

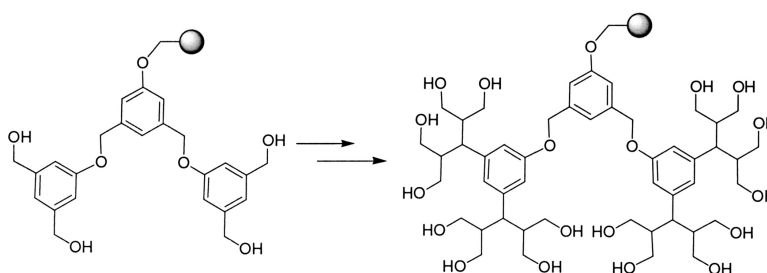
Report

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Synthesis of Tetrafurcated Dendritic Units on Solid Support

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Solid-phase synthesis, one of the core technologies of combinatorial chemistry, has undergone intense development over the past decade.¹ Along with numerous advantages, there are several drawbacks associated with the technique. Among these is the relatively low loading of the active sites (typically <1.6 mmol substrate/g polymer). This property of the supports is reflected in the difficulties in the evaluation and identification of the final products when combinatorial approaches, such as “split-and-mix” synthesis, are implemented. Super-high-loading resins, for instance, are required if characterization of a compound from a single bead is a target. An additional advantage of high-loading beads is their application as supports for reagents or scavengers in parallel or combinatorial solution-phase synthesis.²

Dendronization is one of the ways to increase the per-bead loading of a support.³ Bradley and co-workers demonstrated that dendronization of macroporous beads enabled monitoring and characterization from a single bead.⁴ Effective nucleophile and electrophile scavengers were constructed using dendronized support.⁵ Moreover, a few research groups recently demonstrated that dendronization can significantly improve the properties of catalysts immobilized on polymeric support.⁶

Although the majority of the dendritic compounds were prepared using orthodox solution chemistry, an increasing number of reports are dedicated to the preparation of dendrons on solid support.^{3–8} Solid-phase synthesis can provide solutions to a number of problems associated with dendron preparation and, particularly, the time-consuming purification. Solid-phase synthesis can also markedly improve the yield and homogeneity of the formed dendrons.

All dendritic molecules assembled on support, as well as the overwhelming majority of those prepared in solution, are based on monomeric furcated units of type AB₂ or AB₃. Herein, we present the design of a furcated unit of type AB₄ that will cause a substantial increase in the loading for each generation.

The success of dendrimer synthesis in general, and its solid-phase assembly in particular, is based on the ready accessibility of the monomer. Usually commercially available compounds or units that can be prepared in solution via one to two high-yielding steps are utilized. Unfortunately, preparing monomers in solution via longer synthetic sequences is

a tiresome, costly, and labor-intensive task that frequently fails to provide the desired monomers in sufficient quantities. Herein, we report an approach in which the monomers are assembled on the support. The approach makes use of the advantages of solid-phase synthesis not only for the dendron assembly from the monomer, but also the preparation of the monomeric unit itself. The building blocks used for its assembly are inexpensive and commercially available.

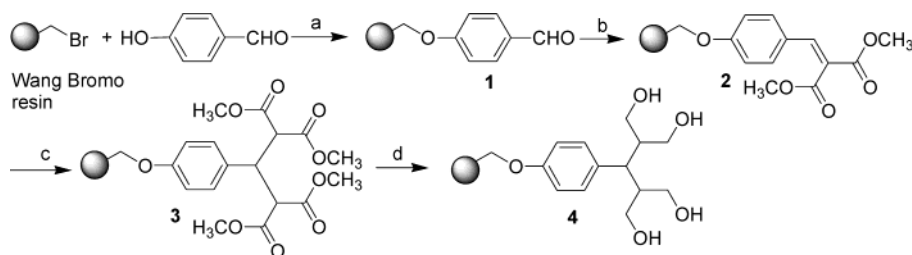
The synthesis is based on the attachment of the commercial 4-hydroxybenzaldehyde to Bromo Wang resin using the Williamson reaction (Scheme 1). The conjugated diester-terminated resin **2** is obtained via the Knoevenagel condensation with dimethyl malonate using a catalytic amount of piperidinium acetate. The best result was achieved using a dimethyl malonate/toluene 1:1 mixture. For higher yield, the reaction was repeated twice until complete disappearance of the aldehyde signal in the ¹H NMR of the cleavage solution occurred. Already at this stage, a trace amount of the tetraester **3**, a product of the Michael addition of dimethyl malonate to **2**, accompanied **2** on the resin. However, despite the precedence in solution synthesis,⁹ we have not been able to push the conversion to **3** above 10% with piperidinium acetate as a catalyst. Much better results were achieved with DBU as a promotor. Unfortunately, this Michael addition is reversible, and under standard conditions, complete conversion was not possible due to the base-induced retro-Michael reaction. Following intensive optimization efforts, we established that using a large excess of dimethyl malonate with 1 equiv of DBU in THF leads to a quantitative yield. It is noteworthy that even in solution, similar synthetic schemes required the use of a large excess of malonate.⁹ ¹H NMR of the cleavage solution of **3** in TFA/CDCl₃ 1:1 demonstrated that the two types of aliphatic protons in the dendron backbone overlap exhibiting a singlet at 4.25 ppm (instead of a triplet and doublet). Evaporation of the cleavage solution, neutralization of the residue with NaHCO₃, and redissolution in chloroform led to separation of the signals, forming the expected AB₂ pattern.

