ORGANIC LETTERS

1999
Vol. 1, No. 4
685−687

A Rapid, Orthogonal Synthesis of Poly(benzyl ester) Dendrimers via an “Activated” Monomer Approach

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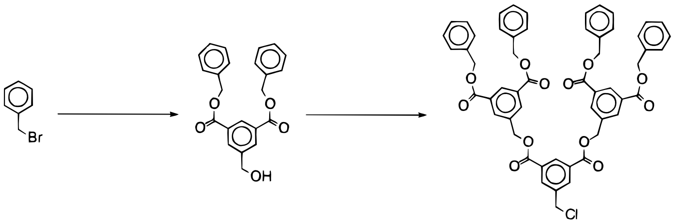
Received June 29, 1999

ABSTRACT



Herein we introduce the concept of an “activated” monomer approach to the synthesis of convergent dendrimers. In this method a set of chemically orthogonal monomers, one of which is an “activated” analogue of the other, is used to rapidly synthesize large, perfect dendrimers with one additional generation being added in each reaction. This method is exemplified by the efficient preparation of a new family of poly(benzyl ester) dendrimers described below.

Despite the tremendous structural and architectural diversity found in dendrimers,[1−3] only two primary synthetic methodologies have been developed for their preparation, either divergent[4] or convergent approaches.[5,6] Several clever strategies have been devised to accelerate the normal stepwise activation/coupling sequences employed in both methods. These include the double-stage convergent[7,8] and double exponential growth approaches,[9] as well as the use of AB_n building blocks (typically $n \geq 4$) termed “hypermonomers”.[10,11] The use of chemically orthogonal monomers, which precludes the need for activation of surface or focal point moieties to continue dendrimer growth, allows large, perfect dendrimers to be prepared in only a few transformations.[12,13]

Herein we describe the synthesis of a set of monomers based on 5-(hydroxymethyl)isophthalic acid **2** (Scheme 1). The AB_2 monomers **3** and **4** are chemically orthogonal and thus can afford large, perfect dendrons and dendrimers at the rate of one generation per coupling reaction. Because these monomers are already “activated” with respect to reaction with one another, once incorporated into the monodendron, growth can continue without the need for further activation.

Both monomers chosen are derived from 5-(hydroxymethyl)isophthalic acid[14] **2**, itself made from the corresponding commercially available diethyl ester **1**. Hence, saponification of the diester with aqueous KOH in a refluxing

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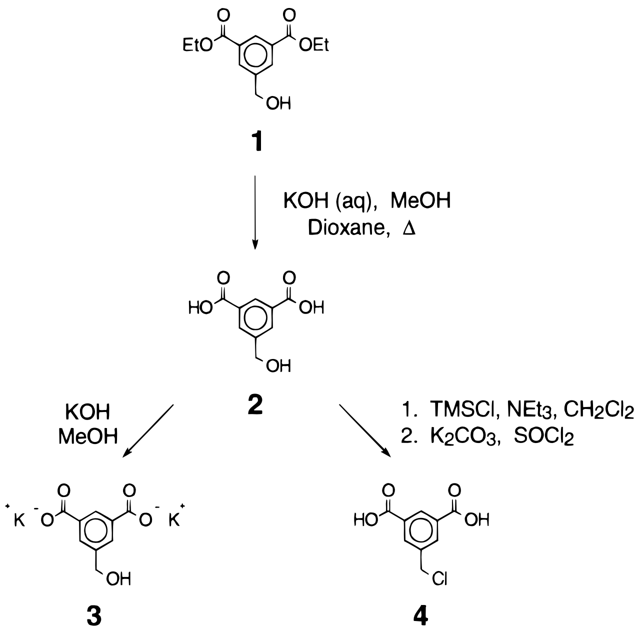
10.1021/ol9907724 CCC: $18.00

