Tetrahedron 66 (2010) 878–886

Contents lists available at ScienceDirect

Tetrahedron

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

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]

[a] Department of Biological Chemistry, Ariel University Center of Samaria, Ariel 40700, Israel
[b] The 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.

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).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.106

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.

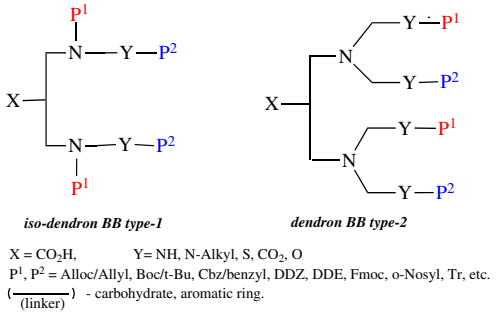


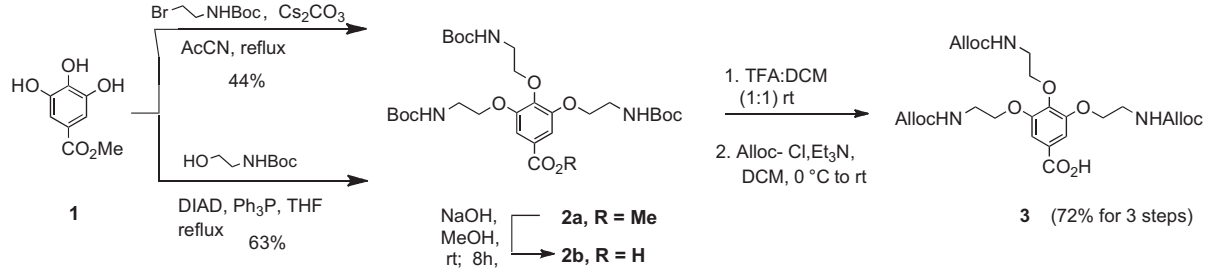
Figure 1. Schematic structure of dendron building blocks (BB) of types **1** and **2**.

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.

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-bromoaminoethane[16] to methyl 3,4,5-trihydroxybenzoate (Scheme 1) via phenolic alkylation[17] 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 $BocNHCH_2CH_2OH$ under standard Mitsunobu conditions consistently yielded **2a** in higher yield (63%) than the standard alkylation with $BocNHCH_2CH_2Br$ (44%), even if a stronger base, Cs_2CO_3 instead of K_2CO_3, 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 reprotection 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 $AllocNHCH_2CH_2OH$ 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.



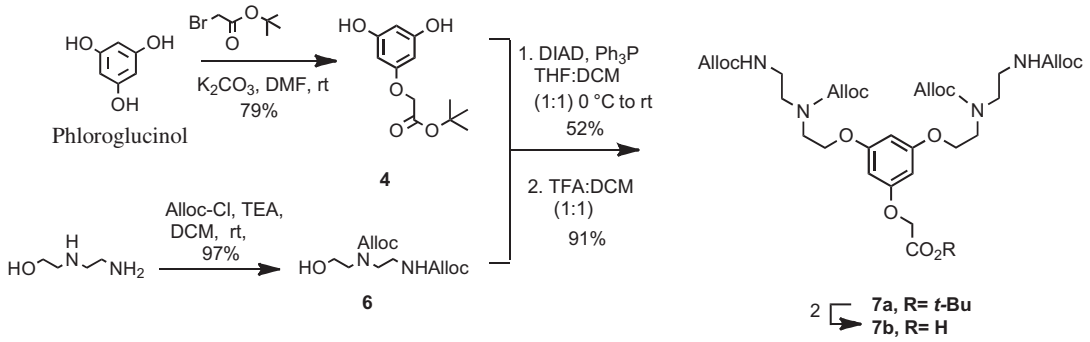
Scheme 1. Solution-phase synthesis of tri-Alloc-protected 3,4,5-trihydroxybenzoic acid **3**.

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 surface[10] and internal[11] 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 alkylation[14] 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 CO_2H 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.

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 (K_2CO_3, 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, Ph_3P 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



Scheme 2. Solution-phase synthesis of tetra-Alloc-protected dendron BB type 1—**7b.**

the final dendron BB type 1 **7b** in 91% yield after purification. At this point of our work we decided to move to solid-phase chemistry to improve the overall yield in the assembly process of the building blocks.

2.2. Solid-phase synthesis of tetra-Alloc-protected dendron BB type 1

As stated above, fast solid-phase organic chemistry (SPOC) has two clear advantages over solution chemistry. First, solvent, excess reagents and side products are easily removed from the reaction mixture by suction, replacing laborious chromatography. Second, repeated reactions can be employed for improving the yield.

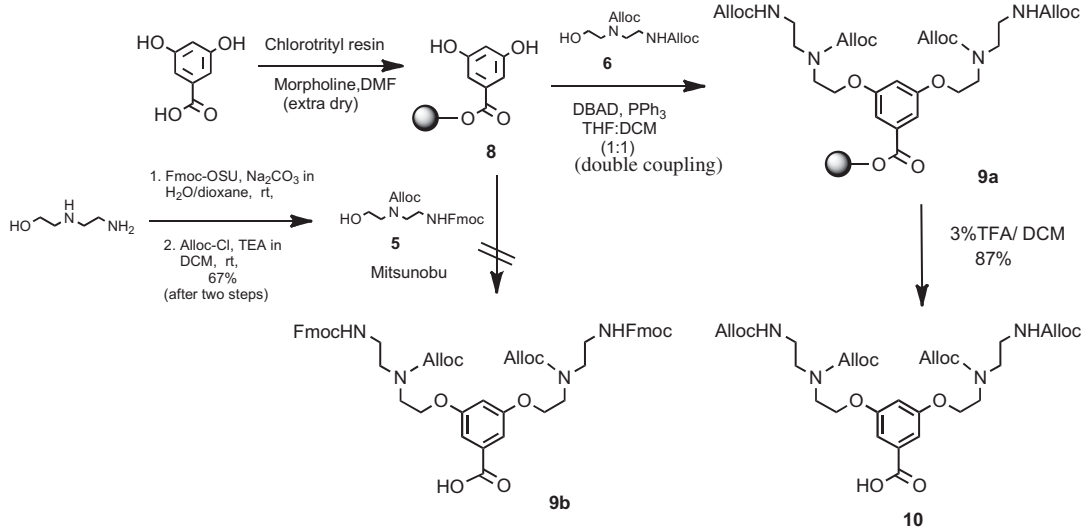
In this work, the solid-phase synthesis of dendron building block **10**, analogous to **7b**, started by loading of 3,5-dihydroxybenzoic acid on the chlorotrityl resin (0.64 mmol/g) in anhydrous DMF/morpholine followed by capping of the unreacted resin (Scheme 3). As expected, the loading proceeded through the more nucleophilic carboxylate anion, leaving the hydroxy groups untouched and ready for the following double Mitsunobu condensation. Thus, **8** was reacted with linker **6** (5 equiv) initially using diisopropyl azodicarboxylate (DIAD, 5 equiv) with Ph_3P (5 equiv) in THF/DCM. After first condensation, a test of a small sample by HPLC detected insufficient condensation (mixture of mono- and dicondensed products). Repeated condensation under the same conditions and subsequent cleavage (3% TFA in DCM) afforded dicondensed product **10** in good yield (84%) after fast purification by solid-phase extraction pack (RP-18, first washed with water and then extracted with acetonitrile). Noteworthy, we identified unreacted DIAD in the ^{1}H NMR spectrum of crude **10** even after several washing steps of **9a** before the cleavage.

Therefore, we decided to use the acid-sensitive di-*t*-butyl azodicarboxylate (DBAD) instead of DIAD, which is degradable under acid cleavage conditions. Finally, upon submitting **8** to two repeated double Mitsunobu reactions with DBAD followed by cleavage (3% TFA/DCM) and purification by RP-18 solid-phase extraction, building block **10** was obtained in 87% yield.

