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AB_3 building blocks for the synthesis of polyester dendrimers

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ABSTRACT

Syntheses of several examples of a new type of trivalent building blocks for the preparation of aliphatic polyester dendrimers are presented. Starting from the well-known mono-*O*-benzylidenepentaerythritol, AB_3 type acid dendrons can be obtained in high yield in only two steps. Other triprotected bis-2,2-(hydroxymethyl)-3-hydroxypropanoic acid derivatives with varying protecting groups were also synthesized readily. This type of dendron was used in combination with 2,2′-bis(hydroxymethyl) propanoic acid (bis-HMPA) divalent dendrons to produce low generation mixed polyester dendrimers with increased number of branching points.

Polyester dendrimers are of particular interest because they are easily synthesized, non-toxic, and they have been shown to have applications in many fields.[1] They are particularly useful for biomedical applications including as smart carriers for drug delivery.[1,2] However, the synthesis of polyester dendrimers has largely relied on the use of the 2,2′-bis(hydroxymethyl) propanoic acid (bis-HMPA) dendrons.[1,3] Since the 1990s, this aliphatic building block has continued to be the dendron of choice. The use of bis-HMPA has allowed easy preparation of higher generation polyester dendrimers because it is not sterically hindered, and most importantly, the resulting polyester dendrimers are non-toxic and biodegradable, which make them attractive for biological and drug delivery applications.[2a,d,g,3c,4]

The field of polyester dendrimers is still in its infancy. Consequently, dendritic architectures, properties, and applications are still essentially unexplored. The preparation of different types of polyester dendrimers with new properties and new potential applications depends largely on the ability of researchers to synthesize dendrimers with increasing structural diversity. The use of new building blocks is one way of achieving this goal. Herein we report the design and preparation of dendrons derived from pentaerythritol that have three branching points. Dendrons with three branching points can allow the synthesis of polyester dendrimers that are more highly branched (per generation) than previously reported polyester dendrimers. Such dendrimers should have the advantage that they are less easily hydrolyzed in vivo than previously synthesized polyester dendrimers, but share the advantages of synthesis under mild conditions of other polyester dendrimers and potential biological release of bioactive molecules either trapped or conjugated.

Dibutylstannylene acetals have shown to be useful for selective chemical manipulations of diols and polyols.[5] They are formed readily from diols[6] and have served as convenient intermediates for the formation of monobenzyl ethers from diols or polyols by reacting with benzyl bromide in benzene or toluene in the presence of tetrabutylammonium bromide[6a,7] or in DMF in the presence of cesium fluoride.[6b,8] Issidorides and Gulen[9] described an efficient procedure for the synthesis of 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane, also known as mono-*O*-benzylidenepentaerythritol **1**. Following the procedure developed earlier in this laboratory,[10] **1** was refluxed with one equivalent of dibutyltin oxide in toluene followed by the subsequent benzylation in situ, to give isomers **2** and **3** as thick colorless syrups (Scheme 1). When *p*-methoxybenzaldehyde is employed as in Scheme 2, the resulting isomers **5** and **6** are colorless crystalline solids.

These isomers were separated as previously described,[10] characterized using ^1H NMR and ^{13}C NMR spectroscopy, and their structures were assigned. While clean NMR spectra for **2**, **3**, and **5** could be obtained in chloroform-*d*, pure samples of **6** equilibrated whenever dissolved in chloroform-*d* to give 3:2 mixtures of **5** to **6**. The same ratio was observed independent of the amount of time the sample was left in chloroform-*d* (e.g., 0, 2, or 36 h after dissolving the sample in chloroform-*d*). It is known that

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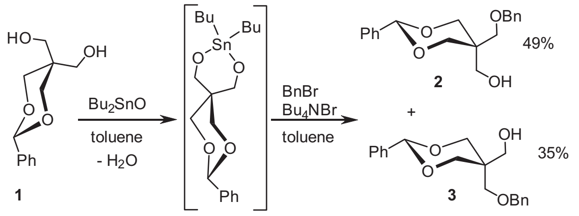
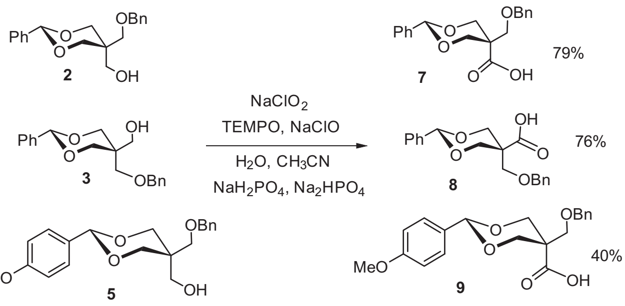


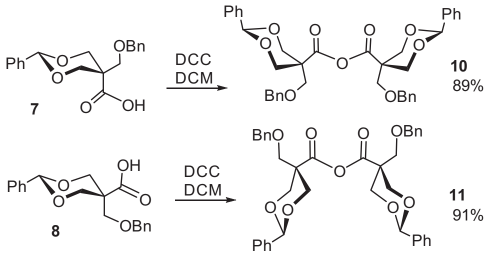
Scheme 1. Mono-*O*-benzylation.