Scheme 1

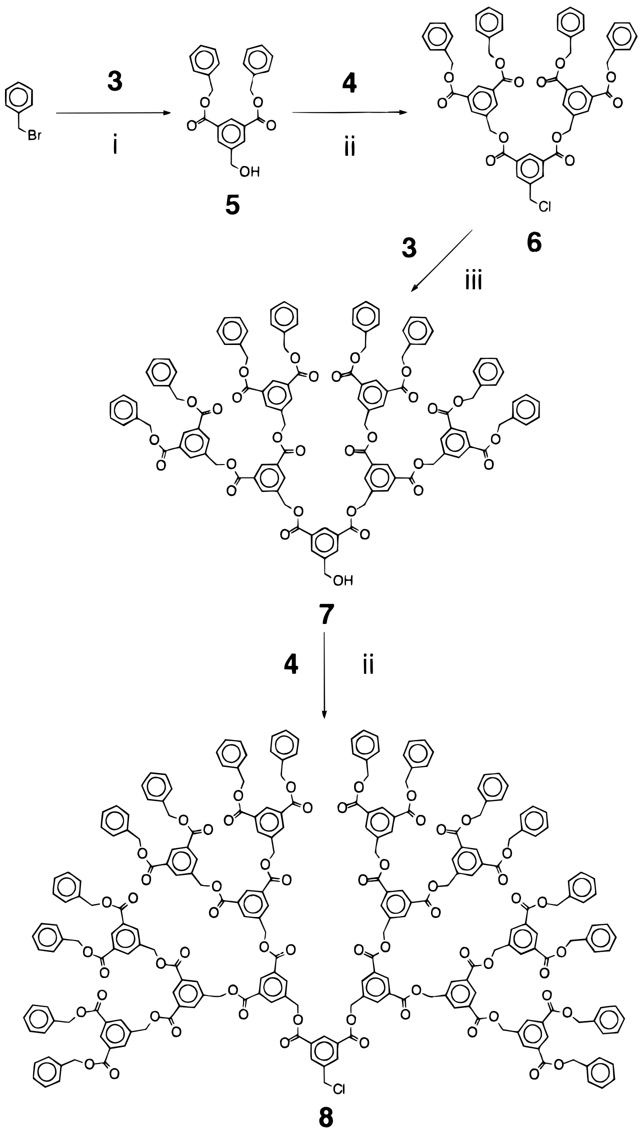


mixture of MeOH and dioxane afforded the hydroxy acid **2** in 65% yield. Titration of **2** with methanolic KOH followed by removal of the solvent and several azeotropes with benzene quantitatively yielded monomer **3**. The complementary activated monomer **4** was prepared from **2** in 85% yield by first protecting the carboxyl groups of **2** as their trimethylsilyl esters, followed by in situ chlorination of the remaining hydroxymethyl moiety with $SOCl_2$.[15] Both monomers **3** and **4** were isolated as shelf-stable, white solids.

Monomers **3** and **4** were designed to promote the rapid growth of high-generation dendrons via an iterative and alternating sequence of carboxylate salt alkylations and DCC/DPTS-mediated esterifications,[16] respectively. The reactions were selected because they are known to be extremely mild, fast, and afford high conversions. More importantly, the use of these conditions is generally not accompanied by complicating side products. Of utmost importance is the fact that the reaction conditions required for introduction of one monomer do not adversely affect functionality already present within either the dendrimer or the complementary monomer.

The orthogonal coupling sequence used to prepare convergent poly(benzyl ester) dendrimers based upon monomers **3** and **4** possessing benzyl ester surfaces is depicted in Scheme 2. Thus, refluxing **3** and benzyl bromide in CH_3CN in the presence of a catalytic amount of 18-crown-6 afforded the [G-1] alcohol **5** in 94% yield within 2 h. Coupling of alcohol **5** with monomer **4** in the presence of DCC and catalytic DPTS cleanly yielded the [G-2] chloride **6** in 86% yield after purification. The third-generation alcohol **7** was prepared by alkylation of the carboxylates of **3** with a slight excess of monodendron **6**. Unlike the preparation of **5**, CH_3CN could not be used for this alkylation due to the poor solubilities of both the starting and product dendrons. Use of either refluxing acetone or 2-butanone, both better solvents for the dendrons, resulted in sluggish reactions that were accompanied by the formation of increased amounts of side products (presumably the result of increased ester hydrolysis or transesterification). However, by employing anhydrous DMF as solvent, a stoichiometric amount of KBr, and 1 drop of *N*,*N*-diisopropylethylamine (DIPEA), both the solubility and reactivity were enhanced so extensively that high conversions were observed within less than 1 h at 80 °C. These conditions proved to be so efficient and general that they were used throughout the remainder of the syntheses. In this way the

Scheme 2[a]



[a] (i) 18-crown-6, K_2CO_3, CH_3CN, Δ; (ii) DCC, DPTS, CH_2Cl_2, THF; (iii) KBr, DIPEA (1 drop), DMF, 80 °C.

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(14) The only reference for the use of **2** in dendrimers was reported by Seebach, D.; Herrmann, G. F.; Lengweiler; U. D.; Amrein, W. *Helv. Chem. Acta* **1997**, *80*, 989.

(15) The preparation of other chloro acids using this method has been previously reported by Shiozaki, M.; Ishida, N.; Iino, K.; Hiraoka, T. *Tetrahedron* **1980**, *36*, 2735.