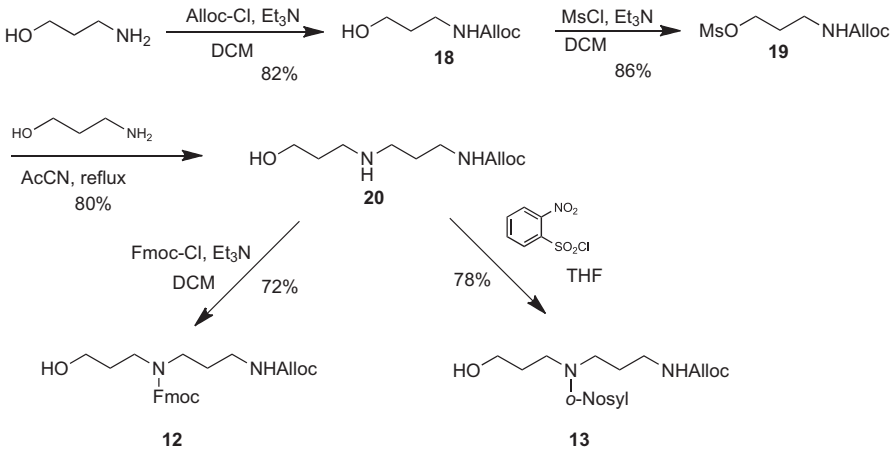
2.3. Solid-phase synthesis of orthogonally protected dendron BB type 1

In the next step we decided to expand the scope of dendron BB synthesis by coupling orthogonally protected linkers to **8**. First, we prepared linker **5**, bearing two orthogonal protecting groups Fmoc and Alloc (Scheme 3). The synthesis of **5** started from mono Fmoc protection of *N*-(2-hydroxyethyl) ethylenediamine with Fmoc-Osu (0.5 equiv) in alkali (Na_2CO_3) dioxane/water mixture. Under these conditions only the primary amine reacts.[19] After work up, the intermediate was submitted to the subsequent Alloc protection with Alloc-Cl in DCM in the presence of TEA, yielding the desired linker **5** in 67% overall yield. Unfortunately, our attempts to condense **5** with **8** to give **9b** failed, most probably due to unfavorable interactions of the protecting groups with the phenol.[20] This phenomenon may indicate that the length of the linker and protecting group positions along the linker are crucial parameters for the successful Mitsunobu condensation to the phenolic scaffold.

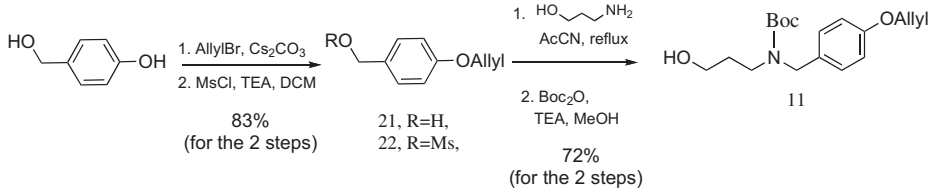
In order to overcome this problem, we prepared a series of longer linear linkers **12**, **13** (Scheme 4) and phenolic linker **11** (Scheme 5), which has a benzene spacer. These linkers, bearing various orthogonal protecting groups applicable in Fmoc SPOC,[21] were prepared by a previously reported procedure.[22] Initially, the



Scheme 3. Solid-phase synthesis of tetra-Alloc-protected dendron BB type 1—**10**.



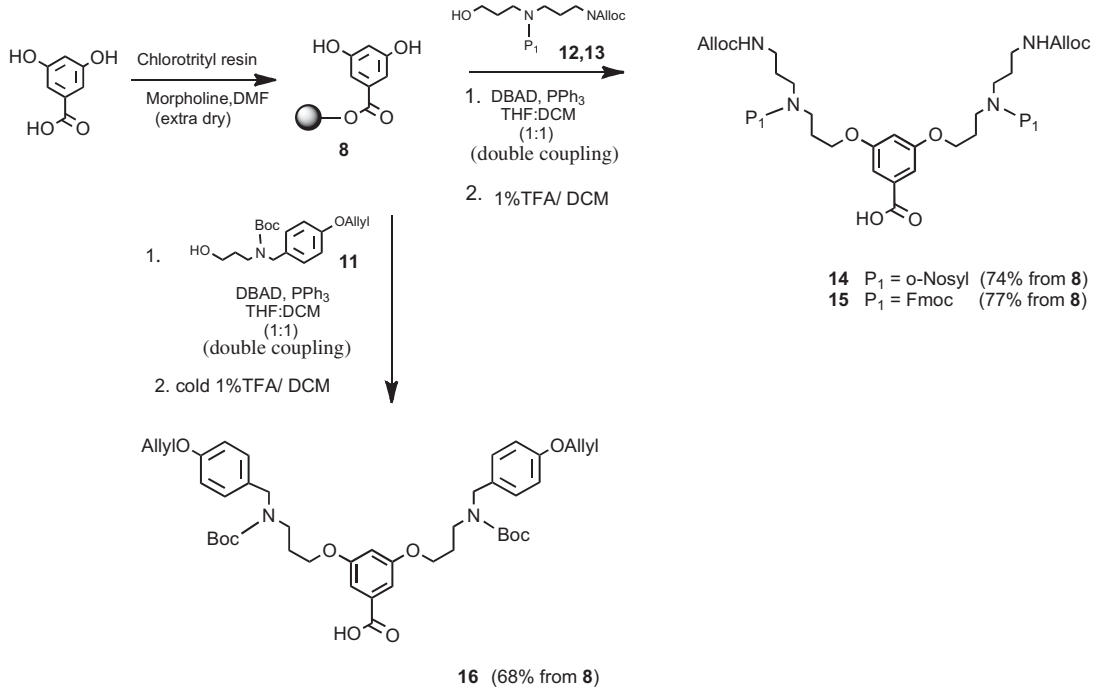
Scheme 4. Synthesis of orthogonally protected 3-(3-aminopropylamino)propan-1-ol linkers **12**, **13**.



Scheme 5. Synthesis of orthogonally protected 4-((3-hydroxypropylamino)methyl)phenol linker **11**.

quantitative Alloc protection of 3-aminopropanol gave the corresponding carbamate **18**, which was then *O*-sulfonylated to give the respective mesylate **19** in 86% yield (Scheme 4). The mesylate (without any purification) was further displaced with 3-aminopropanol to give the secondary amine intermediate **20**, which was *N*-Fmoc-protected or *N*-*o*-Nosyl-protected, leading after flash chromatography purification (EtOAc) to hydroxyl linkers **12** and **13**, respectively, in reasonable overall yields (72% for **12**, 78% for **13**). Similarly, 4-hydroxybenzyl alcohol was etherified by Allyl-Br exclusively on the phenol ring to afford intermediate **21**, which after reacting with MsCl gave **22** as a viscous oil (Scheme 5). Compound **22** was further reacted with 3-aminopropanol to afford, after sequential Boc protection and purification, the desired linker **11** in overall 67% yield. Noteworthy, this synthetic approach is applicable to various orthogonally protected diamino alcohol linkers, generating bi-functional arms varying in length and linking moiety.

Having the orthogonally protected linkers **12**, **13**, and **11** in hand, we moved to the synthesis of dendritic building blocks **14**, **15**, and **16** correspondingly, using the previously immobilized **8** (Scheme 6). Finally, after submitting the above linkers to repeated Mitsunobu

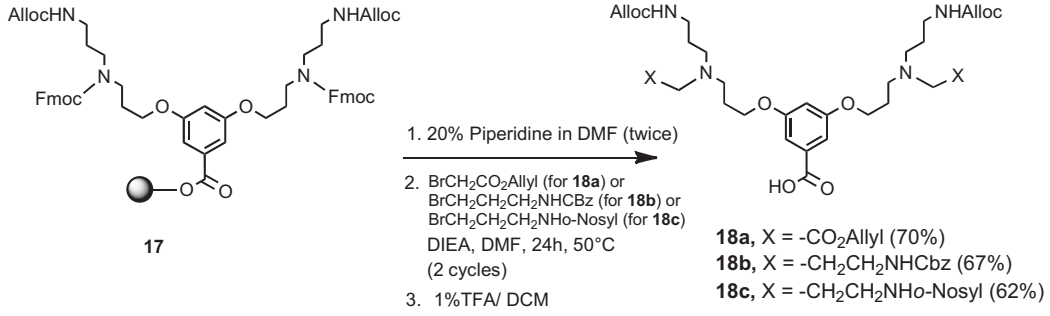


Scheme 6. Solid-phase synthesis of orthogonally protected dendron BB type 1—**14**, **15**, and **16**.

condensations ([THF:DCM (1:1), DBAD, Ph_3P, overnight]×2) with **8** and subsequent mild acidic cleavage, the desired orthogonally protected units **14**, **15**, and **16** were obtained in reasonable yields from resin-bound 3,5-dihydroxybenzoate **8** (74% for **14**, 77% for **15** and 68% for **16**) after purification by fast RP-18 solid-phase extraction. The purity of dendron BBs was determined by HPLC and ranged between 87% and 93%.

2.4. Solid-phase synthesis of orthogonally protected dendron BB type 2

Next we explored whether dendron building blocks of type 1 can serve as precursors for more versatile dendron building units of type 2. For this purpose we employed the resin-bound Fmoc/Alloc protected unit **17** in alkylation with various functional bromoalkyl groups. Thus, pre-made **17** (which is actually **15** before cleavage) (Scheme 7) was submitted first to Fmoc deprotection (20% piperidine in DMF, 10 min, twice), followed by double cycled dialkylation (NMP, DIEA, 50 °C, 18 h, 2 cycles) with allyl α-bromoacetate, benzyl 3-bromopropylcarbamate, and *N*-(3-bromopropyl)-2-nitrobenzenesulfonamide. Finally, cleavage from the resin (3%TFA in DCM,) and RP-18 solid-phase extraction afforded relatively pure (86–92% purity by HPLC) orthogonally protected type 2 dendron building blocks **18a**, **18b**, and **18c** in 62–70% yield from **17**.



