# Rapid Synthesis of Dendrimers by an Orthogonal Coupling Strategy

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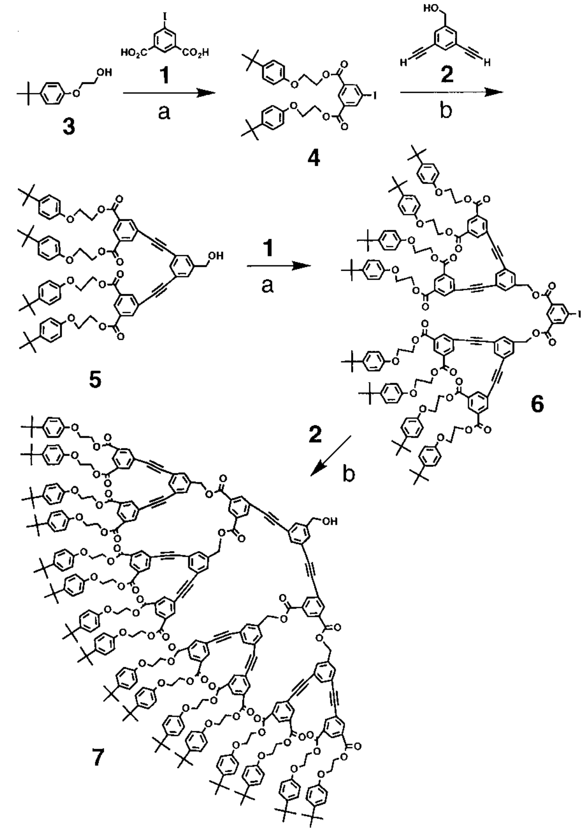
Dendrimers are polymers that radiate out from a central core, with the number of branch points on a given arm increasing exponentially from the core to the periphery.[1] Because of their novel properties, dendrimers have found many uses, including as unimolecular micelles,[2] novel amphiphiles,[3] complexation agents,[4] and MRI contrast agents.[5] These and other applications will benefit from more efficient methods of dendrimer preparation because the iterative synthetic approaches to even small dendrons are multistep. In particular, both the divergent approach developed by Tomalia[6] and Newkome[7] and the convergent method of Fréchet[8] minimally require a deprotection or activation step in addition to the coupling step that adds each new generation. Several successful attempts to shorten these synthetic sequences were reported;[9−11] however, these approaches still require (de)protection or activation chemistry.

Several years ago, Baranay and Merrifield[12] defined an orthogonal system as "a set of completely independent classes of protection groups, such that each class can be removed in any order and in the presence of all other classes." Orthogonal protecting group strategies have found widespread use in peptide chemistry, and recently Ogawa[13] used two independent (orthogonal) glycosylation reactions to accelerate the synthesis of oligosaccharides. We now describe a rapid synthesis of dendrimers using an orthogonal coupling strategy wherein each synthetic step adds a generation to the existing dendrimer.[14]

In the orthogonal approach the protection or activation steps are eliminated by sequential use of two different building blocks in two orthogonal coupling reactions. The current study uses $AB_2$ monomer units **1** and **2**[15] which contain two pairs of complementary coupling functionality. These monomer units were designed to couple by the Mitsunobu esterification reaction[16] or by the Sonogashira reaction of a terminal acetylene with an aryl iodide.[17] The latter reaction has been used extensively by Moore in the preparation of phenylacetylene dendrimers and other nanostructures.[18] It was anticipated that both pairs of functional groups and their resulting coupling products would be inert to the conditions of the other coupling reaction, orthogonality that would allow **1** and **2** to be employed consecutively in either order.

**Scheme 1**[a]



[a] Reaction conditions: (a) $PPh_3$, diethyl azodicarboxylate (DEAD), THF; (b) $Pd(PPh_3)_2Cl_2$, CuI, or $Pd_2(dba)_3$, CuI, $PPh_3$, $Et_3N$, $PhCH_3$.

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(14) To our knowledge, orthogonal dendrimer syntheses have been attempted only twice: (a) Twyman, L. J.; Beezer, A. E.; Mitchell, J. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 407−411. (b) Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 913−918. Both syntheses were carried to the third-generation stage. In ref 14a orthogonality was not demonstrated, whereas in ref 14b it was achieved, but the third-generation dendrimer could not be separated from byproducts.

