), 4.23 (m, 4H), 6.18 (t, *J* = 2.1 Hz, 2H), 6.81 (d, *J* = 2.2 Hz, 4H), 8.63 (br, 2H); C NMR (acetone-d, 75 MHz) δ 32.94, 58.71, 64.26, 65.19, 69.55, 96.08, 97.76, 141.39, 153.91, 161.18

Generation two acetate: H NMR (CDCl3, 300 MHz) δ 2.02 (m, 48H), 3.74 (m, 4H), 3.96 (t, *J* = 6.0 Hz, 24H), 4.20 (t, *J* = 6.3 Hz, 24H), 4.27 (m, 4H), 6.14 (t, *J* = 2.1 Hz, 6H), 6.56 (m,

4H), 6.62 (d, *J* = 1.6 Hz, 8H), 6.99 (br, 2H) 7.13 (br, 4H); C NMR (CDCl3, 75 MHz) δ 20.92, 28.50, 28.72, 61.23, 61.74, 64.37, 69.23, 96.63, 97.39, 97.60, 139.52, 139.85, 153.39, 160.24, 171.08
Generation two alcohol: H NMR (acetone-d, 300 MHz) δ 1.92 (m, 16H), 2.08 (m, 8H), 2.85 (br, 8H), 3.70 (m, 20H), 4.03 (m, 24H), 4.26 (m, 12H), 6.17 (m, 6H), 6.79 (m, 8H), 6.83 (m, 4H), 8.63 (m, 6H); C NMR (acetone-d, 75 MHz) δ 26.63, 33.26, 59.03, 62.10, 64.63, 65.16, 65.54, 69.85, 96.42, 96.66, 98.08, 98.26, 141.76, 154.24, 161.27, 161.47.

Dendrimers from triethylene glycol

Generation one acetate: H NMR (CDCl3, 300 MHz) δ 2.02 (m, 20H), 3.67 (s, 4H), 3.73 (t, *J* = 5.9 Hz, 4H), 3.95 (t, *J* = 6.0 Hz, 8H), 4.19 (t, *J* = 6.2 Hz, 8H), 4.30 (t, *J* = 4.5 Hz, 4H), 6.13 (m, 2H), 6.60 (d, *J* = 1.0 Hz, 4H), 7.03 (br, 2H); C NMR (CDCl3, 75 MHz) δ 20.91, 28.50, 61.21, 64.35, 69.51, 70.79, 96.73, 97.54, 139.68, 153.34, 160.27, 171.03.
Generation one alcohol: H NMR (acetone-d, 300 MHz) δ 1.92 (quint, *J* = 6.2 Hz, 8H), 3.61 (s, 4H), 3.70 (m, 16H), 4.04 (t, *J* = 6.3 Hz, 8H), 4.22 (t, *J* = 4.7 Hz, 4H), 6.18 (t, *J* = 2.2 Hz, 2H), 6.82 (d, *J* = 2.1 Hz, 4H), 8.63 (br, 2H); C NMR (acetone-d, 75 MHz) δ 33.28, 59.03, 64.65, 65.53, 69.99, 71.20, 96.45, 98.12, 141.74, 154.28, 161.48.

Generation two acetate: H NMR (CDCl3, 300 MHz) δ 2.02 (m, 48H), 3.67 (s, 4H), 3.74 (m, 4H), 3.94 (m, 24H), 4.24 (m, 28H) 6.13 (m, 6H), 6.64 (m, 12H), 7.21 (br, 6H); C NMR (CDCl3, 75 MHz) δ 20.89, 28.47, 28.70, 60.07, 61.21, 61.68, 64.33, 64.55, 69.44, 70.93, 96.59, 97.52, 139.69, 139.87, 153.43, 160.21, 171.06
Generation two alcohol: H NMR (acetone-d, 300 MHz) δ 1.93 (m, 24H), 3.72 (m, 32 H), 4.04 (m, 32H), 4.28 (t, *J* = 6.5 Hz, 4H), 6.18 (m, 6H), 6.80 (m, 12H), 8.55 (m, 6H).