Scheme 7. Solid-phase synthesis of orthogonally protected dendron BB type 2—**18a**,**b**,**c**.

In summary, the fast solid phase synthetic methodology described in this paper can yield orthogonally protected dendron building blocks of type 1 and 2 for generation of more complex dendron architectures by SPOC. Attempts to facilitate the reactions, including the use of microwave-assisted chemistry, as well as the implementation of our dendron building blocks for convergent dendrimer synthesis on solid support are in progress.

3. Conclusions

We demonstrated a simple and convenient synthesis of two types of orthogonally protected bi-functional dendritic building blocks from phenolic templates in solid phase via the Mitsunobu reaction for convergent dendrimer growth. The type 1 building block carries on each branch a protected main chain secondary amine and a terminal primary amine or phenol groups. The type 2 building block, on the other hand, is the result of simple alkylation of the deprotected secondary amine in dendron BB type 1 precursor, presenting a tertiary amine junction and a protected peripheral primary amine or carboxyl groups. The key step in preparation of these dendron units involves multiple Mitsunobu condensation of orthogonally protected functional linkers to di- and trihydroxybenzene core structures. The repeated Mitsunobu cycle is necessary for achieving sufficient yields and purity. Steric factors of the protecting groups appears to be important for the successful preparation of the building blocks, suggesting that the minimal distance of the first protecting group on the linker from the phenolic core should be at least four atoms.

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 enabling fast generation of versatile dendritic architectures by SPOC.

4. Experimental

4.1. General

Analytical HPLC was performed on a 250×4.2 mm Lichroprep RP-18 column from Merck, with a 1 mL/min flow and detection at 214 nm. The eluents were triply distilled water and HPLC-grade CH_3CN containing 0.1% TFA or MeOH. The concentration of all the samples was 0.5%. Mass spectra were measured in the positive and negative modes using a quadrupole mass spectrometer equipped with an electro spray ionization source and cross-flow inlet. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$. Assignments in the final products were supported by 2D COSY, TOCSY, NOESY, ROESY, HMBC, and HMQC spectroscopy. All chemical shifts are reported with respect to TMS. SPE was performed on LiChrospher 60 RP-18® columns purchased from Agilent Technologies. Chromatography was carried out by standard flash chromatography and TLC on silica-gel (Merck 7735).

*4.1.1. Methyl 3,4,5-tris(2-(tert-butoxycarbonylamino)ethoxy)benzoate (**2a**). Method A*: To a solution of $BocNHCH_2CH_2Br$ (1.28 g, 5.7 mmol) in acetonitrile (50 mL) was added methyl trihydroxybenzoate **1** (0.35 g, 1.8 mmol) and Cs_2CO_3 (4.55 g, 13.3 mmol). The reaction mixture was refluxed at 80 °C under nitrogen overnight. The reaction mixture was filtered and evaporated to give a brown oil, which was dissolved in DCM (50 mL). The organic phase was washed sequentially with water, saturated $NaHCO_3$ solution, and brine (50 mL each), dried over anhydrous Na_2SO_4 and evaporated. Chromatography (EtOAc/PE 1:1) gave **2a** as a brown oil (0.52 g, 44% yield). *Method B*: To the dry solution of $BocNHCH_2CH_2OH$ (1.12 g, 5.7 mmol) in THF (50 mL) were added DIAD (0.31 mL, 1.33 mmol) and PPh_3 (0.34 g, 1.33 mmol) under a nitrogen atmosphere. The reaction mixture was stirred overnight, and then diluted with ether (150 mL), and washed with saturated aqueous sodium bicarbonate solution (2×100 mL). The organic layer was dried over sodium sulfate. Excess solvent was removed under reduced pressure initially on a rotary evaporator and then under high vacuum (0.2 mm for 5 h at 40 °C). The resulting oil was dissolved in ether (40 mL) and while stirring hexane (40 mL) was added. After careful decantation the resulting oil was dried under vacuum and chromatographed (EtOAc/PE 1:1) to give **2a** as a brown oil (0.73 g, 63% yield). R_f=0.75 (EtOAc/PE, 1:1), HRMS *m*/*z* 614.3332 (MH^+, calculated 614.3243 for $C_{29}H_{47}N_3O_{11}$); ν_{max} (KBr): 1685, 1650, 1305,

1235 cm^{-1}; ^1H NMR: δ 7.26 (s, 2H), 4.14–4.08 (m, 6H), 3.88 (s, 3H), 3.59–3.56 (m, 4H), 3.42 (m, 2H), 1.43 (s, 27H); ^{13}C NMR: δ 167.0 (C), 157.3 (C), 143.4 (C), 143.0 (C), 131.2 (CH), 123.7 (C), 60.3 (C), 59.6 (CH_2), 41.0 (CH_2), 31.3 (CH_3).

*4.1.2. 3,4,5-Tris(2-(tert-butoxycarbonylamino)ethoxy)benzoic acid (**2b**).* To **2a** (0.44 g, 0.7 mmol) in MeOH (20 mL) was added a solution of 1 N NaOH (10 mL). The reaction mixture was stirred at rt for 8 h, and then DCM (100 mL) and water (50 mL) were added, followed by 1 N HCl to adjust pH=4. The organic phase was washed with brine (2×50 mL), dried over anhydrous Na_2SO_4 and evaporated to give intermediate benzoic acid **2b** as a yellow oil (0.40 g, 89% yield). The acid **2b** was used in the next step without any purification. R_f=0.40 (EtOAc), HRMS *m/z* 600.324 (MH^+, calculated 600.310 for $C_{28}H_{45}N_3O_{11}$); ν_{max} (KBr): 3500–3100 br s, 1690, 1650, 1340, 1180 cm^{-1}; ^1H NMR: δ 7.30 (s, 2H), 4.14–4.10 (m, 6H), 3.60–3.57 (m, 4H), 3.42 (bd, *J*=6.5 Hz, 2H), 1.47 (s, 9H), 1.43 (s, 18H).

*4.1.3. 3,4,5-Tris(2-(allyloxycarbonylamino)ethoxy)benzoic acid (**3**).* To acid **2b** (0.22 g, 0.6 mmol) was added a 4 °C cold solution of TFA:DCM (1:1, 20 mL). The mixture was stirred at 0 °C for 15 min and then warmed to rt and stirred for additional 1 h. The solvents were evaporated to give a brown oil, which was further treated with DCM (30 mL) and triethylamine (4 mL). The reaction mixture was stirred at 0 °C for 15 min and followed by dropwise addition over 20 min of a solution of Alloc-Cl (0.39 mL, 3.6 mmol) in DCM (20 mL). The reaction mixture was stirred at rt overnight under a nitrogen atmosphere. After evaporation of the solvent, the resulting yellow semi-solid was taken in DCM (20 mL), the organic phase was washed sequentially with HCl 1 N and brine (20 mL each), dried over anhydrous Na_2SO_4 and evaporated to give a brownish oil, which after chromatography (EtOAc) afforded **3** as a yellow oil (0.31 g, 72% yield). R_f=0.50 (EtOAc/PE, 1:1), HRMS *m/z* 552.2237 (MH^+, calculated 552.2194 for $C_{25}H_{33}N_3O_{11}$); ν_{max} (KBr): 3450–3120 br s, 1695, 1655,1450, 1270 cm^{-1}; ^1H NMR: δ 7.38 (s, 2H), 5.92 (ddt, *J*=17.1, 10.5, 5.7 Hz, 3H), 5.31 (dd, *J*=17.1, 1.8 Hz, 3H), 5.23 (dd, *J*=10.5, 1.8 Hz, 3H), 4.57 (d, *J*=5.7 Hz, 6H), 3.62–3.58 (m, 6H), 3.33–3.27 (m, 6H); ^{13}C NMR: δ 168.0 (C), 158.1 (C), 145.3 (C), 142.4 (C), 133.8 (CH), 122.9 (C), 116.4 (CH_2), 106.6 (CH), 69.1 (CH_2), 68.8 (CH_2), 64.7 (CH_2), 40.3 (CH_2).

