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Tetrahedron Letters

Tetrahedron Letters 46 (2005) 1027–1030

Synthesis of polyester dendrimers and dendrons starting from Michael reaction of acrylates with 3-hydroxyacetophenone

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Received 7 October 2004; revised 26 November 2004; accepted 1 December 2004
Available online 22 December 2004

Abstract—A new AB_2 type building block for synthesis of dendritic compounds is made starting from Michael addition of 2 equiv of 3-hydroxyacetophenone to acrylate, followed by decarboxylation and deprotection of either carboxyl or hydroxyl protecting groups. [G1]–[G4] dendrons and [G2] dendrimer were synthesized by the reiterative [hydrogenolysis then DCC/DPTS coupling] sequence using a combination of convergent and divergent growth methods.

Dendrimers are globular macromolecules consisting of a core molecule and symmetrically arranged branches with a well-defined number of reactive end groups matching to each generation.[1] They have demonstrated unique properties that make their use possible in encapsulation of guest molecules,[2] catalysis,[3] and drug delivery systems,[4] etc. To further develop dendrimers, it is not enough only to modify end groups of known skeletons, but also to exploit dendrimers of new structure. They are often classified according to functional group that combines building blocks together such as polyamine, polyamide, or poly ether type, etc. Among them, polyester-type dendrimers attract considerable attention especially for application to drug delivery systems where biocompatibility and easy hydrolytic nature inside cells are important.[5] In addition, due to high solubility and miscibility in ordinary organic solvents and reactivity of end carboxyl or hydroxyl groups, they can be used as versatile tools in various fields. Herein, we present a synthesis of new polyester-type dendrons and dendrimers starting from two equivalents of acrylic ester and 3-hydroxyacetophenone and giving a new AB_2 type building block by Michael reaction.

Scheme 1 shows a synthetic route for the AB_2 building blocks, **2** and **3**, using Michael addition of 3-hydroxyacetophenone to acrylate ester. Two sets of orthogonal protecting groups, *t*-butyldimethylsilyl (TBDMS) and benzyl on the one hand, and benzyl and *t*-butyl on the other for the hydroxyl and carboxyl, respectively, were selected. TBDMS ether of 3-hydroxyacetophenone was treated with 0.8 equiv of NaH in benzene followed by reaction with 2 equiv of benzyl acrylate in refluxing benzene to afford 4-[3′-*t*-butyldimethylsilyloxybenzoyl]heptanedioic acid dibenzyl ester **1a** in 50% yield. Under these reaction conditions, the yield of the mono-adduct of acrylate was negligible. On the other hand, reaction of *t*-butyl acrylate with benzyl ether of 3-hydroxyacetophenone gave higher yield (77%) of di-*t*-butyl ester, **1b**. Hydrogenolysis of **1a** in the presence of 10% Pd/C at atmospheric pressure in ethyl acetate gave dicarboxylic acid **2a** in 99%. Deprotection of TBDMS group was conducted using 1.1 equiv of tetrabutylammonium fluoride (TBAF) in THF to afford **3a** (94% yield).[6] Another Michael addition product, **1b** was deprotected either by TFA to give **2b** (94%) or by hydrogenolysis to give **3b** (95%).

Keywords: Polyester dendrimers; New AB_2 building blocks; 3-Hydroxyacetophenone; Michael reaction.

