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Multi-Tier Dendrimers with an Aromatic Core

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Dedicated to the memory of Dr. Darshan Ranganathan

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We report various multi-tier designer dendritic molecules that incorporate an aromatic core and heterocyclic and peptide units. The 5-(azidomethyl)benzene-1,3-dicarbonyl unit was chosen as the scaffold as this unit allows two identical units and a reactive end to be incorporated, thus generating a dendron suitable for dendrimer synthesis. The design and synthesis of dendrimers with multi-tier architectures will be useful for generating dendritic structures with various functions.

Introduction

Dendrimers are molecules with a tree-like architecture, having a central core, branching units and surface functionalities. Owing to their multivalent nature, dendrimers can increase binding to receptors, thus enhancing biological effects.[1] Dendritic molecules with multiple functionalities can act as matrix structures for many biological applications, including multiple antigen peptides (MAP),[2] carrier molecules,[3,4] vaccine developments,[5] artificial enzymes[6] and globular protein mimetics.[7] Biocompatible dendrimers[8] are much sought after for biological applications because the success of dendrimers as carriers or biomaterials is dependent upon their biocompatibility, that is, the ability of compounds to exist or perform in a biological environment without any undesired toxic effects. In general, toxicity is related mostly to the size, charge and surface functionality of the dendrimers.

The various beneficial attributes of dendrimers create a strong impetus for the design and synthesis of these tree-like macromolecules.[9,10] An ideal dendrimer synthesis is one that provides the opportunity to incorporate a variety of functional groups into the dendrimer by design and has a robust synthetic strategy, a simple purification procedure and a good yield. However, many accounts of dendrimer synthesis reported in the literature do not meet all the above criteria and the development of a versatile dendrimer synthesis is therefore highly warranted. There are two key approaches to the synthesis of dendrimers: convergent and divergent approaches.[11] In the convergent approach, dendrons are synthesized separately and then linked together in a modular fashion, converging to form a dendrimer.[12] In the divergent approach, the dendrimer is built stepwise and diverges outward.[13]

We herein report various dendritic molecules that incorporate an aromatic core and heterocyclic and peptide units. As biological molecules, peptides are an attractive choice for incorporation into dendritic structures.

Results and Discussion

Lysine, with N^{α} and N^{ε} amino groups as its reactive ends, is a suitable amino acid for forming a branching unit by sequential propagation of lysines. The N^{α} and N^{ε} amino groups can be functionalized with lysine units to double the number of terminal amino groups. The sequential addition of Lys units will generate a dendron with a large number of Lys units with a single C-terminal moiety. Reaction with propargylamine and BocLys(Boc)-OH in the presence of *N*-hydroxysuccinimide and DCC produced propargyl amide, which on deprotection and coupling with BocLys(Boc)-OH produced Lys-dendron **2** with a C-terminal alkyne moiety (Scheme 1).

In order to have carboxylate groups on the surface of the dendrimer we chose aspartic acid as the monomer unit. The C^{α} and C^{β} carboxylic acid groups are able to act as branching units by the sequential addition of Asp units (Scheme 2). Boc-Asp on reaction with Asp.diOMe in the presence of *N*-hydroxysuccinimide and DCC produced Asp-(Asp.diOMe)Asp.diOMe. Sequential addition of Asp units can generate an Asp-based dendron ideal for dendrimers with peripheral methoxycarbonyl groups.