*4.1.4. (3,5-Dihydroxy-phenoxy)-acetic acid tert-butyl ester (**4**).* A solution of phloroglucinol dehydrate (10 g, 61.6 mmol) in DMF (20 mL) was added dropwise over 2 h to a solution of potassium carbonate (12.64 g, 91.5 mmol), and *t*-butyl bromoacetate (2.953 g, 20.5 mmol) in DMF (20 mL). The reaction mixture was stirred overnight. Then water (100 mL) was added and the pH was adjusted to 6 by careful addition of 1 N HCl. DCM (50 mL) was added, the phases were separated, and the organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated to give **4** as an orange oil (3.79 g, 79% yield based on $BrCH_2CO_2t$-Bu), which was used in the next step without further purification. R_f=0.45 (EtOAc), MS (CI): *m/z* 240 (MH^+, 78%), 185 (100%); ν_{max} (KBr): 3500–3100 br s, 1700, 1430, 1170 cm^{-1}; ^1H NMR: δ 6.02 (br s, 1H), 5.99–5.97 (br s, 2H), 4.40 (s, 2H), 1.42 (s, 9H); ^{13}C NMR: δ 166.2 (C), 155.2 (C), 142.1 (C), 133.8 (CH), 116.4 (CH), 69.3 (C), 67.6 (CH_2), 30.7 (CH_3).

*4.1.5. Allyl 2-(N-(2-hydroxyethyl)oxycarbonyl)-(9H-fluoren-9-yl)-methyl ethyl carbamate (**5**)*[16]. 2-Aminoethylaminoethanol (2 mL, 19.8 mmol) was dissolved in a 1:1 mixture of 1 N Na_2CO_3/dioxane (60 mL) and Fmoc-Osu (5.07 g, 15 mmol) was added in small portions over 5 min at 0 °C. The reaction mixture was stirred for an additional 5 h at rt. The reaction volume was then reduced to a third under vacuum and the residue was taken in DCM (100 mL). The organic phase was washed with aqueous sodium carbonate solution and brine (100 mL each), dried over anhydrous Na_2SO_4 and evaporated to give Fmoc-protected intermediate as a colorless oil (4.2 g) ready for the next step without further purification.

The Fmoc-protected intermediate was then dissolved in DCM (100 mL) and triethylamine (20 mL) and the mixture was cooled to 0 °C. A solution of Alloc-Cl (2.14 mL, 20 mmol) in DCM (20 mL) was added dropwise over 10 min and the mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm up to rt, and the solution was stirred overnight under a nitrogen atmosphere. The organic phase was washed twice with 1 N HCl, aqueous sodium carbonate and brine (50 mL each), dried over anhydrous Na_2SO_4, evaporated and chromatography (EtOAc) to give linker **5** as a yellowish oil (4.9 g, 79% yield). R_f=0.80 (EtOAc/PE, 1:1), MS (CI): *m/z* 411 (MH^+, 80); ν_{max} (KBr): 3470–3150 br s, 1655, 1610, 1500, 1430 cm^{-1}; ^1H NMR: δ 7.78–7.73 (m, 2H), 7.52–7.48 (m, 2H), 7.43–7.41 (m, 4H), 5.90 (ddt, *J*=17.1, 10.5, 5.4 Hz, 1H), 5.32 (dd, *J*=17.1, 1.2 Hz, 1H), 5.25 (dd, *J*=10.5, 1.2 Hz, 1H), 4.60 (d, *J*=4.2 Hz, 2H), 4.50 (d, *J*=5.4 Hz, 2H), 4.14 (t, *J*=4.2 Hz, 1H), 3.70–3.67 (m, 2H), 3.17–3.14 (m, 4H), 3.00–2.97 (m, 2H).

*4.1.6. Allyl 2-(N-(2-hydroxyethyl)allylcarbamate)ethylcarbamate (**6**)*[16]. A solution of 2-aminoethylaminoethanol (1.94 mL, 19.2 mmol) and triethylamine (26.76 mL) in DCM (120 mL) was stirred at 0 °C under a nitrogen atmosphere for 20 min. A solution of Alloc-Cl (4.49 mL, 42 mmol) in DCM (20 mL) was added dropwise over 10 min and the mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm up to rt, and the solution was stirred overnight under a nitrogen atmosphere. The organic phase was washed twice with 1 N HCl, aqueous sodium carbonate solution and brine (60 mL each), dried over anhydrous Na_2SO_4 and evaporated to give linker **6** as a colorless oil (2.6 g, 50% yield) ready for the next step without further purification. R_f=0.55 (EtOAc/PE, 1:1), MS *m/z* 272.1 (MH^+, 100); ν_{max} (KBr): 3300–2900 br s, 1650,1390, 1030 cm^{-1}; ^1H NMR: δ 5.91 (ddt, *J*=17.5, 10.5, 5.4 Hz, 2H), 5.28 (dd, *J*=17.4, 1.8 Hz, 2H), 5.21(dd, *J*=10.5, 1.8 Hz, 2H), 4.74(d, *J*=5.4 Hz, 4H), 3.78 (m, 2H), 3.45–3.41 (m, 6H).

*4.1.7. (3,5-Bis-{2-[allyloxycarbonyl-(2-allyloxycarbonylamino-ethyl)-amino]-ethoxy}-phenoxy)-acetic acid (**7b**).* To a dry solution of linker **6** (2.72 g, 10.0 mmol) and **4** (1.08 g, 4.5 mmol) in THF (60 mL) were added DIAD (1.35 mL, 10.0 mmol) and PPh_3 (1.50 g, 10.0 mmol) under nitrogen atmosphere. The reaction mixture was stirred overnight, and then diluted with ether (150 mL), and washed with saturated aqueous sodium bicarbonate solution (2×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and the excess solvent was removed under reduced pressure initially on a rotary evaporator and then under high vacuum (0.2 mm for 5 h at 40 °C). The resulting oil was dissolved in ether (50 mL) and, while stirring, hexane (50 mL) was added. After careful decantation, the resulting oil was dried under vacuum and chromatographed (EtOAc/PE 1:1) to give **7a** as yellow oil (1.70 g, 52% yield). Compound **7a** was taken into a cold mixture of TFA/DCM (1:1, 40 mL) and after stirring for 1 h at rt, the solvent was evaporated, and the residue was purified by chromatography (EtOAc) to give **7b** as yellowish oil (1.46 g, 91% yield). R_f=0.40 ($CHCl_3$), HRMS *m/z* 693.2928 (MH^+, calculated 693.2906 for $C_{32}H_{44}N_4O_{13}$); ν_{max} (KBr): 3550–3150 br s, 1705, 1660, 1405, 1120 cm^{-1}; ^1H NMR (600 MHz): δ 6.53(br s,3H), 5.88 (ddt, *J*=16.2, 10.5, 5.6 Hz, 4H), 5.70 (br s, 1H), 5.25 (dd, *J*=16.0, 2.0 Hz, 4H), 5.18 (dd, *J*=10.5, 2.0 Hz, 4H), 5.02 (br s, 2H), 4.68 (d, *J*=5.6 Hz, 4H), 4.52 (d, *J*=5.6 Hz, 4H), 4.17–4.15 (m, 4H), 3.73–3.71 (m, 4H), 3.54–3.53 (m, 4H), 3.44–3.42 (m, 4H); ^{13}C NMR (150 MHz): δ 172.3 (C), 160.6 (C), 158.2 (C), 156.8 (C), 147.7 (C), 131.8 (CH), 120.3 (CH_2), 111.4 (CH), 106.0 (CH), 73.3 (CH_2), 66.4 (CH_2), 64.9 (CH_2), 40.6 (CH_2), 48.3 (CH_2), 42.5 (CH_2).

*4.1.8. 3,5-Bis(2-((allyloxycarbonyl)(2-(allyloxycarbonyl-amino)ethyl)amino) ethoxy) benzoic acid (**10**).* To 2-chlorotrityl resin (0.2 g, 0.28 mmol loading) in a reactor was added a solution of

dihydroxybenzoic acid (0.04 g, 0.26 mmol) in dry DMF (3.5 mL) and after addition of diisopropylethylamine (DIEA, 185 μL, 1.04 mmol) the reaction mixture was shaken for 1.5 h. After completion of the loading, dry MeOH (1.5 mL) was poured into the reactor and shaking was continued for additional 20 min. The solvent was filtered out and the following washings were sequentially performed: 2×DCM:MeOH:DIEA (17:2:1), 2×DCM, 2×DMF, 2×DCM, 2×DCM:DMF (1:1) (3 mL each). To the loaded resin **8** in the reactor was added, under a nitrogen atmosphere, linker **6** (0.361 g, 1.33 mmol) in dry THF:DCM (1:1, 5.2 mL), DBAB (0.306 mL, 1.33 mmol), and PPh_3 (0.348 g, 1.33 mmol). After shaking overnight, the solution was filtered out and the following washings were sequentially performed: 1×THF, 1×DCM, 1×10% DIEA/DMF, 1×DMF, 3×MeOH, 3×DMF, 3×DCM (3 mL each). The coupling and the washings were repeated to yield **9a**.