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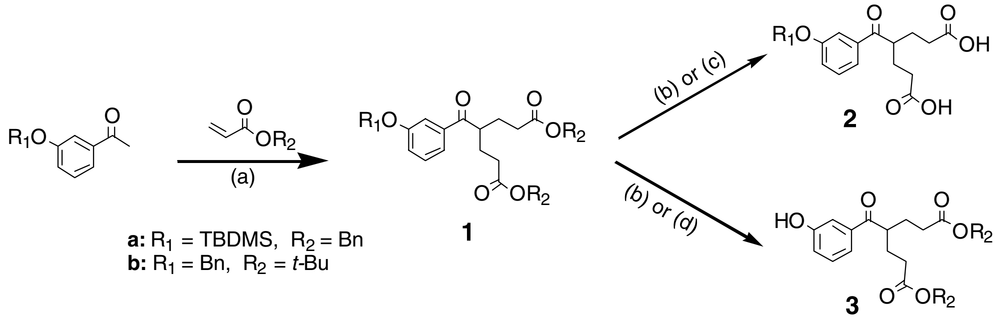
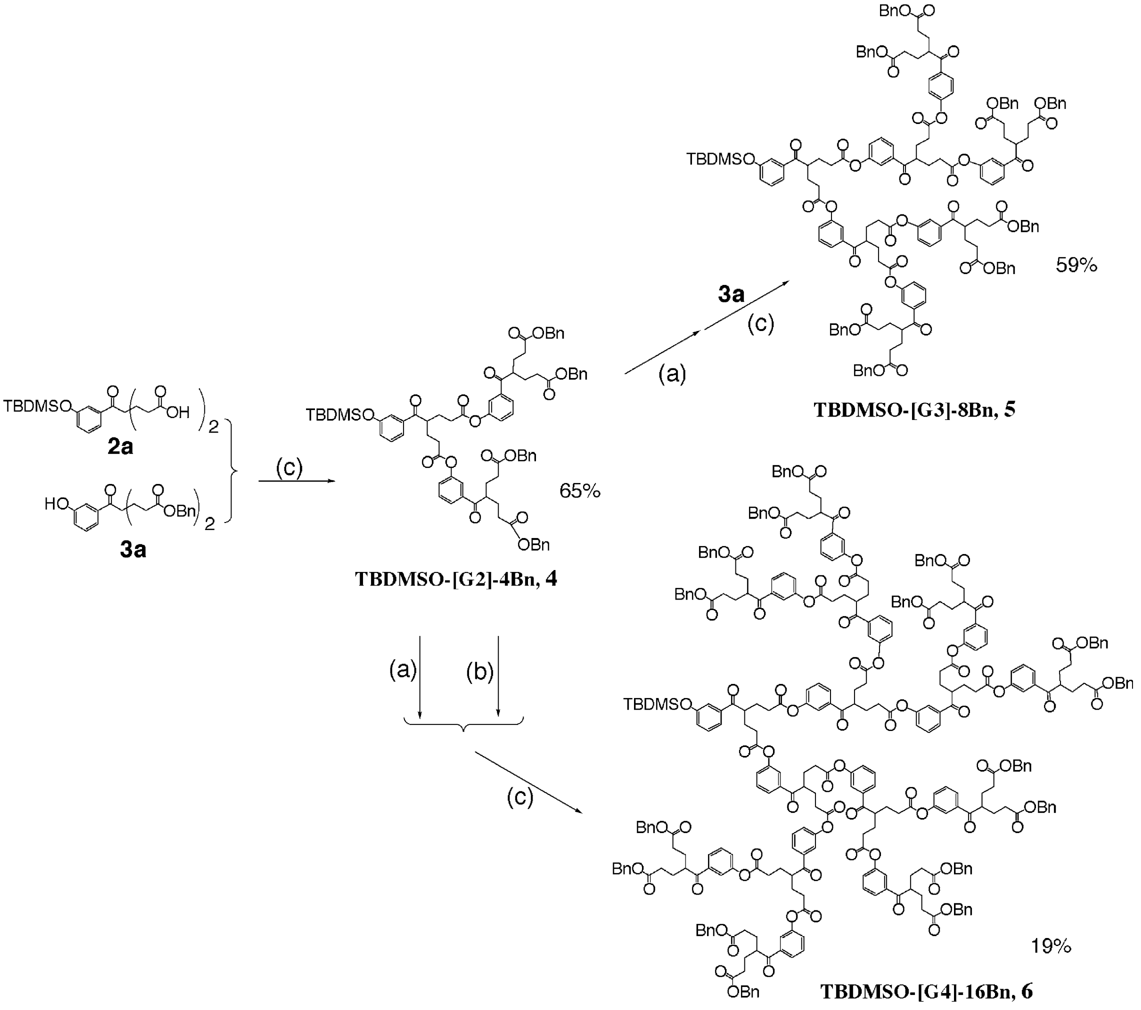
doi:10.1016/j.tetlet.2004.12.004



Scheme 1. Synthesis of the building blocks **2** and **3**. Reagents and conditions: (a) NaH, C_6H_6; (b) 10% Pd/C, H_2, AcOEt; (c) TFA, CH_2Cl_2; (d) TBAF, THF.



Scheme 2. Synthesis of the dendrons **4**, **5**, and **6**. Reagents and conditions: (a) H_2, 10% Pd/C, AcOEt; (b) TBAF (AcOH), THF; (c) DCC (EDCI), DPTS, CH_2Cl_2–DMF.

Scheme 2 shows a strategy for synthesizing a fourth generation dendron, TBDMSO-[G4]-16Bn **6**, from dibenzyl ester **2a** by a combination of divergent and convergent methods. **2a** was coupled with 2.1 equiv of **3a** in the presence of *N*,*N*′-dicyclohexylcarbodiimde (DCC, 3 equiv) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS, 0.5 equiv)[7] in CH_2Cl_2/DMF (3:1) to give dendron, TBDMSO-[G2]-4Bn **4**, in 65% yield. Hydrogenolysis of **4** in the presence of Pd/C followed by coupling with **3a** by DCC-DPTS gave dendron, DBDMSO-[G3]-8Bn **5**, in 59% yield. Coupling of benzyl-deprotected **4** with TBDMS deprotected **4** (4 equiv) using DCC-DPTS in CH_2Cl_2/DMF (3:1) afforded dendron **6** in 19% yield. Reaction of TBDMS deprotected

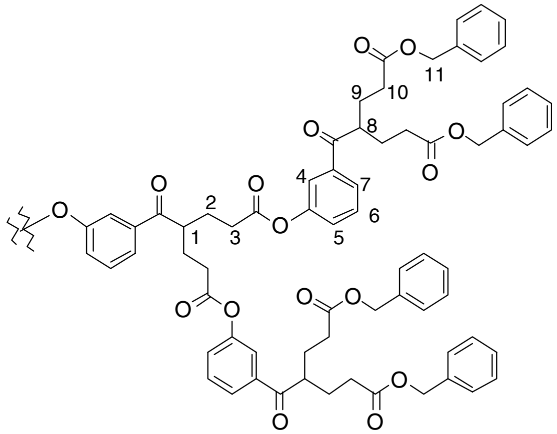


Figure 1. Numbering of the skeleton of [G2] dendron.