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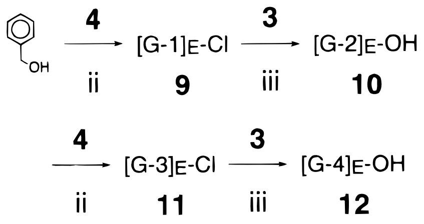
[G-3] alcohol **7** was prepared in 89% yield after purification. Finally, condensation of **7** with monomer **4** using the same DCC/DPTS conditions as described above afforded the [G-4] chloride **8**, again in excellent yield (90%) after purification.

The versatility of this approach was demonstrated by the fact that the synthesis of these dendrons could begin with either monomer **3** or **4**. In this way, starting from benzyl alcohol and monomer **4,** the complementary dendrons ([G-1]$_E$-Cl **9** (97%), [G-2]$_E$-OH **10** (81%), [G-3]$_E$-Cl **11** (85%), [G-4]$_E$-Cl **12** (84%)) could be prepared using the same chemistry described above with similar yields observed for each step (Scheme 3).

Scheme 3

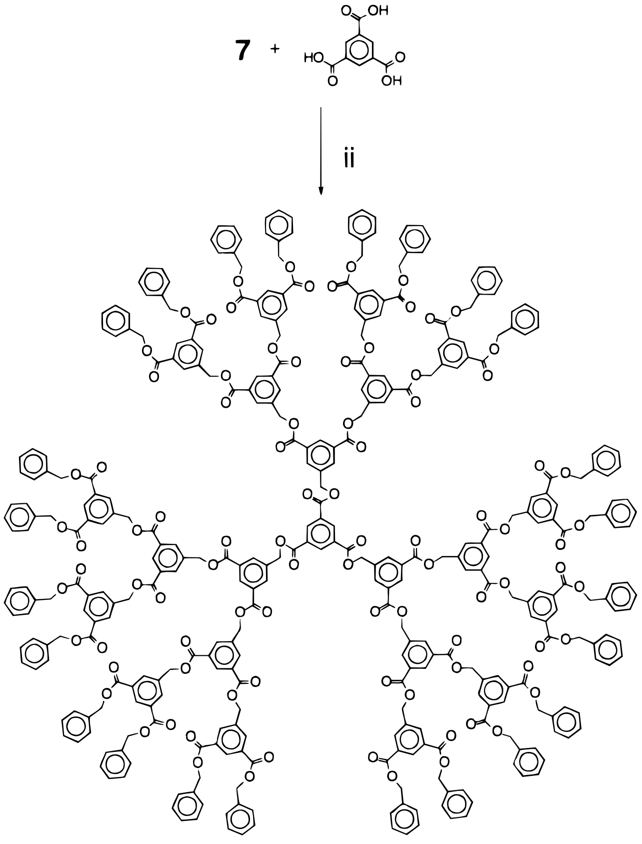


In addition, perfect dendrimers based upon these poly(benzyl ester) monodendrons were prepared, again using the same coupling conditions described above. Thus coupling dendron **7** with trimesic acid in the presence of DCC/DPTS afforded the [G-3] tricore dendrimer **13** very cleanly in 85% yield after purification by flash chromatography (Scheme 4).

While all of the dendrons and dendrimers described herein were purified by flash chromatography, it must be emphasized that the clean and highly converting nature of the reactions employed facilitated product isolation. The small amounts of impurities formed were generally more polar than the product dendrons and hence could be removed with relative ease. The combination of the orthogonal "activated" monomer strategy, the fast reactions employed, and the ease of purification makes it possible to prepare large dendrimers (i.e., [G-4]) of this type in as little as 3 days. The structure and purity of all the dendrons described herein has been confirmed using ^{1}H and ^{13}C NMR, mass spectroscopy (EI MS for [G-1] dendrons and MALDI-TOF MS for all others), and elemental analyses.

In conclusion, we have introduced to the concept of the orthogonal "activated" monomer approach for the rapid synthesis of large, perfect dendrimers and demonstrated that this, in combination with judicious choices of chemical reactions, can be used to efficiently prepare a new family of poly(benzyl ester) dendrimers. We believe that this strategy is extremely general and will find widespread applicability in the synthesis of many families of dendrimers including aliphatic polyesters and polyethers. While the poly(benzyl ester) dendrimers described herein clearly lack the structural robustness of some of their predecessors,[1−3] the facility with which they can be synthesized may offset these weaknesses. This family of dendrimers will surely find uses as molecular scaffolds,[17] as building blocks for site isolation,[18] or in materials applications where eventual degradation of the dendrimer is desired.[19]

Scheme 4



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Acknowledgment. This research was supported by a grant from the AFOSR MURI program. Additional fellowship support from Lucent Technologies for A.W.F. is gratefully acknowledged.

OL9907724

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