The resin was transferred to a vial for cleavage and a 4 °C cold solution of 1% TFA in DCM (2 mL) was added. After shaking for 30 min, the solution was collected and the resin was washed several times with DCM (3 mL each). After combining the organic solutions, the solvent was evaporated first by N_2 stream and then in vacuum to give **10** as an orange oil (0.12 g, 68% yield). R_f=0.30 ($CHCl_3$), HRMS *m*/*z* 663.2475 (MH^+, calculated 663.2754 for $C_{31}H_{43}N_4O_{12}$); ν_{max} (KBr): 3300–3080 br s, 1700, 1655, 1320, 1080 cm^{-1}; ^1H NMR (600 MHz): δ 7.20 (br s,2H), 6.67(br s,1H), 5.91 (ddt, *J*=16.8, 10.8, 5.4 Hz, 4H), 5.58 (br s, 1H), 5.30 (dd, *J*=16.8, 1.8 Hz, 4H), 5.20 (dd, *J*=10.8, 1.8 Hz, 4H), 4.61 (d, *J*=5.4 Hz, 4H), 4.55 (d, *J*=5.4 Hz, 4H), 4.16–4.13 (m, 4H), 3.70–3.67 (m, 4H), 3.58–3.55 (m, 4H), 3.47–3.44 (m, 4H); ^{13}C NMR (150 MHz): δ 170.1 (C), 159.5 (C), 159.19 (C), 157.8 (C), 157.1 (C), 132.3 (CH), 118.1 (CH_2), 108.4 (CH), 107.0 (CH), 66.8 (CH_2), 65.9 (CH_2), 39.8 (CH_2), 40.3 (CH_2), 47.3 (CH_2).

*4.1.9. Allyl 3-hydroxypropylcarbamate (**18**)*[16]. A solution of 3-aminopropanol (1.69 mL, 22.1 mmol) and triethylamine (6.97 mL, 15 mmol) in DCM (120 mL) was stirred at 0 °C for 15 min and a solution of Alloc-Cl (2.59 mL, 24.3 mmol) in DCM (25 mL) was added dropwise over 20 min. The reaction mixture was stirred at rt overnight under a nitrogen atmosphere. The organic phase was washed three times with 1 N HCl, aqueous sodium carbonate solution, and brine (100 mL each), dried over anhydrous Na_2SO_4 and evaporated to give linker **18** as yellow oil (2.94 g, 82% yield). R_f=0.60 (MeOH:$CHCl_3$, 1:99), MS (CI): *m*/*z* 160 (MH^+, 100); ν_{max} (KBr): 3350–3020 br s, 1650, 1220 cm^{-1}; ^1H NMR: δ 5.89 (ddt, *J*=17.1, 10.8, 5.1 Hz, 1H), 5.29 (dd, *J*=17.1, 1.2 Hz, 1H), 5.18 (dd, *J*=10.8, 1.2 Hz, 1H), 4.49 (d, *J*=5.1 Hz, 2H), 3.78 (t, *J*=6.3 Hz, 2H), 3.32 (t, *J*=6.3 Hz, 2H), 1.85 (q, *J*=6.3 Hz, 4H).

*4.1.10. Allyl 3-(3-hydroxypropylamino)propylcarbamate (**20**).* A solution of **18** (2.94 g, 18.4 mmol) and triethylamine (25.6 mL, 184 mmol) in DCM (50 mL) was stirred at 0 °C under a nitrogen atmosphere for 20 min. MsCl (3.7 mL, 41 mmol) was added dropwise over 10 min. The mixture was stirred for 1 h at 0 °C and then at rt overnight. The solution was cooled to 0 °C and cold 4 N NaOH (32 mL) was added. The organic phase was washed with water (2×50 mL), dried over anhydrous Na_2SO_4 and evaporated to give intermediate methanesulfonate **19** as a yellow oil (3.7 g, 86% yield), which was used in the next step without further purification. R_f=0.85 (EtOAc/PE, 1:1); ^1H NMR: δ 5.90 (ddt, *J*=17.1, 10.8, 5.1 Hz, 1H), 5.29 (dd, *J*=17.1, 1.2 Hz, 1H), 5.19 (dd, *J*=10.8, 1.2 Hz, 1H), 4.99 (br s, 1H), 4.55 (d, *J*=5.1 Hz, 2H), 4.55 (t, *J*=6.3 Hz, 2H), 3.32 (t, *J*=6.3 Hz, 2H), 3.02 (s, 3H), 1.96 (quint, *J*=6.3 Hz, 2H).

Next, mesylate **19** (3.7 g, 15.6 mmol) and aminopropanol (4.77 mL, 62.4 mmol) were dissolved in acetonitrile (40 mL). The reaction mixture was refluxed under nitrogen overnight, cooled to rt and evaporated to give a yellow oil, which was redissolved in DCM (30 mL). The organic phase was washed with saturated Na_2CO_3 solution (30 mL), dried over anhydrous Na_2SO_4 and evaporated to afford **20** as a yellow oil (4.22 g, 80% yield). The purity of the crude **20** was satisfactory for the next step. R_f=0.50 (MeOH:$CHCl_3$, 1:20), MS (CI): *m*/*z* 217 (MH^+, 100); ν_{max} (KBr): 3400–3100 br s, 1650, 1310 cm^{-1}; ^1H NMR: δ 5.91 (ddt, *J*=17.1, 10.8, 5.1 Hz, 1H), 5.30 (dd, *J*=17.1, 1.2 Hz, 1H), 5.21 (dd, *J*=10.8, 1.2 Hz, 1H), 4.55 (d, *J*=5.1 Hz, 2H), 3.81 (t, *J*=5.7 Hz, 2H), 3.24 (t, *J*=6.3 Hz, 2H), 2.87 (t, *J*=5.7 Hz, 2H), 2.68 (t, *J*=5.7 Hz, 2H), 1.65–1.72 (m, 4H); ^{13}C NMR: δ 157.6 (C), 135.4 (C), 120.3 (C), 67.4 (CH_2), 65.3 (CH_2), 42.8 (CH_2), 34.3 (CH_2), 26.1 (CH_2), 20.8 (CH_2).

*4.1.11. 4-(Allyloxy)phenyl methanol (**21**).* To a solution of K_2CO_3 (22.6 g, 0.16 mmol) in DMF (200 mL) was added under vigorous stirring over 30 min 4-hydroxybenzyl alcohol (10 g, 0.08 mol) and allyl bromide (10 mL, 0.10 mol). The reaction mixture was stirred overnight at rt and after completion of the reaction (TLC:MeOH/EtOAc, 1:99) 1 N HCl (400 mL) was added and the aqueous phase was washed with diethyl ether (4×40 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated to give crude **21** as a colorless oil (11.9 g, 90% yield), which was used in the next step without further purification. R_f=0.65 (EtOAc); ^1H NMR: δ 7.13 (d, *J*=8.5 Hz, 2H), 6.89(d, *J*=8.5 Hz, 2H), 5.96 (ddt, *J*=17.1, 10.5, 5.7 Hz, 1H), 5.40 (dd, *J*=17.1, 1.2 Hz, 1H), 5.28 (dd, *J*=10.5, 1.2 Hz, 1H), 4.51 (d, *J*=5.7 Hz, 2H), 4.20 (s, 2H); ^{13}C NMR: δ 153.4 (C), 133.7 (C), 128.8 (CH), 126.2 (CH), 118.3 (CH_2), 114.5 (CH), 69.1 (CH_2), 63.2 (CH_2).

*4.1.12. 4-(Allyloxy)benzyl methanesulfonate (**22**).* To a solution of **22** (5.95 g, 36.2 mmol), and triethylamine (10.16 mL, 0.10 mol) in DCM (100 mL) at 0 °C, methanesulfonyl chloride (14.2 mL, 0.18 mol) was added dropwise over 30 min under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h and slowly warmed to rt and stirred overnight under nitrogen. The reaction mixture was then cooled to 0 °C, and a 4 M NaOH solution (32 mL) was added slowly with vigorous stirring. The organic phase was separated and washed twice with water and brine (50 mL each), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuum to give mesylate **22** as a brown oil (7.90 g, 92% yield), which was immediately reacted in the next step. R_f=0.70 (EtOAc/PE, 1:2), ^1H NMR: δ 7.15 (d, *J*=8.5 Hz, 2H), 6.93 (d, *J*=8.5 Hz, 2H), 5.98 (ddt, *J*=17.1, 10.5, 5.4 Hz, 1H), 5.40 (dd, *J*=17.1, 1.2 Hz, 1H), 5.28 (dd, *J*=10.5, 1.2 Hz, 1H), 4.51 (d, *J*=5.4 Hz, 2H), 4.55 (s, 2H), 3.14 (s, 3H); ^{13}C NMR: δ 156.0 (C), 135.3 (C), 130.1 (CH), 128.7 (CH), 120.6 (CH_2), 117.9 (CH), 71.0 (CH_2), 65.3 (CH_2), 36.4 (CH_3).