Dendrimers from compound (3)

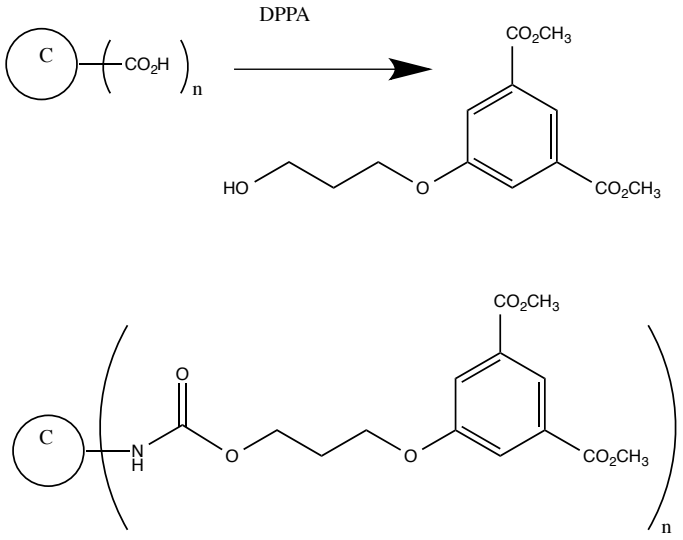
Generation one acetate: H NMR (CDCl3, 300 MHz) δ 2.03 (m, 24H), 3.99 (m, 12H), 4.21 (t, *J* = 6.3 Hz, 8H), 4.33 (t, *J* = 6.2 Hz, 4H), 6.15 (t, *J* = 2.0 Hz, 2H), 6.56 (m, 4H), 6.81 (s, 4H); C NMR (CDCl3, 75 MHz) δ 20.92, 28.51, 28.98, 61.20, 62.15, 64.38, 96.77, 97.53, 115.46, 139.60, 153.04, 153.22, 160.30, 171.03
Generation one alcohol: H NMR (acetone-d, 300 MHz) δ 1.92 (m, 12H), 3.70 (m, 12H), 4.04 (t, *J* = 6.4 Hz, 12H), 4.28 (t, *J* = 6.3 Hz, 4H), 6.18 (t, *J* = 2.2 Hz, 2H), 6.79 (d, *J* = 2.1 Hz, 4H), 6.86 (s, 4H), 8.01 (s, 2H); C NMR (acetone-d, 75 MHz) δ 32.56, 33.27, 59.02, 62.13, 65.64, 68.00, 96.40, 98.08, 116.23, 139.40, 152.13, 154.06, 161.47

Generation two acetate: H NMR (CDCl3, 300 MHz) δ 2.04 (m, 52H), 3.96-4.11 (m, 28H), 4.20-4.26 (m, 28H), 6.13-6.18 (m, 6H), 6.57-6.63 (m, 12H), 6.91 (m, 4H); C NMR (CDCl3, 75 MHz) δ 20.92, 28.51, 29.67, 61.06, 61.13, 64.42, 97.12, 98.32, 115.08, 140.35, 156.06, 160.14, 160.46, 171.06.
Generation two alcohol: H NMR (methanol-d, 300 MHz) δ 1.97 (m, 28H), 3.71 (m, 28H), 4.01 (t, *J* = 6.2 Hz, 16H), 4.10 (t, *J* = 6.2 Hz, 12H), 6.14 (t, *J* = 2.2 Hz, 6H), 6.58 (m, 12H), 7.01 (s, 4H), 7.90 (s, 6H).

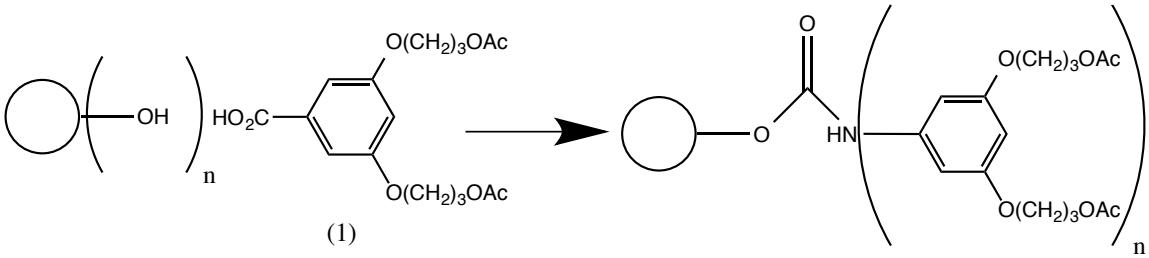
## Results/Discussion

Our initial studies were intended to produce dendrimers identical to those prepared by our previous divergent syntheses. Such a strategy would involve a poly-acid core and growth through a hydroxy diester linking piece to create each generation (Scheme I). Saponification of the ester groups to expose the new carboxylate groups for further reaction. In our initial work, we found that the proliferation of carboxylate groups led to difficulties in the solubility of the reactants. While such difficulties may not be intractable, we found that a strategy of a polyol core and growth through a carboxylic acid diester (1) was more effective (Scheme 2).