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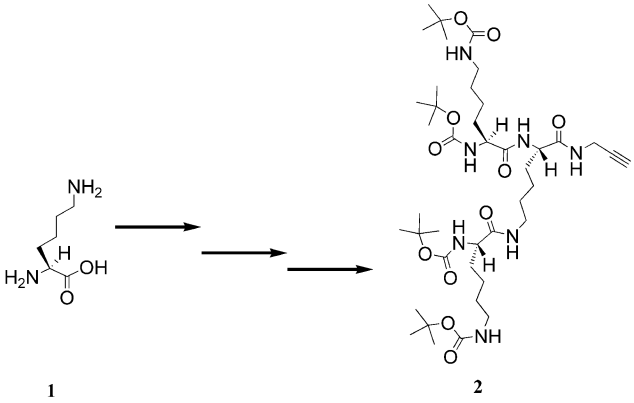
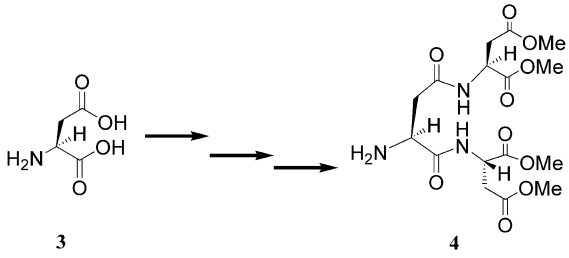


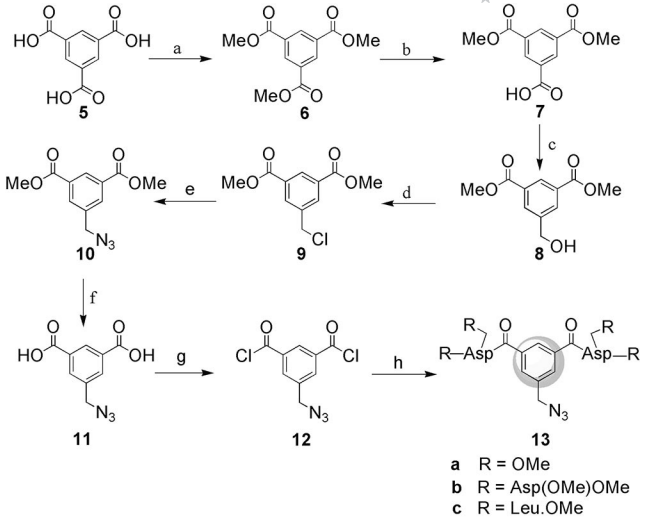
Scheme 1. Synthesis of the Lys-based dendron.



Scheme 2. Synthesis of Asp-based dendron.

The 5-(azidomethyl)benzene-1,3-dicarbonyl unit was chosen as the scaffold because this unit allows us to incorporate two identical units and a reactive end, thus generating a dendron suitable for dendrimer synthesis. The 1,3,5-benzenetricarboxylic acid was converted into 5-(azidomethyl)benzene-1,3-dicarbonyl dichloride in seven steps by a literature method (Scheme 3).[14] In a typical procedure, 1,3,5-benzenetricarboxylic acid (**5**) was converted into trimethyl ester **6** in the presence of a small amount of acid. The triester **6** was selectively hydrolysed to mono acid **7**, which on reduction with $BH_3{\cdot}Me_2S$ furnished mono alcohol **8**. The alcohol **8** thus generated was converted into the azide **10** by treatment with thionyl chloride followed by reaction with sodium azide. The mono azide **10** was converted into the diacid **11** by base hydrolysis and further converted into the acid chloride by reaction with thionyl chloride under reflux. The reaction of H_2N-Asp.diOMe, H_2N-Asp(Asp.diOMe)-Asp.diOMe or H_2N-Asp(Leu.OMe)-Leu-.OMe with 5-(azidomethyl)benzene-1,3-dicarbonyl dichloride (**12**) afforded the azido-substituted dendrons **13a**, **13b** and **13c**, respectively (Scheme 3).

The mono azide **13b** was allowed to react, in the presence of cuprous iodide (CuI), with Lys-dendron **17** containing a C-terminal alkyne unit, which provided unsymmetrical dendrimer **22** in 55% yield (Scheme 4). The fully protected dendron **17** was deprotected by using 25% TFA in CH_2Cl_2, affording cationic dendron **16**, which on reaction with **13a** provided the cationic dendrimer **21**. Dendrimer **21** can also be synthesized from the fully protected dendrimer by treating it with 50% TFA in dry CH_2Cl_2.