(15) (a) Monomer **1** was prepared by diazotization of commercially available 5-aminoisophthalic acid followed by treatment with sodium iodide (72% yield). Alcohol **2** was prepared from methyl 3,5-dibromobenzoate by reduction, coupling to (trimethylsilyl)acetylene, and deprotection with potassium carbonate (79% overall yield). (b) All compounds had spectral data in full accord with the assigned structures. Each compound except **14−16** was submitted for combustion analysis and gave passing results. The purity of **14−16** was estimated to be >97% from SEC and HPLC traces which each showed a single sharp peak. (c) Of course, the three steps do not include the several steps needed to make **8** and **9**. The important point is that the orthogonal strategy minimizes the number of steps in the actual dendrimer synthesis, where purification is particularly difficult. The **13** to **14−16** conversion was carried out on a 200−600 mg scale; all other reactions were carried out on >1 g scale.

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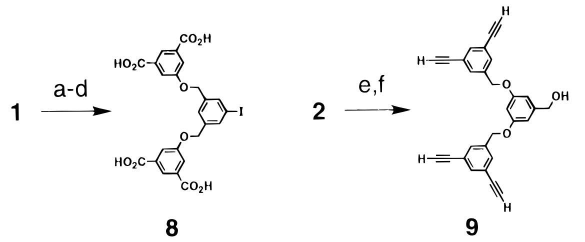
**Scheme 2**[a]



[a] Reaction conditions: (a) MeOH, $H_2SO_4$ (96%); (b) $LiAlH_4$, $Et_2O$ (79%); (c) Dimethyl 5-hydroxyisophthalate (**10**), $PPh_3$, DEAD (73%); (d) KOH, $H_2O$ (93%); (e) $PPh_3$, $CBr_4$ (87%); (f) 3,5-Dihydroxybenzyl alcohol (**11**), $K_2CO_3$ (82%).

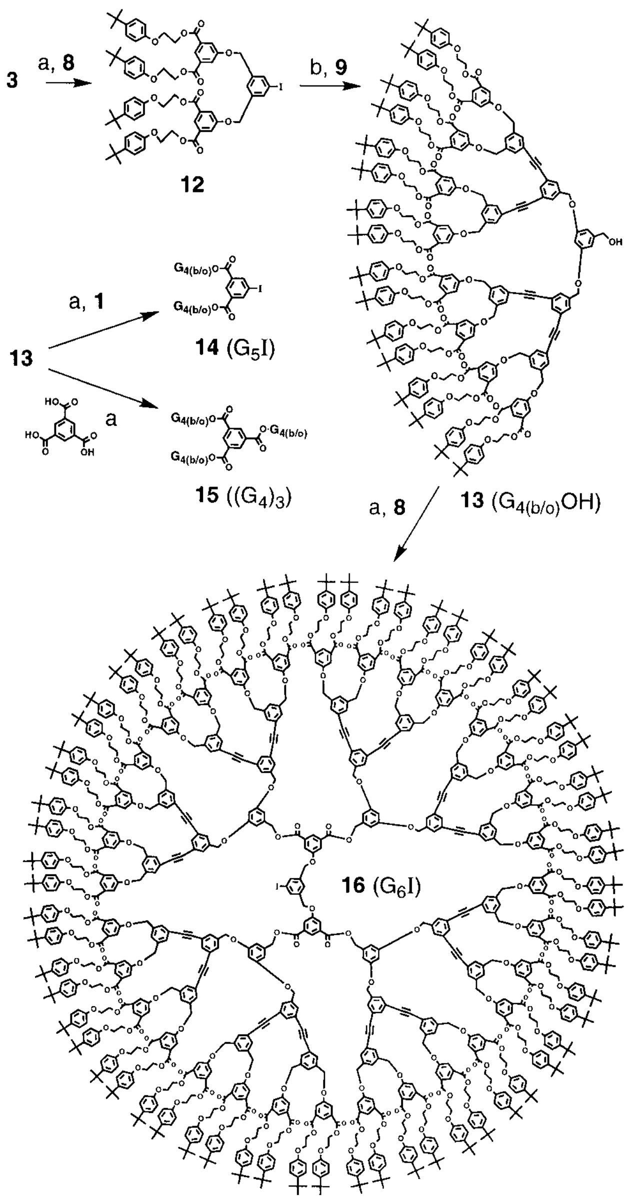
The application of this orthogonal coupling strategy to the synthesis of a fourth-generation dendron is outlined in Scheme 1. (4-*tert*-Butylphenoxy)ethanol (**3**) was coupled to **1** under Mitsunobu conditions to give first-generation dendron **4** in 80% yield. At the focal point of dendron **4** is an iodide group, which coupled to **2** using the Sonogashira reaction to form second-generation dendron **5** in 82% yield. The alcohol group at the focal point of this dendron was set to react with diacid **1**, again under Mitsunobu conditions. In the event, coupling of **1** and **5** afforded third-generation dendron **6** in 80% yield. In a final iteration, **6** coupled to **2** to produce fourth-generation dendron **7** in 78% yield. By alternate use of **1** and **2** in their respective orthogonal reactions, the fourth-generation dendron **7** was synthesized in four steps.