Reduction of the tetraester to the tetraol resin **4** was a very challenging task. The aforementioned retro-Michael reaction is readily induced by most reduction reagents due to their basic nature. Thus, a variety of reagents, such as LiBH₄, Red-AL, and LiAlH₄ gave a mixture of products. Neutral 9-BBN reacted only at an elevated temperature (THF reflux), but gave a product of low purity. Fortunately, use of a solution of DIBAL-H in THF at room temperature gave the final product in high yield and purity.

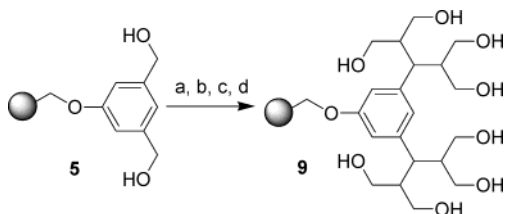
As expected from the symmetry properties of the molecule, four different signals of the methylene protons are observed in the cleavage solution of **4**: three double doublets overlap at 4.53 ppm, while another appears at 4.25 ppm.

In addition to measuring the loading of the dendritic constructs, using an internal standard in the cleavage solution (CDCl₃/TFA, 1:1), we also attempted photometric measurement of the loading of the terminal OH groups.¹⁰ Thus, we

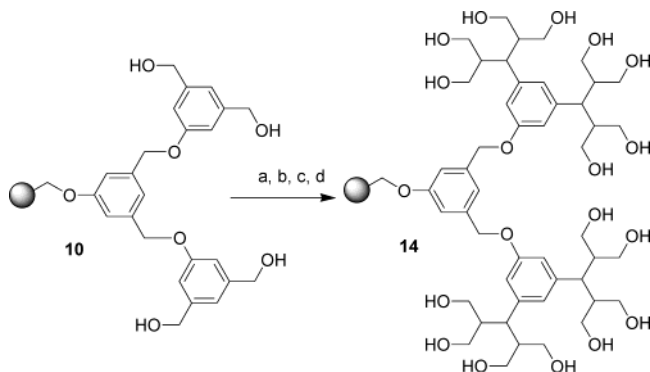
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Scheme 1^a

^a Reagents and conditions: (a) LiH, TBAI, DMF, 60 °C, 12 h; (b) dimethyl malonate, piperidine, AcOH, toluene, 80 °C, 24 h; (c) dimethyl malonate, DBU, THF, 67 °C, 48 h; (d) DIBAL-H, THF, rt, 12 h.

Scheme 2^a

^a Reagents and conditions: (a) SO₃·Py, Et₃N, DMSO, rt, 5 h; (b) dimethyl malonate, piperidine, CH₃CO₂H, toluene, 80 °C, 24 h; (c) dimethyl malonate, DBU, THF, 67 °C, 48 h; (d) DIBAL-H, THF, rt, 12 h.

Scheme 3^a

^a Reagents and conditions: (a) SO₃·Py, Et₃N, DMSO, rt, 5 h; (b) dimethyl malonate, piperidine, CH₃CO₂H, toluene, 80 °C, 24 h; (c) dimethyl malonate, DBU, THF, 67 °C, 48 h; (d) DIBAL-H, THF, rt, 12 h.

attached Fmoc-Gly-OH to the OH terminal groups. Photometric determination, following the cleavage of the Fmoc groups with piperidine, showed loading corresponding to only a 50% overall yield. However, attachment of Fmoc-6-aminohexanoic acid to the hydroxy terminal groups exhibited loading corresponding to a 90% overall yield (reduction + immobilization of the acid), a result close to that of the ¹H NMR measurement. The failure to functionalize **4** with Fmoc-Gly-OH, bearing the bulky Fmoc group close to the reacting carboxylate site, must be attributed to the severe steric congestion of the reacting sites of **4** and implies that spacers may be needed for immobilization of bulky reagents on the dendron periphery. The loading of the OH groups on the dendronized resin was more than 3-fold greater than that on the starting Wang resin.

To prepare a resin with even higher loading, we used, as a starting material, resins **5** and **10** that were already modified with first- and second-generation aryl benzyl ether dendrons according to our recent report (Schemes 2 and 3).^{8b} The

CHO-terminal groups (resins **6** and **11**) were formed via oxidation of the CH₂OH groups with sulfur trioxide pyridine complex in DMSO. Using the reaction sequence of Knoevenagel condensation (resins **7** and **12**), Michael addition (resins **8** and **13**), and reduction (resins **9** and **14**) under the aforementioned conditions gave dendrons with 8 and 16 terminal OH groups.

The loading of the OH groups on the dendronized resins increased six- and 10-fold, respectively, as compared with that of the starting Wang resin. This reaction sequence produced the octa- and hexadeca-ol products with very high yield and purity.

In conclusion, we demonstrated the construction of new high-loading dendronized resins using an unprecedented tetrafurcated module. The novel submonomeric approach, based on a four reaction sequence, was used for the assembly of dendrons on solid support.

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Supporting Information Available. Experimental procedures and ¹H, ¹³C NMR, and MS data of all new compounds are available as Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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