Tetrahedron 69 (2013) 6810–6820

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of novel polyesteramine dendrimers by divergent and convergent methods

Hitoshi Akiyama, Kazuyuki Miyashita, Yoshiyuki Hari, Satoshi Obika *, Takeshi Imanishi

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

ARTICLE INFO

Article history:
Received 20 April 2013
Received in revised form 1 June 2013
Accepted 8 June 2013
Available online 14 June 2013

Keywords:
Dendrimer
Polyester
Adamantine
Click chemistry
Divergent
Convergent

ABSTRACT

Novel dendrimers having an adamantane structure as a core were synthesized such that even low generation dendrimers had a globular structure. Moreover we tried to give them biodegradable function by using ester bonds. Synthesis of the dendrimers, particularly at higher generations, proved difficult via a stepwise procedure, and thus a convergent route was used in which the adamantane core is coupled to the dendritic segments in the final step. We achieved the synthesis of two separate dendrimers with convergent methods till the third generations. The convergent dendrimers were synthesized in good yields compared with divergent one and both dendrimers were found to have narrow polydispersities by GPC analysis.

1. Introduction

Dendrimers are very interesting macromolecules with highly branched structures and globular shapes. Molecular sizes of dendrimers are increased stepwise via repeated reaction sequences. Since the first dendrimers were synthesized by Tomalia et al. [1–3], many kinds of dendrimers have been synthesized [4], used not only for chemical applications but also for biomedical applications [5–11]. For example, commercially available polyamidoamine (PAMAM) and polypropylenimine (PPI) dendrimers are widely used as drugs [6], gene delivery systems [7], and MRI contrast agents [9]. Additionally, these dendrimers provide a high gene transfer efficiency into mammalian cells [12–15]. This transfer efficiency is considered to be a result of the many interior tertiary amines, which exist in the dendrimer, leading to an effect known as a proton sponge [16]. Moreover, these dendrimers have many functional groups such as amino groups and hydroxyl groups on their periphery [12–15,17], and modification of these surface groups with various molecules offers the chance for other potential applications [18–23]. However, for medical applications, dendrimers must be less toxic and more biodegradable than such dendrimers. Recently polyester dendrimers called 'biodendrimers' have been reported [24–26], which have building blocks known to be biocompatible or degradable to natural metabolites in vivo. Other types of polyester dendrimers have been synthesized [27–29] and have shown an antitumor effect [29]. Furthermore, a robust and biodegradable PEGylated dendrimer based on a polyester-polyamide hybrid core has been synthesized and biodistribution and chemotherapy study in tumored mice have been evaluated [30]. However, there are few reports on polyester dendrimers including primary and tertiary amines. To form complexes with plasmid DNA, antisense oligonucleotide or siRNA and other biological molecules, it is necessary for the dendrimers to have primary amines. These amino groups would not only allow complex formation, but would also interact with cellular membranes and enable conjugation with various ligands.

In this study, we designed novel polyester dendrimers **X**–**Z** named 'polyesteramine dendrimers' (Fig. 1).

As the core of the dendrimer, we selected an adamantane structure. Typically, planar or linear molecules, such as ammonia, ethylenediamine, 1,4-diaminobutane, benzene derivatives, lactic acid, succinic acid, adipic acid, and ethylene glycol, have been used for the dendrimer core [4,24–26,28]. These dendrimers maintain a planar structure in lower generations. Adamantane, on the other hand, has a three-dimensional structure, and dendrimers having an adamantane core are expected to have a more globular structure than dendrimers such as PAMAM even in lower generations. In terms of synthesis, PAMAM dendrimers are synthesized by a typical stepwise and iterative two-step reaction sequence [1–3], consisting of amidation of methyl acrylate with ethylenediamine and Michael

* Corresponding author. Tel.: +81 6 6879 8200; fax: +81 6 6879 8204; e-mail address: obika@phs.osaka-u.ac.jp (S. Obika).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.06.024

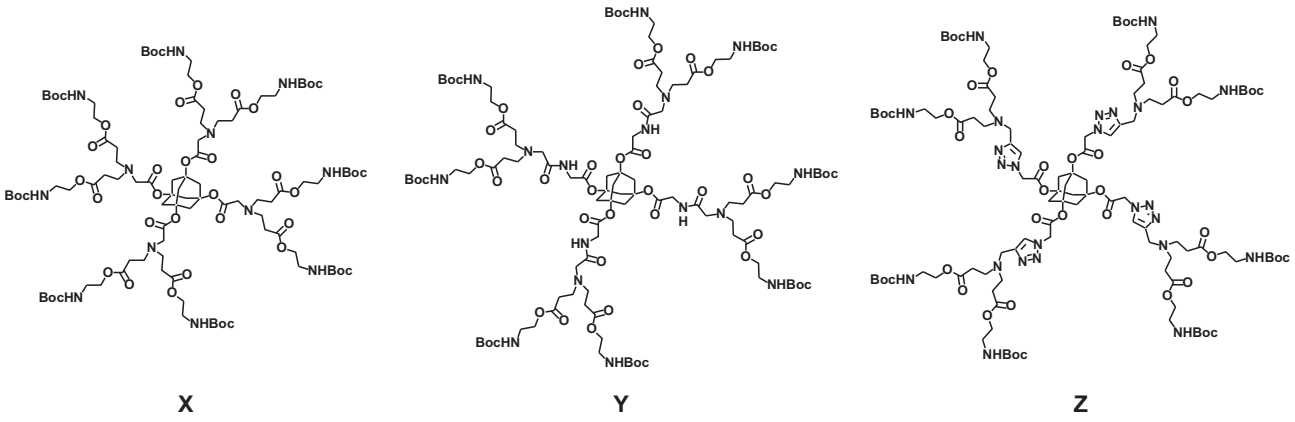


Fig. 1. Structures of polyester dendrimers **X**, **Y**, and **Z**.