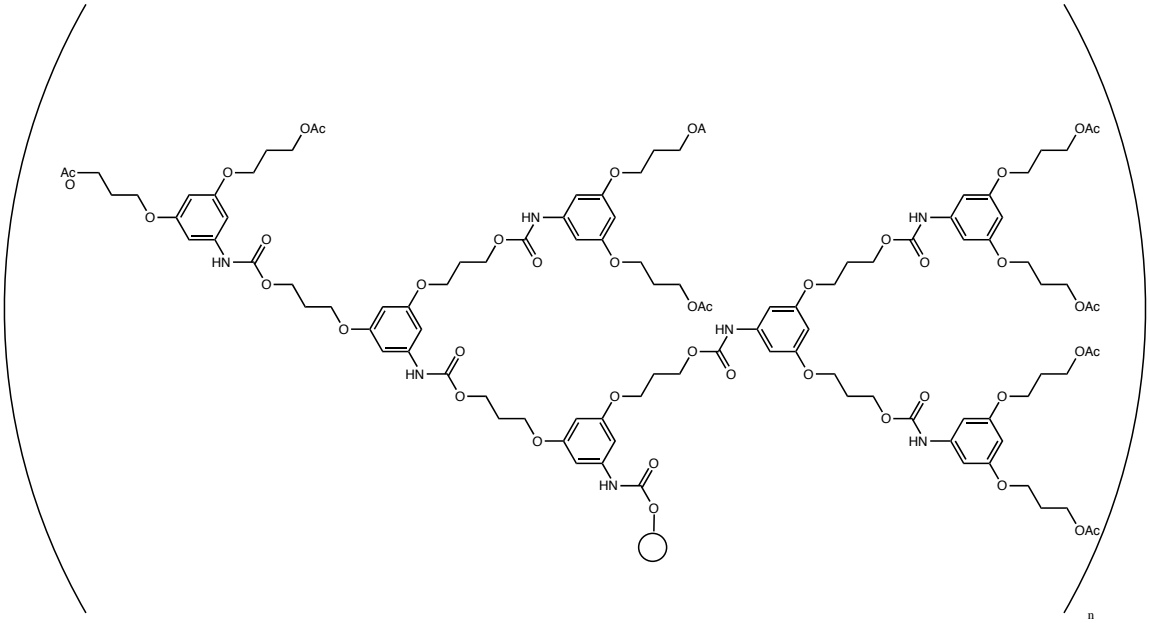
Scheme 1 – First synthetic approach using polyacids




Scheme 2 – revised synthetic approach

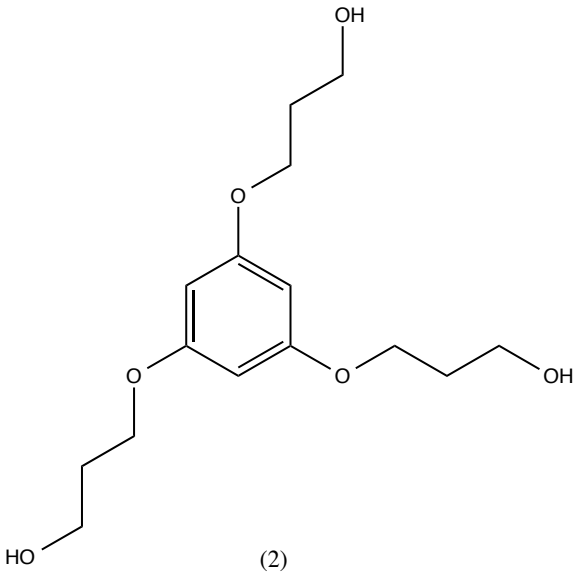



After several iterations of the process:



Preparation of 3,5-bis-(3-acetoxypropoxy)benzoic acid (1) was carried out in three steps from methyl 3,5-dihydroxybenzoate in 54% overall yield. With this material in hand, we surveyed the effectiveness of our strategy on a variety of core alcohols.

*Polyurethane dendrimer from an aromatic triol*. The conversion of 1,3,5-benzenetriol to our trivalent core alcohol (2) was accomplished in one step. The synthesis was iterated through the third generation. While the NMR data is reported in the experimental section, the signals overlap to a great extent. Full purification was carried out at the acetate step and the MALDI-TOF data confirms full substitution.