chloroform-*d* decomposes slowly on standing to release dichlorocarbene and HCl. When acetone-d_6 was used for NMR experiments on **6**, no equilibration was observed (see Supporting information). Scheme 3 shows the likely mechanism of the equilibrium in chloroform-*d*. Presumably, **6** equilibrates more readily than **5** because of the greater bulk of the axial CH_2OBn group in **6**. In addition, isomer **5** is likely stabilized by hydrogen bonding between the downward pointing 1,3-dioxane ring oxygen(s) and the axially-oriented hydroxymethyl group.

Oxidation is a fundamental transformation in organic synthesis and numerous methods have been reported for the desired transformation.[11] When the starting alcohols have labile functional groups that can cleave under acidic conditions as it is the case here for **2**, **3**, **5**, and **6**, fewer methods exist for the transformation to carboxylic acids. Here, we found that Zhao's method, the so-called 'Merck oxidation',[12] worked efficiently either on the individual isomers or the mixture of isomers. The reaction between the primary alcohol and a stoichiometric amount of sodium chlorite in the presence of catalytic TEMPO and bleach at 38 °C for 12 h in a buffered solution, gave the corresponding acid dendrons in good yield (Scheme 4).

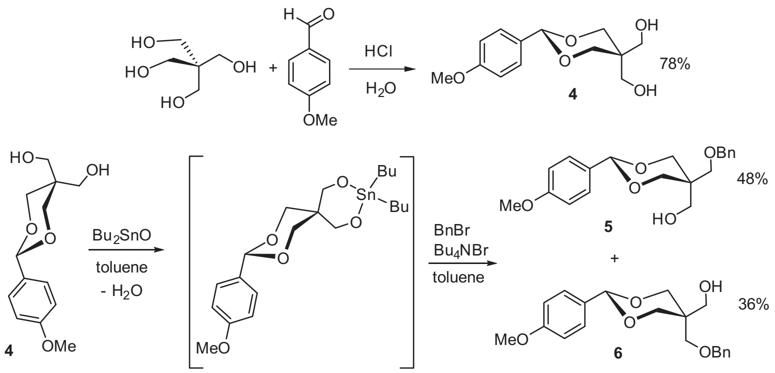


Scheme 4. Merck oxidation of primary alcohols.

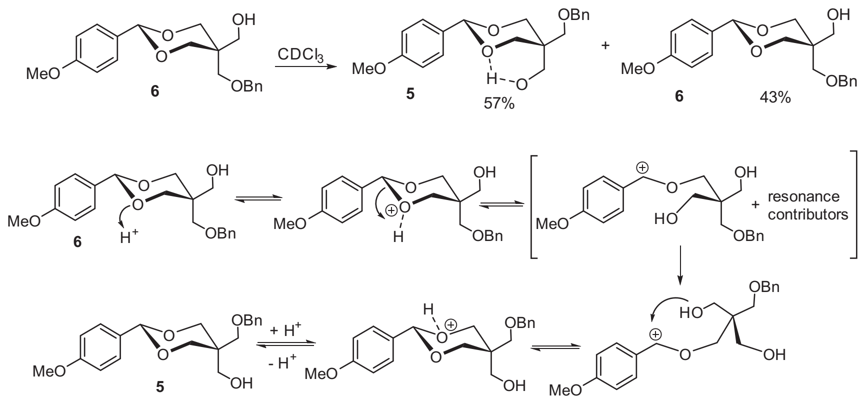


Scheme 5. Dendron activation.

The activated anhydride dendrons were synthesized from the respective individual isomeric carboxylic acids (**7** and **8**) using DCC as illustrated in Scheme 5. Anhydrides **10** and **11** are crystalline products and they remained stable over a period of several months at room temperature. It is important to mention that for



Scheme 2. Mono-*O*-benzylation.



Scheme 3. Acid-catalyzed equilibrium of **5**/**6**.

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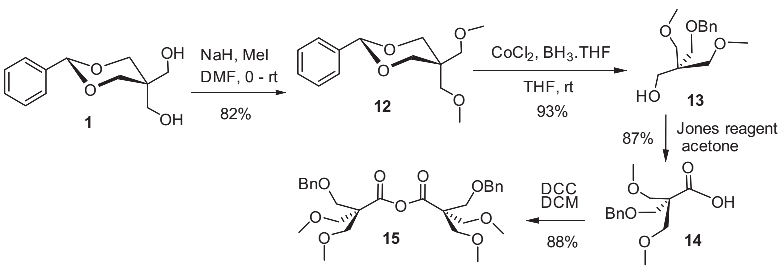
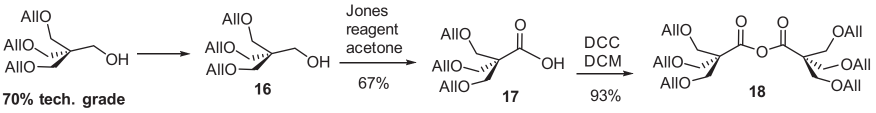