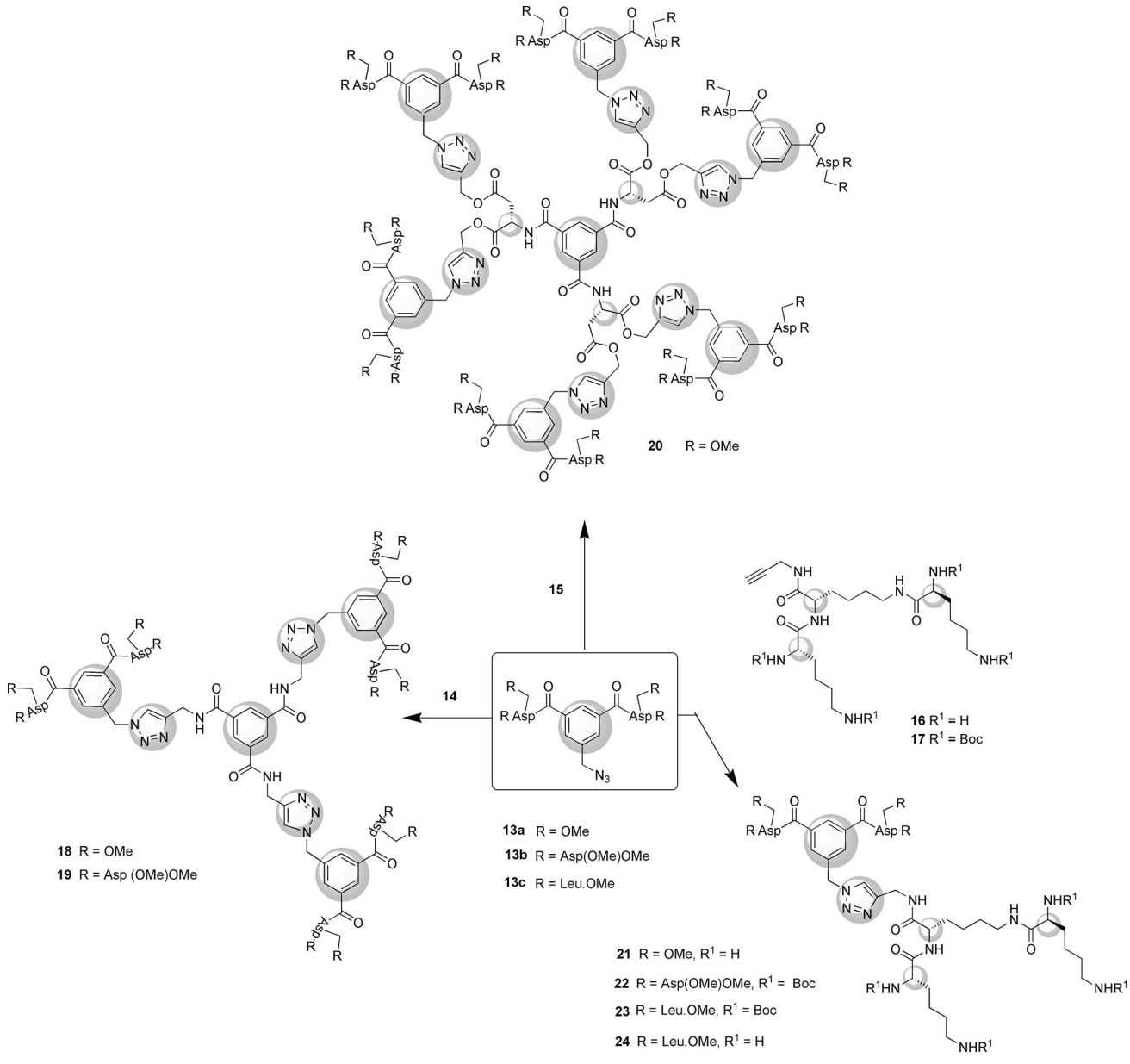


Scheme 3. Synthesis of aryl-anchored dendrons **13a**, **13b** and **13c**. Reagents and conditions: (a) $MeOH/H_2SO_4$; (b) 1 equiv. of NaOH; (c) $BH_3{\cdot}Me_2S$; (d) $SOCl_2$, reflux; (e) NaN_3; (f) 2 M NaOH; (g) $SOCl_2$, reflux; (h) i. Asp.diOMe HCl, NEt_3; ii. Asp(Asp.diOMe)-Asp.diOMe, NEt_3; iii. Asp(Leu.OMe)Leu.OMe, NEt_3.