To further increase the efficiency of this strategy, the orthogonal coupling method was merged with Fréchet's branched-monomer approach.[10] Two new "branched monomers" **8** and **9**, already at the second-generation stage, were used for this purpose. These compounds contain the same functionality as do **1** and **2** but are expanded by an ether linkage and have four peripheral reaction sites. Compound **8** was obtained in four steps from **1** (Scheme 2). The desired monomer **9** was prepared in two steps by conversion of **2** to the corresponding bromide which was coupled to **11**.

Scheme 3 illustrates the synthesis of a sixth-generation dendron from **8** and **9** using the orthogonal coupling approach. Tetraesterification of alcohol **3** with tetraacid **8** under Mitsunobu conditions afforded second-generation iodide **12** in 84% yield. Coupling of this iodide with tetraacetylene **9** under Sonogashira conditions afforded fourth-generation dendron **13** in 66% yield. Alcohol **13**, an analog of **7**, was used to synthesize higher generation dendrimers. Thus, esterification of **13** with diacid **1**, trimesic acid, and tetraacid **8** under Mitsunobu conditions afforded the corresponding dendron **14** (G5I), dendrimer **15** ($(G4)_3$), and dendron **16** (G6I) in 80%, 46%, and 62% yield, respectively. The yields of these coupling reactions are based on relatively low conversions of **13** to **14** (46%), **15** (41%), and **16** (22%), which likely reflects the congestion at the focal point.[19] Thus, from **8** and **9**, the synthesis of sixth-generation dendron **16** required only three steps and two chromatographic separations.[15c]

All the dendrimers were characterized by standard spectroscopic methods[15b] and by size-exclusion chromatography (SEC) with differential refractometer index (DRI) and dual-angle laser light scattering (LLS) detectors. The molecular weights were determined directly by LLS and from their retention times using polystyrene standards. Although the latter method underestimated the molecular weight of high-generation ($>4$) dendrimers because of their compactness,[8a] results from the laser light scattering technique were in good agreement with the theoretical values.[20] The dendrimers were also characterized by mass spectrometry using matrix-assisted laser desorption ionization (MALDI). In the MALDI spectra, the major peaks often appeared 23 or 39 mass units higher than the corresponding molecular ions, presumably representing sodium or potassium ion adducts.[21]

**Scheme 3**[a]



[a] Same reaction conditions as in Scheme 1.

In comparison to the most efficient dendrimer syntheses available, the orthogonal coupling approach halves the number of steps needed by obviating (de)protection or activation steps. Each synthetic step adds at least one generation to the dendrimer. As a case in point, sixth-generation dendron **16**, with molecular formula $C_{1292}H_{1369}IO_{242}$ and a molecular weight of 20 896 g mol$^{-1}$, was synthesized in just three steps from **8** and **9**. There is nothing special about the reactions and subunits in Schemes 1–3; they were chosen simply to demonstrate the orthogonal coupling strategy, an approach that should be broadly applicable to dendrimer synthesis using any series of orthogonal coupling reactions.

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**Supporting Information Available:** Spectral and chromatographic data for **4**–**7** and **12**–**16** (48 pages). Ordering information is given on any current masthead page.

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(19) This represents a general disadvantage of the convergent approach to dendrimer synthesis. However, the Mitsunobu and Sonogashira reactions are sterically demanding and were partly chosen as a stringent test of the orthogonal approach to dendrimer synthesis. Other coupling reactions are expected to proceed with higher yields and conversions.

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