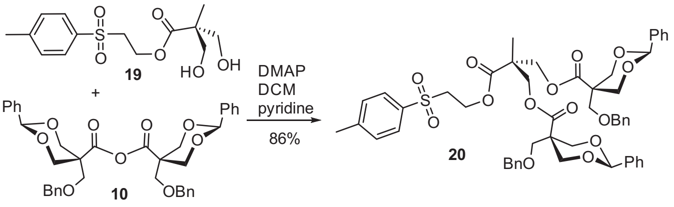
Scheme 6. Preparation of anhydride **15**.



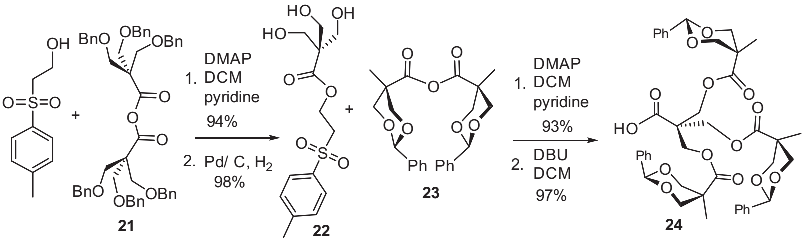
Scheme 7. Preparation of allyl-protected anhydride **18**.

the purpose of polyester dendrimer synthesis, the separation of the isomeric alcohols (**2** and **3**), precursors to the carboxylic acids (**7** and **8**) is not necessary, because the deprotection step, involving removal of the benzylidene acetal, eliminates the *cis*/*trans* isomerism.

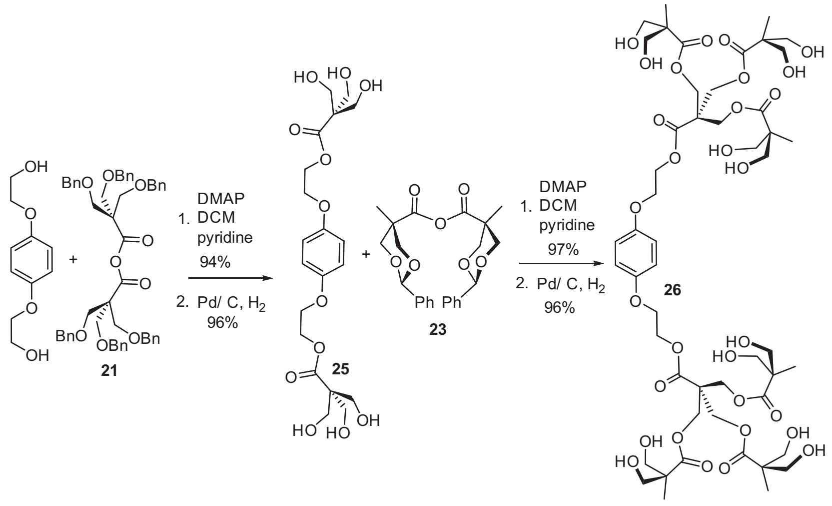
We have previously reported the synthesis of an AB_3 symmetrical dendron prepared by selective reduction of known[13] di-*O*-benzyl-*O*-benzylidenepentaerythritol to tri-*O*-benzylpentaerythritol followed by Jones oxidation and dendron activation with DCC.[14] A similar approach using methyl iodide (see Scheme 6) leads to a new dendron **14** in good yield. Dendrons such as compound **14**



Scheme 8. Preparation of second generation mixed polyester dendron **20**.



Scheme 9. Preparation of second generation mixed acid dendron **24**.[15]



Scheme 10. Preparation of second generation mixed polyester dendrimer **26**.[14]

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can be activated at a single position for the next round of reactions, which could be important for alleviating steric hindrance at higher dendrimer generations and/or for dendrimer surface functionalization.

Another tribranched dendron was obtained when technical-grade tri-*O*-allylpenterythritol, the commercially available tri-*O*-allylpenterythritol (stated to have 70% purity, containing both monoallylpentaerythritol and diallylpentaerythritol, easily removed using column chromatography), was oxidized using Jones oxidation to give acid dendron **17**, which was transformed into the corresponding acid anhydride with DCC (Scheme 7).

The successful synthesis of these dendrons leaves the desire to investigating how versatile they are in the preparation of polyester dendrimers. This new type of building blocks will allow dendrimer researchers to have more options in the synthesis and exploration of new polyester dendritic species. Even though tribranched dendrons are known to be sterically congested and may not be versatile particularly at higher generations, early examples indicate that these can easily be mixed with bis-HMPA dendrons to create mixed polyester dendrimer species in good yield (see Schemes 8–10).

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Supplementary data

Supplementary data (experimental procedures for all syntheses and ^{1}H and ^{13}C NMR spectra of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.073.

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