4 and 1,3,5-benzene tricarbonylchloride in the presence of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 gave dendrimer, [G2]-12Bn **7**, in 92%.

Under similar reaction conditions, condensation of **2b** and **3b** gave [G2] and [G3] dendrons in 63%, 25% yield, respectively. However, use of strongly acidic TFA for dedprotection of end *t*-butyl groups in the course of divergent synthesis of dendron sometimes led to cleavage of the ester bonds. Since dendrimer synthesis from **2a** and **3a** does not require acidic condition, the Michael addition product **1a** was used in spite of lower yield than that of **1b**.

Dendrimer synthesis starting from *p*-hydroxyacetophenone was also attempted. Michael addition of 4-benzyloxyacetophenone to *t*-butyl acrylate gave quantitative yield of a building block. Although [G1]dendrimer was synthesized by the reaction with 1,3-5-tris[bromomethyl]benzene in moderate yield, it was found to be too susceptible to hydrolysis even in the presence of a trace amount of water to use for synthesis of dendrimers of higher generation.

All the dendrons and dendrimers are colorless viscous oil that are soluble in halogenated solvents or ethyl acetate and insoluble in methanol or water. They were mostly purified by preparative GPC since purification by silica gel chromatography was difficult. The structural determination was carried out by NMR, ESI-MS, and elemental analysis. ^{1}H NMR signals at 3.5–3.9 ppm (ArCOC*H*–) are particularly useful in diagnosing the dendrimer and dendron formation. While the methyne proton signal of the building block **1a** ([G1]) and the outermost shells (H_8 in Fig. 1) of **4** ([G2]), **5** ([G3]), and **6** ([G4]) are observed at 3.5–3.6 ppm (as the X part of fine-structured A_2B_2X quintet, $J = 5.7$ Hz) that of the inner shells (H_1) are at 3.7–3.8 ppm (as the X part of fine-structured A_2B_2X quintet, $J = 5.7$ Hz). The ratio of integration of these two signals changes according to dendrimer and dendron generation number. In addition, signals at 2.5–2.7 ppm due to $-CH_2COO-$ (H_3) of the inner shells are also useful. ESI-MS spectra were taken with LiI for ionization of the samples and peaks of $[M+Li]^+$ and/or $[M+2Li]^{2+}$ were clearly observed. [G2] dendron **4** showed *m/z* 1286.78 for $[M+Li]^+$ (calcd 1286.52), [G3] dendron **5** showed *m/z* 2696.17 for $[M+Li]^+$ (calcd 2696.08), and [G4] dendron **6** showed *m/z* 2761.15 for $[M+2Li]^{2+}$ (calcd 2761.076). To study conformation of these dendrons in $CDCl_3$, H–H ROESY 2D NMR technique was used. [G2] dendron **4** showed NOE cross-peaks between non-adjacent end benzyl methylene (H_{11}) and inner methyne (H_8) and aromatic (H_4, H_5, and H_6) protons. [G4] dendron **6** showed only cross-peaks derived from outermost shell protons (between H_{11} and H_4, H_5) and any other cross-peaks were not observed. These observations suggest that, while end benzyl group is folded so as to locate in the vicinity of the nearest aromatic ring, the ester skeleton of [G4] dendron takes predominantly extended chain conformation at least in $CDCl_3$. These results are consistent with those for conformation of DAB dendrimers recently studied by Chai et al.[8]

In summary, we have demonstrated synthesis of new polyester type dendritic compounds from 3-hydroxyacetophenone and acrylic ester. [G1]–[G4] dendrons and [G2] dendrimer are synthesized by the reiterative [hydrogenolysis then DCC/DPTS coupling] sequence using a combination of convergent and divergent growth methods. These dendritic compounds have some unique structural features, such as unsymmetrical branching due to connection via meta substituents of benzene ring, having longer distance between two benzene rings and wider void space inside than other known dendrimers containing aromatic rings.[1] Therefore, although the product yield is not satisfactory high, they will have the opportunities for use in new polymer architectures, molecular recognition, or catalysis.

Acknowledgements

We are grateful for partial support of this research by a Grant-in-Aid for Scientific Research No 13680677 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.004. Experimental procedures for the synthesis of the building block, the dendrons and the dendrimer are available.

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