



Phenols-useful templates for the synthesis of bi-functional orthogonally protected dendron building blocks via solid phase Mitsunobu reaction

Gary Gellerman^{a,*}, Sagit Shitrit^{a,b}, Tzachi Shalit^{a,b}, Orit Ganot^{a,b}, Amnon Albeck^b

^aDepartment of Biological Chemistry, Ariel University Center of Samaria, Ariel 40700, Israel

^bThe Julius Spokojny Bioorganic Chemistry Laboratory, Department of Chemistry, Bar-Ilan University, Ramat Gan 52900, Israel

ARTICLE INFO

Article history:

Received 30 June 2009

Received in revised form

10 November 2009

Accepted 26 November 2009

Available online 1 December 2009

Keywords:

Dendron building block

Mitsunobu coupling

Orthogonal protection

Solid-Phase Organic Chemistry (SPOC)

ABSTRACT

Bi-functional dendritic building blocks for convergent dendrimer growth were successfully synthesized from phenolic templates in the solid phase via a Mitsunobu reaction. Each arm of the dendron building block carries an orthogonally protected secondary amine along the arm, and a peripheral primary amine or phenol group (building block type 1) or a tertiary amine junction with orthogonally protected peripheral primary amine or carboxyl groups (building block type 2). The synthetic routes reported in this work are general and applicable for the preparation of diverse building blocks, controlling protection, arm length, and peripheral moieties. These novel dendron units can form unusual dendritic architectures by solid-phase chemistry, which may be incorporated into specific complex structures expanding the scope of dendrimer science.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Dendrites are branched synthetic macromolecules with many arms emanating from a central core. Important features of the dendritic architecture include a high degree of structural symmetry and a defined number of terminal groups at the surface, which may be distinguished from the interior core. Depending on their size (generation or order), dendrons not only have an impact on the backbone conformation and flexibility but also allow the introduction of a large number of functional groups at the periphery. The combination of these features creates an environment within the dendrimer molecule, which facilitates new discoveries in many important research areas, such as material and biomedical sciences.¹ Current syntheses of dendrimers require exhaustive control of the critical molecular design parameters, such as size, surface chemistry, flexibility, and topology.^{1a,2–4} Effective techniques include the Starburst divergent strategy,^{2,3} the convergent growth strategy,⁵ and the self-assembly strategy.⁶ These synthetic approaches are effective in creating macromolecules with a unique combination of properties.^{7,8} However, most dendronized polymers known today carry only one kind of functional group (usually either

amine or hydroxyl), which are typically blocked with only one type of protecting group.⁹ This feature limits the choices for ‘surface’ engineering to modify either all groups at once or a certain amount of these randomly distributed over the entire macromolecule. The orthogonal introduction of two different chemical modifications is therefore not possible. Overcoming this limitation and thus increasing the options for surface chemical derivatization can be achieved by the development of dendronized macro-monomers and polymers, which carry orthogonally protected peripheral groups at each repeat unit. Selective deprotection should then allow the introduction of predetermined numbers of molecular components to each repeat unit.

Solution synthesis is the most common synthetic methodology for the preparation of dendrimers.¹ However it suffers major problems when it comes to practical synthesis, in particular, the necessity for repeated and time-consuming purifications. The solid-phase synthesis of dendrimers on the other hand has a major advantage: a large excess of reagents, which pushes the reaction to completion, can be used without the problems usually associated with purification, which becomes only a matter of extensive washing. It should also be noted that resin-bound dendrimers can enhance resin loading. This seems extremely important nowadays, because of the huge demand for solid-phase synthetic resins with increased loading capacity and reduced cost.

Here we report the synthesis of bi-functional dendron building blocks (BB) from phenolic templates via Mitsunobu reaction for convergent dendrimer growth on solid support. These building blocks are attributed to two types, differing from each other by the

Abbreviations: Alloc, allyloxycarbonyl; Boc, *t*-butyloxycarbonyl; Cbz, benzyloxycarbonyl; DCM, dichloromethane; *o*-Nosyl, 2-nitrophenylsulfone; Fmoc, 9-Fluorenylmethoxycarbonyl; NMM, *N*-methyl morpholine; PE, petrol ether; SPOC, Solid-Phase Organic Chemistry.

* Corresponding author.

E-mail address: garyg@ariel.ac.il (G. Gellerman).

number and nature of the peripheral groups (Fig. 1). The protecting groups used in this work were matched to the orthogonal or semi-orthogonal combinations utilizing Alloc/Allyl, *o*-Nosyl, Fmoc, Boc, and Cbz. The comparison between solution- and solid-phase approaches for the synthesis of our dendronic building blocks is also discussed.

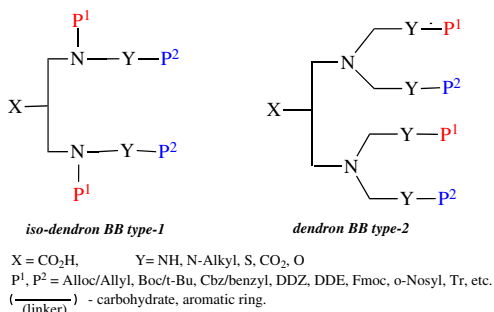
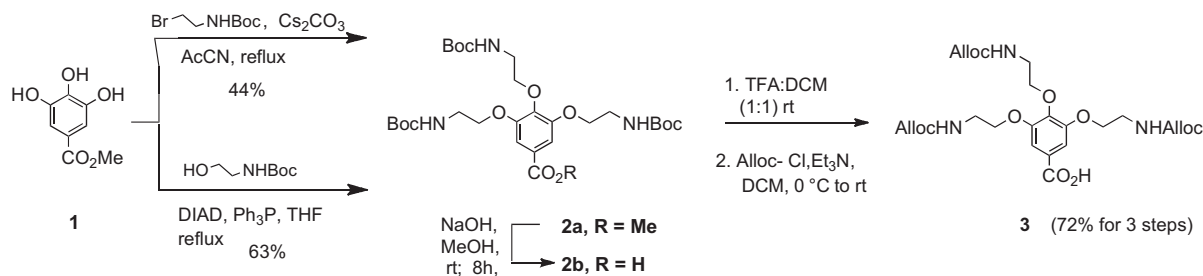


Figure 1. Schematic structure of dendron building blocks (BB) of types 1 and 2.