*4.1.13. tert-Butyl 4-(allyloxy)benzyl(2-hydroxyethyl)carbamate (**11**).* Mesylate **22** (5.90 g, 24.5 mmol) and 3-aminopropanol (13.8 g, 0.18 mol) were dissolved in acetonitrile (80 mL). The mixture was stirred at 75 °C under a nitrogen atmosphere overnight. After completion of the reaction (TLC:EtOAc, R_f=0.6) the solution was concentrated under reduced pressure. The residue was dissolved in DCM (80 mL) and washed with aqueous sodium carbonate (3×50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to give intermediate crude 3-(4-(allyloxy)benzylamino)propan-1-ol as a yellowish oil (2.52 g, 83% yield) with satisfactory purity for the next step. R_f=0.50 (MeOH:$CHCl_3$, 1:20), MS (CI): *m*/*z* 208 (MH^+, 100); ν_{max} (KBr): 3400–3000 br s, 1650, 1130 cm^{-1}; ^1H NMR: δ 7.02 (d, *J*=8.7 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 5.89 (ddt, *J*=17.1, 10.8, 5.4 Hz, 1H), 5.28 (dd, *J*=17.1, 1.2 Hz, 1H), 5.26 (dd, *J*=10.8, 1.2 Hz, 1H), 4.49 (d, *J*=5.4 Hz, 2H), 4.1 (s, 2H), 3.53–3.51 (m, 2H), 3.21–3.19 (m, 2H), 1.64–1.62 (m, 2H).

A solution of 3-(4-(allyloxy)benzylamino)propan-1-ol (2.33 g, 10.5 mmol) in a solution of triethylamine/MeOH (1:7, 300 mL) was stirred at 0 °C for 10 min, followed by dropwise addition over 10 min of a solution of di-tertbutyl dicarbonate (3.43 g, 15.7 mmol) in MeOH (95 mL). After stirring for 1 h at 0 °C, the temperature was allowed to warm gradually to rt, and the solution was continued stirring overnight under a nitrogen atmosphere. After evaporation

of the solvent under reduced pressure, the yellow oily residue was taken in DCM (100 mL) and the organic phase was washed with water and brine (50 mL each). After separation, the organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a yellow residue, which after chromatography (EtOAc) yielded linker **11** as a yellowish oil (3.18 g, 87% yield). R_f=0.60 (EtOAc/PE, 1:1), MS (CI): *m/z* 308 (MH^+, 20), 208 (MH^+−Boc 100); ν_{max} (KBr): 3500–3100 br s, 1660, 1650, 1280 cm^{-1}; ^1H NMR: δ 7.14 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 6.06 (ddt, *J*=17.1, 10.8, 5.4 Hz, 1H), 5.41 (dd, *J*=17.1, 1.2 Hz, 1H), 5.29 (dd, *J*=10.8, 1.2 Hz, 1H), 4.53 (d, *J*=5.4 Hz, 2H), 4.31 (s, 2H), 3.55–3.53 (m, 2H), 3.36–3.34 (m, 2H), 1.69–1.67 (m, 2H), 1.47 (s, 9H); ^{13}C NMR: δ 157.1 (C), 154.7 (C), 134.1 (C), 127.7 (CH), 122.1 (CH), 115.6 (CH_2), 112.8 (CH), 77.3 (CH_2), 60.6 (CH_2), 57.5 (CH_2), 50.7 (CH_2), 42.1 (CH_2), 28.7 (CH_2), 27.6 (CH_3).

*4.1.14. Allyl 3-(N-(3-hydroxypropyl)-2-(9H-fluoren-9-yl)methoxycarbonyl) propyl carbamate (**12**).* A solution of **20** (2.11 g, 9.7 mmol) and DIEA (5 mL, 28.8 mmol) in DCM (35 mL) was stirred at 0 °C for 20 min under a nitrogen atmosphere and a solution of Fmoc-Cl (2.98 g, 11.5 mmol) in DCM (35 mL) was added dropwise over 20 min. The reaction mixture was stirred at rt overnight under a nitrogen atmosphere. The organic phase was washed three times with 1 N HCl, aqueous sodium carbonate solution and brine (40 mL each), dried over anhydrous Na_2SO_4 and evaporated to give **12** after chromatography (EtOAc) as a yellow oil (3.05 g, 72% yield). R_f=0.75 (EtOAc/PE, 1:1), MS (CI): *m/z* 439 (MH^+, 100); ν_{max} (KBr): 3430–3100 br s, 1650, 1600, 1520, 1300 cm^{-1}; ^1H NMR: δ 7.76–7.75 (m, 2H), 7.58–7.57 (m, 2H), 7.42–7.40 (m, 4H), 5.91 (ddt, *J*=17.1, 10.5, 5.4 Hz, 1H), 5.3 (dd, *J*=17.1, 1.2 Hz, 1H), 5.22 (dd, *J*=10.5, 1.2 Hz, 1H), 4.70 (d, *J*=4.2 Hz, 2H), 4.54 (d, *J*=5.4 Hz, 2H), 4.20 (t, *J*=4.2 Hz, 1H), 3.73–3.72 (m, 2H), 3.21–3.19 (m, 4H), 2.94–2.93 (m, 2H), 1.84–1.83 (m, 2H), 1.73–1.71 (m, 2H); ^{13}C NMR: δ 157.6 (C), 156.1 (C), 144.0 (C), 140.3 (C), 135.4 (C), 128.2 (CH), 126.5 (CH), 123.7 (CH), 120.3 (C), 68.0 (CH_2), 67.4 (CH_2), 65.3 (CH_2), 45.8 (CH), 42.8 (CH_2), 34.3 (CH_2), 26.1 (CH_2), 20.8 (CH_2).

*4.1.15. Allyl 3-(N-(3-hydroxypropyl)-2-nitrophenylsulfonamido)propyl carbamate (**13**).* *o*-Nitrobenzenesulfonyl chloride (4 g, 18.04 mmol) in DCM (15 mL) was added dropwise over 30 min to an ice cold solution of triethylamine (6.2 mL, 44.8 mmol) and **20** (3.91 g, 18.04 mmol) in dry DCM (35 mL). The mixture was stirred overnight at rt, washed with a 10% aqueous solution of $NaHCO_3$ (3×25 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was taken into diethyl ether (25 mL) and the solvent was evaporated. The crude was triturated with $CHCl_3$ and *n*-hexanes (1:9) and chromatographed (EtOAc), to give **13** as a yellow oil (5.63 g, 78% yield). R_f=0.55 (EtOAc/PE, 1:1), MS (CI): *m/z* 402 (MH^+, 100); ν_{max} (KBr): 3500–3100 br s, 1650, 1610, 1480, 1290 cm^{-1}; ^1H NMR: δ 8.00 (m, 1H), 7.67–7.65 (m, 3H), 5.91 (ddt, *J*=17.1, 10.5, 5.1 Hz, 1H), 5.21 (dd, *J*=17.1, 1.5 Hz, 1H), 5.21 (dd, *J*=10.5, 1.5 Hz, 1H), 4.55 (d, *J*=5.4 Hz, 2H), 3.68–3.66 (m, 2H), 3.39–3.37 (m, 4H), 3.23–3.22 (m, 2H), 2.02–2.01 (m, 2H) 1.79–1.77 (m, 2H); ^{13}C NMR: δ 157.6 (C), 146.7 (C), 136.0 (CH), 135.8 (CH), 135.4 (C), 134.3 (C), 132.3 (CH), 126.9 (C), 120.3 (C), 67.0 (CH_2), 65.3 (CH_2), 44.8 (CH_2), 42.6 (CH_2), 36.6 (CH_2), 27.0 (CH_2), 21.7 (CH_2).

*4.1.16. 3,5-Bis(3-(N-(3-(allyloxycarbonylamino)propyl)-2-nitrophenylsulfonamido) propoxy)benzoic acid (**14**).* Compound **14** was synthesized in the same manner as for **10** from 2-chlorotrityl resin (0.2 g, 0.28 mmol loading), dihydroxybenzoic acid (0.04 g, 0.27 mmol) and linker **13** (0.53 g, 1.33 mmol). After the usual work up (fast purification by solid-phase extraction pack RP-18, first washed with water and then extracted with acetonitrile, 5 mL each), **14** was obtained as orange oil (0.16 g, 74% yield). R_f=0.60 (EtOAc/PE, 2:1), HRMS *m/z* 921.2415 (MH^+, calculated 921.2563 for $C_{39}H_{48}N_6O_{16}S_2$); ν_{max} (KBr): 3430–3100 br s, 1700, 1650, 1600, 1520, 1300 cm^{-1}; ^1H NMR: δ 8.00–7.98 (m, 2H), 7.90–7.88 (m, 2H), 7.61–7.59 (m, 4H), 7.26–7.25 (m, 2H), 6.53 (m, 1H), 5.90 (ddt, *J*=17.1, 10.5, 5.1 Hz, 2H), 5.35 (dd, *J*=17.1, 1.8 Hz, 2H), 5.23 (dd, *J*=10.5, 1.8 Hz, 2H), 4.58 (d, *J*=5.1 Hz, 4H), 3.91–3.88 (m, 4H), 3.47–3.44 (m, 8H), 3.27–3.25 (m, 4H), 2.05–2.03 (m, 5H) 1.84–1.82 (m, 4H); ^{13}C NMR: δ 170.7 (C), 159.6 (C), 159.2 (C), 157.2 (C), 137.2 (C), 135.8 (C), 134.7 (CH), 133.8 (CH), 132.5 (CH), 128.9 (CH), 124.4 (CH), 118.1 (CH_2), 108.5 (CH), 107.3 (CH), 68.1 (CH_2), 66.2 (CH_2), 45.1 (CH_2), 44.4 (CH_2), 38.8 (CH_2), 29.8 (CH_2), 29.0 (CH_2).