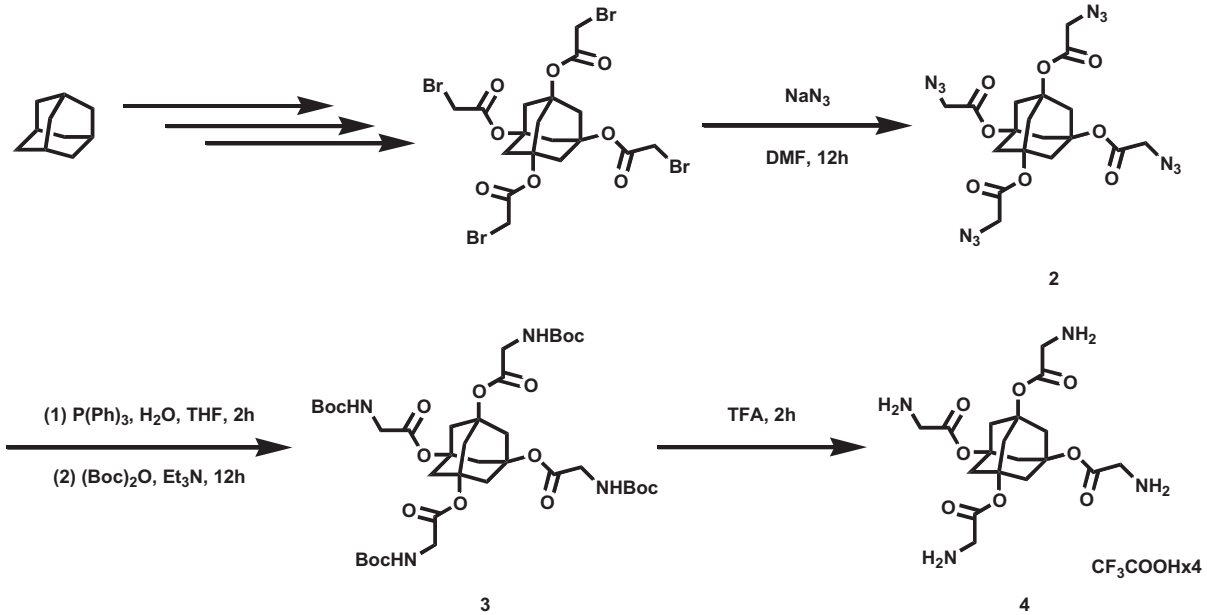
addition of primary amines with methyl acrylate. But it is known that this method sometimes leads to a lot of structural defects and also requires a long reaction time, which is a critical impediment for obtaining dendrimers with a uniform molecular weight, particularly in higher generations [1,2]. Separation of dendrimers having primary amines in the periphery is also a difficult task. In order to resolve these problems, we designed a novel dendrimer having a three-dimensional adamantane core, and synthesized dendrimers via two separate convergent routes employing amidation and Huisgen [3+2] cycloaddition reaction as the key coupling reactions, respectively.

2. Results

1,3,5,7-Tetrakis(aminoacetoxy)adamantane core **4** was synthesized as shown in Scheme 1. 1,3,5,7-Tetrakis(bromoacetoxy)adamantane, prepared according to a literature procedure, was treated with NaN_3 to give azidoacetoxy derivative **2** in 73% yield. Although several attempts to obtain **4** by direct reduction of **2** resulted in a complex mixture, Boc-protected derivative **3** was successfully obtained by reduction of **2** using triphenylphosphine and simultaneous Boc-protection in 76% yield. Deprotection of the Boc group of **3** by treatment with trifluoroacetic acid (TFA) smoothly took place, and the desired glycinoyloxy derivative **4** was isolated as a tetratrifluoroacetate salt in 91% yield.

At first, we examined the usual stepwise elongation method for the synthesis of dendrimer **7** as shown in Scheme 2. Michael reaction of **4** with 2-Boc-aminoethylacrylate **1**, prepared from 2-Boc-aminoethanol and acryloyl chloride, proceeded to give the first generation dendrimer **5** in 32% yield accompanied by the deacylated product **6** in 32% yield. Although we examined the reaction under various conditions, it was not possible to prevent formation of the deacylated product **6**. Next, deprotection of dendrimer **5** by TFA followed by Michael reaction was carried out. However, unfortunately, a complex mixture was given. MALDI-TOF-MS analysis of the crude product showed the existence of a number of incompletely reacted products (Fig. 2). The desired second generation dendrimer **7** was also detected by the spectrum, but could not be isolated from the mixture.

These results indicated that it was going to be difficult to obtain higher generation dendrimers having a uniform molecular weight by the present stepwise method. Therefore, we selected a convergent method for the synthesis of the higher generation dendrimers. We planned for the adamantane core to be coupled with dendritic



Scheme 1. Synthesis of two types of adamantane core.