(2)

| | Generation 1 | Generation 2 | Generation 3 |
|---|---|---|---|
| Yield | 83% | 69% | 57% |
| MALDI-TOF | Expt (calc) | Expt (calc) | Expt (calc) |
| M + Na | 1376.45 (1376.54) | 3231.98 (3231.27) | 6940.70 (6940.72) |
| M + K | 1392.43 (1392.52) | 3247.96 (3247.24) | 6957.19 (6956.70) |

*Polyurethane dendrimers from flexible linear diols*. In a similar fashion, three generations of growth were generated from diethylene glycol and triethylene glycol.

Diethylene glycol core

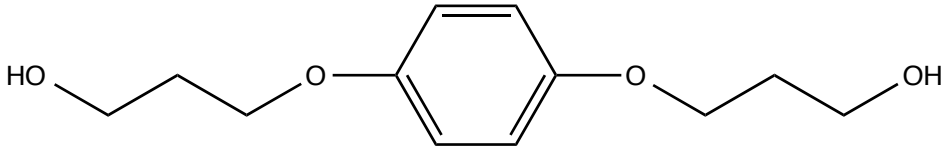
| | Generation 1 | Generation 2 | Generation 3 |
|---|---|---|---|
| Yield | 100% | 87% | 64% |
| MALDI-TOF | Expt (calc) | Expt (calc) | Expt (calc) |
| M + Na | 831.35 (831.32) | 2067.47 (2067.80) | 4542.09 (4542.78) |
| M + K | 847.31 (847.29) | 2083.63 (2083.78) | 4558.94 (4558.75) |

Triethylene glycol core

| | Generation 1 | Generation 2 | Generation 3 |
|---|---|---|---|
| Yield | 87% | 72% | 60% |
| MALDI-TOF | Expt (calc) | Expt (calc) | Expt (calc) |
| M + Na | 875.53 (875.34) | 2111.80 (2111.83) | 4584.51 (4584.80) |
| M + K | 891.39 (891.32) | 2127.77 (2127.80) | 4600.35 (4600.77) |

*Polyurethane dendrimer from a rigid core*

We had envisioned situations in which there might be advantages in separating the growing wedges by a rigid core. Preparation of 1,4-bis-(3-hydroxypropyloxy)benzene (3) was carried out in one step from hydroquinone. In the standard fashion, three generations of growth were generated.




(3)

| | Generation 1 | Generation 2 | Generation 3 |
|---|---|---|---|
| Yield | 75% | 69% | 54% |
| MALDI-TOF | Expt (calc) | Expt (calc) | Expt (calc) |
| M + Na | 951.51 (951.37) | 2187.60 (2187.86) | 4660.75 (4660.83) |
| M + K | 967.46 (967.35) | 2203.60 (2203.83) | 4676.76 (4676.80) |

Preliminary work. We have undertaken a similar study with 2-butyn-1,4-diol. Indications are the generation one level are positive and we feel this dendrimer should also be accessible using this strategy.

## Conclusions

The use of DPPA and especially its polymer-bound version is an effective method for generating the growth of polyurethane dendrimers beginning with a polyol core. This method should prove useful for the preparation of dendrimers with a wide variety of core groups.

## Acknowledgements

The support of Miami University is gratefully acknowledged. Part of this work is taken from the Ph. D. dissertation of Yuhua Lu.

## References

1. Virendra Gajbhiye, Vijayaraj K. Palanirajan, Rakesh K. Tekade and Narendra K. Jain*, Journal of Pharmacy and Pharmacology* **2009**; *61*: 989–1003
2. Didier Astruc* and Francüoise Chardac, *Chem. Rev*. **2001**, *101*, 2991–3023
3. Arpornrat Nantalaksakul, D. Raghunath Reddy, Christopher J. Bardeen and S. Thayumanavan, *Photosynthesis Research*, **2006**, *87*: 133–150
4. A. Sarma Kovvali and K. K. Sircar, *Ind. Eng. Chem. Res*., **2001,** I40 , 2502-2511.
5. Prabal K. Maiti, Tahir Cagun, Guofeng Wang and William A. Goddard, III Macromolecules 2004, 37, 6236-6254
6. Anna Carlmark, Craig Hawker, Anders Hult and Michael Malkoch, ***Chem. Soc. Rev.***, 2009,**38**, 352-362
7. W. James Feast, Steve P. Rannard and Alison Stoddart, Macromolecules 2003, 36, 9704-9706
8. Richard T. Taylor and Uraiwan Puapaiboon, *Tetrahedron Lett.,* **39**, *1998* 8005-8008
9. Yuhua Lu and Richard T. Taylor, *Tetrahedron Lett*,, **44**, *2003*, 9267-9269