*4.1.17. 3,5-Bis(3-((((9H-fluoren-9-yl)methoxy)carbonyl)(3-(allyloxycarbonylamino) propyl)amino)propoxy)benzoic acid (**15**).* Compound **15** was synthesized in the same manner as for **10** from 2-chlorotrityl resin (0.2 g, 0.28 mmol loading), dihydroxybenzoic acid (0.04 g, 0.27 mmol) and linker **12** (0.58 g, 1.33 mmol). After usual work up (fast purification by solid-phase extraction pack RP-18, first washed with water and then extracted with acetonitrile, 5 mL each) **15** was obtained as a yellowish oil (0.18 g, 77% yield). R_f=0.70 (EtOAc/PE, 2:1), HRMS *m/z* 996.4342 (10%), MH^+-Fmoc 773.4316 (100%) (MH^+, calculated 996.4423 for $C_{57}H_{62}N_4O_{12}$); ν_{max} (KBr): 3390–3050 br s, 1700, 1650, 1510, 1430, 1200 cm^{-1}; ^1H NMR: δ 7.73–7.70 (m, 4H), 7.55–7.52 (m, 4H), 7.32–7.28 (m, 8H), 7.01 (m, 2H), 6.52 (m, 1H), 5.92 (ddt, *J*=17.1, 10.5, 5.4 Hz, 2H), 5.30 (dd, *J*=17.1, 1.2 Hz, 2H), 5.25 (dd, *J*=10.5, 1.2 Hz, 2H), 4.61 (d, *J*=4.2 Hz, 4H), 4.54 (d, *J*=5.4 Hz, 4H), 4.20 (t, *J*=4.2 Hz, 2H), 3.81–3.79 (m, 4H), 3.24–3.20 (m, 8H), 2.97–2.95 (m, 4H), 1.94–1.90 (m, 4H), 1.83–1.80 (m, 4H); ^{13}C NMR: δ 170.6 (C), 159.8 (C), 159.7 (C), 159.6 (C), 157.3 (C), 143.7 (C), 141.4 (CH), 131.3 (CH), 127.7 (CH), 127.2 (CH), 124.5 (CH), 119.9 (CH), 117.9 (CH_2), 108.1 (CH), 107.5 (CH), 68.3 (CH_2), 66.8 (CH_2), 65.5 (CH_2), 47.4 (CH_2), 45.1 (CH_2), 43.6 (CH), 38.7 (CH_2), 29.7 (CH_2), 28.9 (CH_2).

*4.1.18. 3,5-Bis(3-((4-(allyloxy)benzyl)(tert-butoxycarbonyl)-amino)propoxy) benzoic acid (**16**).* Compound **16** was synthesized in the same manner as for **10** from 2-chlorotrityl resin (0.2 g, 0.28 mmol loading), dihydroxybenzoic acid (0.04 g, 0.27 mmol) and linker **11** (0.41 g, 1.33 mmol). After the usual work up and cleavage in 4 °C cold 1% TFA/DCM for 10 min, **16** was obtained as colorless oil (0.15 g, 68% yield). R_f=0.65 (EtOAc/PE, 2:1), HRMS *m/z* 761.3825 (MH^+, 5), 661.3847 (MH^+−Boc, 8), 561.3886 (MH^+−Boc-Boc, 100), (MH^+, calculated 761.3932 for $C_{43}H_{57}N_2O_{10}$); ν_{max} (KBr): 3400–3000 br s, 1705, 1655, 1500, 1480, 1190 cm^{-1}; ^1H NMR: δ 7.28–7.26 (m, 2H), 7.12 (d, *J*=8.7 Hz, 4H), 6.89 (d, *J*=8.7 Hz, 4H), 6.60 (m, 1H), 6.01 (ddt, *J*=17.1, 10.5, 5.1 Hz, 4H), 5.38 (dd, *J*=16.8, 1.8 Hz, 4H), 5.20 (dd, *J*=10.8, 1.8 Hz, 4H), 4.61 (d, *J*=5.4 Hz, 4H), 4.55 (d, *J*=5.4 Hz, 4H), 4.14–4.11 (m, 4H), 3.69–3.65 (m, 4H), 3.55–3.52 (m, 4H), 3.43–3.40 (m, 4H), 1.45 (s. 9H); ^{13}C NMR: δ 170.1 (C), 159.5 (C), 159.1 (C), 157.8 (C), 157.11 (C), 132.3 (CH), 118.1 (CH_2), 108.4 (CH), 107.0 (CH), 66.8 (CH_2), 65.9 (CH_2), 39.8 (CH_2), 40.3 (CH_2), 47.3 (CH_2), 32.1 (CH_3).

*4.1.19. 3,5-Bis(3-((2-(allyloxy)-2-oxoethyl)(3(allyloxycarbonyl-amino)propyl) amino) propoxy)benzoic acid (**18a**).* To 2-chlorotrityl resin (0.2 g, 0.28 mmol loading) in a reactor was added a solution of dihydroxybenzoic acid (0.04 g, 0.26 mmol) in dry DMF (3.5 mL) and after addition of diisopropylethylamine (DIEA, 185 μL, 1.04 mmol) the reaction mixture was shaken for 1.5 h. After completion of the loading, dry MeOH (1.5 mL) was poured into the reactor and shaking continued for an additional 20 min. The solvent was filtered out and the following washings were sequentially performed: 2×DCM:MeOH:DIEA (17:2:1), 2×DCM, 2×DMF, 2×DCM, 2×DCM:DMF (1:1) (3 mL each). To the loaded resin **8** in the reactor was added, under a nitrogen atmosphere, linker **12** (0.582 g, 1.33 mmol) in dry THF:DCM (1:1, 5.2 mL), DBAB (0.306 mL, 1.33 mmol) and PPh_3 (0.348 g, 1.33 mmol). After shaking overnight, the solution was filtered out and the following washings were sequentially performed: 1×THF, 1×DCM, 1×10% DIEA/DMF, 1×DMF, 3×MeOH, 3×DMF, 3×DCM (3 mL each). The coupling and the

washings were repeated to yield resin bound **17**. The Fmoc protecting group was removed by reaction with 20% piperidine in NMP (2×15 min, 5 mL each) and subsequent washing (2×DCM, 2×DMF, 5 mL each). Then, a solution of allyl bromoacetate (0.235 g, 1.33 mmol) and DIPA (1 mL) in DMF (4.5 mL) was added to the resin and shaken for 24 h at 40 °C. Then the resin was washed with 2×10% DIPA in DMF, 3×DMF, 3×DCM (3 mL each) and the alkylation procedure was repeated. The resin was transferred to a vial for cleavage and a 4 °C cold solution of 1% TFA in DCM (2 mL) was added. After shaking for 30 min, the solution was collected and the resin was washed several times with DCM (3 mL each). After combining the organic solutions, the solvent was evaporated first by N_2 stream and then in vacuum to give after the usual work up (fast purification by solid-phase extraction pack RP-18, first washed with water and then extracted with acetonitrile, 5 mL each), **18a** as a yellowish oil (0.083 g, 70% yield). R_f=0.80 (MeOH:EtOAc, 1:99), HRMS *m*/*z* 746.8475 (MH^+, calculated 746.8412 for $C_{37}H_{54}N_4O_{12}$); ν_{max} (KBr): 3400–3100 br s, 1700–1660 br s, 1640, 1220, 1170 cm^{-1}; ^1H NMR (600 MHz): δ 7.20 (m,2H), 6.63(m,1H), 5.92–5.88 (m, 4H), 5.50–5.45 (m, 8H), 4.60–4.55 (m, 8H), 4.24 (d, *J*=5.4 Hz, 4H), 3.66–3.62 (m, 6H), 3.55–3.50 (m, 6H), 2.74–2.70 (m, 4H), 1.90–1.80 (m, 8H); ^{13}C NMR (150 MHz): δ 172.8 (C), 157.5 (C), 156.1 (C), 155.8 (C), 152.1 (C), 130.4 (CH), 120.2 (CH_2), 105.4 (CH), 104.0 (CH), 67.3 (CH_2), 65.6 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 37.1 (CH_2).