2. Results and discussion

The dendron building blocks described in this paper can be divided into two classes: type 1 and type 2 (Fig. 1). BB type 1 possess branch arms carrying a protected main chain secondary amine and a terminal primary amine or phenol group. Phenolic BB of type 2, which are more versatile and represent an extended version of dendron BB type 1, are generated from BB type 1 by alkylation of the deprotected secondary amine. BB type 2 present a tertiary amine junction and a protected peripheral primary amine or carboxyl group. Type 2 building block is more versatile in dendrimer synthesis, creating opportunities for variable linkage moieties (primary and secondary amides, carbamates, esters, ureas, etc.), while type 1 is more limited due to the fixation of the secondary amine at the junction.



Scheme 1. Solution-phase synthesis of tri-Alloc-protected 3,4,5-trihydroxybenzoic acid 3.

In order to synthesize the schematic structures in Fig. 1, the methodology must allow the selective incorporation of functionalities within the dendron scaffold. Fréchet showed in a series of publications how the convergent approach can be utilized in the control of surface¹⁰ and internal¹¹ functionality. We aim to achieve a better control in the construction of dendrimers incorporating a variety of compatible building blocks of type 1 and 2 possessing multi-linkage capabilities.

Polyhydroxybenzoic acids are useful starting materials for generating complex macromolecules by tethering of their hydroxyl groups.^{12,13} Therefore we propose the use of phenols as a basic unit in the synthesis of our dendron building blocks. Phenolic scaffolds seem suitable for the synthesis of dendrons via two key steps: phenolic alkylation¹⁴ and the Mitsunobu reaction.¹⁵ The existence of more than one hydroxyl group in combination with the carboxylic acid on the benzene ring provides a versatile starting point for the synthesis of branched dendritic units for

convergent dendrimer growth. The CO₂H moiety on the phenol ring has two functions: it acts as an anchor for assembly or immobilization of the protected dendron building blocks on the acid-sensitive resin (Cl-Trt resin) for fast convergent dendritic growth on solid support, and it could be used for conjugation chemistry after cleavage.

2.1. Solution-phase synthesis of tri-Alloc-protected 3,4,5-trihydroxybenzoic acid and tetra-Alloc-protected type 1 dendron building block

We started our research by the examination of a triple condensation of *N*-Boc-2-bromoaminoethane¹⁶ to methyl 3,4,5-trihydroxybenzoate (Scheme 1) via phenolic alkylation¹⁷ and Mitsunobu reaction.¹⁵ The aim of the experiment was to examine and tune the conditions for the key reaction step before engaging in the assembly of our structurally more complex dendritic building blocks. After saponification of the benzoate ester, the acid-labile Boc group in 2b could be further replaced by Alloc protection, leading to protected unit 3. Actually, this tri-armed unit 3 served as a model toward the incorporation of more complicated linkers containing orthogonally protecting groups. Thus, the triple reaction of 1 with BocNHCH₂CH₂OH under standard Mitsunobu conditions consistently yielded 2a in higher yield (63%) than the standard alkylation with BocNHCH₂CH₂Br (44%), even if a stronger base, Cs₂CO₃ instead of K₂CO₃, was used in the alkylation reaction. Furthermore, the hydrolysis of 2a yielded triply-Boc-protected benzoic acid 2b, which was subjected to deprotection (TFA/DCM, 1:1 at rt) and subsequent re-protection with Alloc-Cl to give 3 in 72% overall yield for the three steps. Noteworthy, the shorter pathway to 3, applying a direct Mitsunobu coupling of AllocNHCH₂CH₂OH to 1, was less successful. Based on these results, we decided to use the more effective Mitsunobu reaction as a key step for assembling the multi-functional dendron building blocks.

Next, we moved to the synthesis of dendron building block of type 1 7b (Scheme 2). The first attempt to synthesize 7b was carried out in solution. This compound bears four Alloc protecting groups, which is a reasonable model for further experiments.

In order to improve the yield of the hydrolysis step,¹⁸ as was observed also for 2b, we initially synthesized dihydroxyl core structure 4 (Scheme 2), which bears a more convenient, acid-labile *t*-Bu ester, instead of base-labile methyl ester as in 2a. The desired monoalkylated 4 was prepared by the reaction of threefold excess of 1,3,5-trihydroxybenzene with *t*-butyl bromoacetate (K₂CO₃, DMF, rt, overnight) in 79% yield. The linker 6 was almost quantitatively prepared from commercially available 2-(2-aminoethylamino)ethanol by standard double protection with Alloc-Cl. Finally, 4 was submitted to the double Mitsunobu condensation (DIAD, Ph₃P in THF:DCM, rt) with 2 equiv of 6 affording tetra-Alloc *t*-butyl ester intermediate 7a in a moderate yield (52%, after chromatography, 1:1 EtOAc/PE). *t*-Butyl removal in TFA/DCM (1:1) gave

Download English Version:

<https://daneshyari.com/en/article/5222109>

Download Persian Version:

<https://daneshyari.com/article/5222109>

[Daneshyari.com](https://daneshyari.com)