*4.1.20. 3,5-Bis(3-((3-(allyloxycarbonylamino)propyl)(2-(benzyloxycarbonylamino)ethyl)amino) propoxy)benzoic acid (**18b**).* Compound **18b** was synthesized in the same manner as for **18a** from 2-chlorotrityl resin (0.2 g, 0.28 mmol loading) bound **17** and benzyl 3-bromopropylcarbamate (036 g, 1.33 mmol). After the usual work up (fast purification by solid-phase extraction pack RP-18, first washed with water and then extracted with acetonitrile, 5 mL each), **18b** was obtained as yellow oil (0.104 g, 67% yield). R_f=0.70 (MeOH:EtOAc, 1:99), HRMS *m*/*z* 841.3073 ($MH^+-C_6H_5CH_3$, calculated 841.4347 for $C_{42}H_{61}N_6O_{12}$); ν_{max} (KBr): 3400–3010 br s, 1680–1650 br s, 1570, 1480, 1180 cm^{-1}; ^1H NMR: δ 7.45–7.38 (m, 6H), 7.10–7.02 (m, 4H), 7.20 (m, 2H), 6.55 (m, 1H), 5.95 (ddt, *J*=17.1, 10.5, 5.1 Hz, 2H), 5.30 (dd, *J*=17.1, 1.8 Hz, 2H), 5.22 (dd, *J*=10.5, 1.8 Hz, 2H), 5.26 (s, 4H), 5.03 (s, 4H), 4.47 (d, *J*=5.1 Hz, 4H), 3.87–3.82 (m, 4H), 3.25–3.18 (m, 8H), 2.11–2.06 (m, 8H) 1.86–1.77 (m, 12H); ^{13}C NMR: δ 172.6 (C), 170.3 (C), 162.5 (C), 154.9 (C), 154.3 (C), 136.0 (C), 135.3 (C), 135.1 (CH), 133.2 (CH), 131.7 (CH), 128.0 (CH), 127.3 (CH), 115.0 (CH_2), 111.6 (CH), 106.0 (CH), 70.9 (CH_2), 64.0 (CH_2), 45.9 (CH_2), 43.7 (CH_2), 40.3 (CH_2), 28.3 (CH_2), 26.5 (CH_2).

*4.1.21. 3,5-Bis(3-((3-(allyloxycarbonylamino)propyl)(2-(2-nitrophenylsulfonamido)ethyl)amino) propoxy)benzoic acid (**18c**).* Compound **18c** was synthesized in the same manner as for **18a** from 2-chlorotrityl resin (0.2 g, 0.28 mmol loading) bound **17** and *N*-(3-bromopropyl)-2-nitrobenzenesulfonamide (0.43 g, 1.33 mmol). After the usual work up (fast purification by solid-phase extraction pack RP-18, first washed with water and then extracted with acetonitrile, 5 mL each), **18c** was obtained as orange oil (0.113 g, 62% yield). R_f=0.60 (MeOH:EtOAc, 1:99), HRMS *m*/*z* 1035.1503 (MH^+, calculated 1035.1478 for $C_{45}H_{62}N_8O_{16}S_2$); ν_{max} (KBr): 3500–3150 br s, 1700–1650 br s, 1605, 1510, 1200 cm^{-1}; ^1H NMR: δ 8.05–8.00 (m, 2H), 7.64–7.58 (m, 6H), 7.24–7.22 (m, 2H), 6.50 (m, 1H), 5.93 (ddt, *J*=17.1, 10.5, 5.1 Hz, 2H), 5.31 (dd, *J*=17.1, 1.8 Hz, 2H), 5.27 (dd, *J*=10.5, 1.8 Hz, 2H), 4.52 (d, *J*=5.1 Hz, 4H), 4.01–3.98 (m, 4H), 3.83–3.77 (m, 4H), 3.28–3.24 (m, 8H), 2.10–2.06 (m, 8H) 1.82–1.78 (m, 12H); ^{13}C NMR: δ 172.1 (C), 160.5 (C), 158.7 (C), 155.9 (C), 136.1 (C), 134.7 (C), 134.1 (CH), 132.5 (CH), 130.3 (CH), 129.0 (CH), 125.3 (CH), 117.0 (CH_2), 110.5 (CH), 107.0 (CH), 69.6 (CH_2), 65.0 (CH_2), 47.5 (CH_2), 44.8 (CH_2), 38.4 (CH_2), 28.9 (CH_2), 27.4 (CH_2).

Acknowledgements

We wish to thank Mr. Vladimir Gaisin for analytical assistance.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.11.106.

References and notes

1. (a) Al-Jamal, K. T.; Ramaswamy, C.; Florence, A. T. *Adv. Drug Delivery Rev.* **2005**, *57*, 2238–2270; (b) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117–132; (c) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466–2468; (d) Tomalia, D. A.; Hall, M.; Hedstrand, D. *J. Am. Chem. Soc.* **1987**, *109*, 1601–1603; (e) Tomalia, D. A.; Berry, V.; Hall, M.; Hedstrand, D. M. *Macromolecules* **1987**, *20*, 1164–1167.
2. (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *102*, 119–128; (b) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 130–141.
3. Tomalia, D. A.; Hedstrand, D. M.; Ferritto, M. S. *Macromolecules* **1991**, *24*, 1435–1444.
4. (a) Nagasaki, T.; Ukon, M.; Arimori, S.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1992**, 608–610; (b) Nagasaki, T.; Kimura, O.; Ukon, M.; Arimori, S.; Hamachi, I.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 75–81.
5. (a) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287–1297; (b) Fréchet, J. M. J. *Science* **1994**, *263*, 1710–1712; (c) Fréchet, J. M. J. *Science* **1995**, *269*, 1080–1082.
6. Zimmerman, S. C.; Zeng, F.; Richert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 10985–10987.
7. Bell, T. W. *Science* **1996**, *271*, 1077–1081.
8. (a) van Hest, J. C. M.; Delnoyer, D. A. P.; Baars, M. W. P. L.; van Genderen, M. H. P.; Meije, E. W. *Science* **1995**, *268*, 1592–1595; (b) Johan, F. G. A.; Janson, J. E.; Meijer, W.; de Brabander-van den Berg, E. M. M. *J. Am. Chem. Soc.* **1995**, *117*, 4417–4426; (c) Johan, F. G. A.; Janson, J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1995**, *266*, 1266–1269; (d) Gopidas, K. R.; Leheny, A. R.; Caminati, G.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 7335–7343.
9. Al-Hellani, R.; Schluter, A. D. *Macromolecules* **2006**, *39*, 8943–8951.
10. Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3868.
11. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
12. Dankwardt, S. M.; Phan, T. M.; Krstenansk, J. L. *Mol. Div.* **1996**, *1*, 113–120.
13. Hardcastle, I.; Barber, A.; Marriott, J.; Jarman, M. *Tetrahedron Lett.* **2001**, *12*, 1363–1365.
14. Basso, A.; Evans, B.; Pegg, N.; Bradley, M. *Chem. Commun.* **2001**, 697–698.
15. Arai, T.; Sekiguti, T.; Iizuka, Y.; Sasaia, H. *Tetrahedron: Asymmetry* **2002**, *13*, 2083–2087.
16. Gelerman, G.; Kremer, M.; Elgavi, A. *J. Pept. Res.* **2001**, *57*, 277–290.
17. (a) Nithyanandhan, J.; Jayaraman, N. *Tetrahedron* **2005**, *61*, 11184–11191; (b) Kasemi, E.; Zhuang, W.; Rabe, J. P.; Schluter, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 5091–5099; (c) Chow, H. F.; Mak, C. C. *Pure Appl. Chem.* **1997**, *69*, 483–488.
18. Lagnoux, D.; Darbre, T.; Schmitz, M. L.; Reymond, J. L. *Chem.— Eur. J* **2005**, *11*, 3941–3950.
19. Atherton, E.; Sheppard, R. C. In *The Fluorenylmethoxycarbonyl Amino Protecting Group in Peptides*; Udenfriend, S., Meienhofer, J., Eds.; Academic: New York, NY, 1987; Vol. 9, p 1.
20. Czerwenka, C.; Lämmerhofer, M.; Lindner, W. *J. Sep. Sci.* **2003**, *26*, 1499–1508.
21. Gellerman, G.; Hazan, E.; Albeck, A.; Shatzmiler, S. *Tetrahedron* **2009**, *65*, 1389–1396.
22. (a) Nagarajan, M.; Xiao, X.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 5712–5724; (b) Kaur, N.; Phanstiel, O. *J. Med. Chem.* **2005**, *48*, 3832–3839.