The advantage of the Cu^I-catalysed azide–alkyne coupling reaction (click reaction)[15,16] is that it can link the unprotected peptide fragments to the central core. This is demonstrated by the synthesis of **21** and **24** in 51 and 72% yields, respectively. The Cu^I-catalysed click reaction exclusively yielded the triazole-1,4-diyl product.[17] Owing to its high chemoselectivity, this highly atom-economic and efficient coupling reaction is a powerful tool for the effective construction of complex dendrimers.[18]

To synthesize various dendrimers, the azide-truncated dendrons **13a** and **13b** were treated with various trialkynes to provide a host of dendrimers. The trialkyne unit **14** was synthesized in 62% yield from 1,3,5-tris(chlorocarbonyl)-benzene and propargylamine (Scheme 5). This trialkyne **14** was treated with azide dendrons **13a** and **13b** to provide 40 and 43% yields of dendrimers **18** and **19**, respectively (Scheme 4).

The dendrimer **18** has a central benzene core, a second tier of heterocyclic triazole units, a third tier of benzene units and peripheral peptide units. To illustrate the versatility of this approach, we decided to synthesize dendrimers that incorporate various structurally distinct units on moving from the central core to the periphery. With this in mind the hexaalkyne **15** was designed and synthesized from Boc-Asp. Propargyl alcohol was treated with Boc-Asp in the presence of *N*-hydroxysuccinimide and DCC to produce propargyl-functionalized aspartic acid, which on deprotection using 25% TFA and further reaction with 1,3,5-tris-(chlorocarbonyl)benzene afforded hexaalkyne **15**. The azide dendron **13a** was treated with hexaalkyne **15** to generate a hybrid dendrimer **20** with a central aromatic ring, a second tier of Asp units, a third tier of triazole units, a fourth tier of benzene rings and a fifth tier of peptide units. All the compounds were characterized and the structures were in accordance with the spectroscopic data.

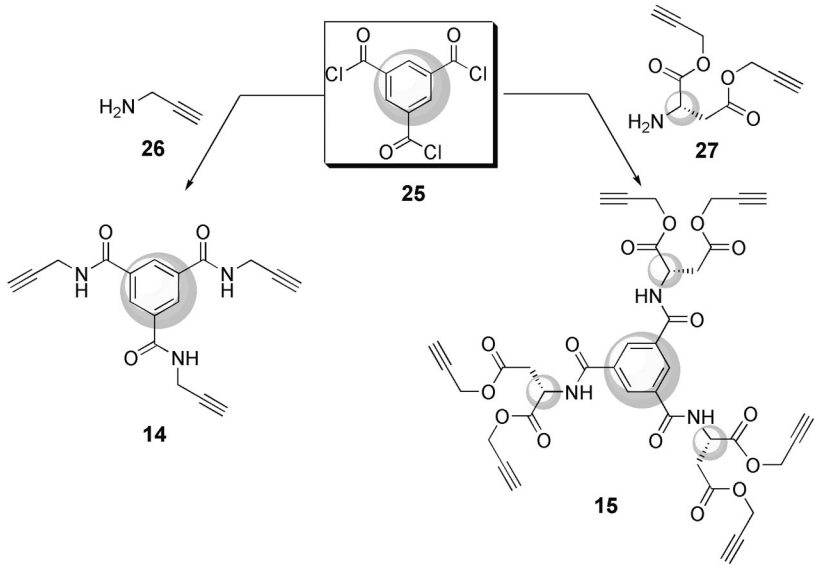


Scheme 4. Synthesis of symmetrical and unsymmetrical dendrimers using click reaction.

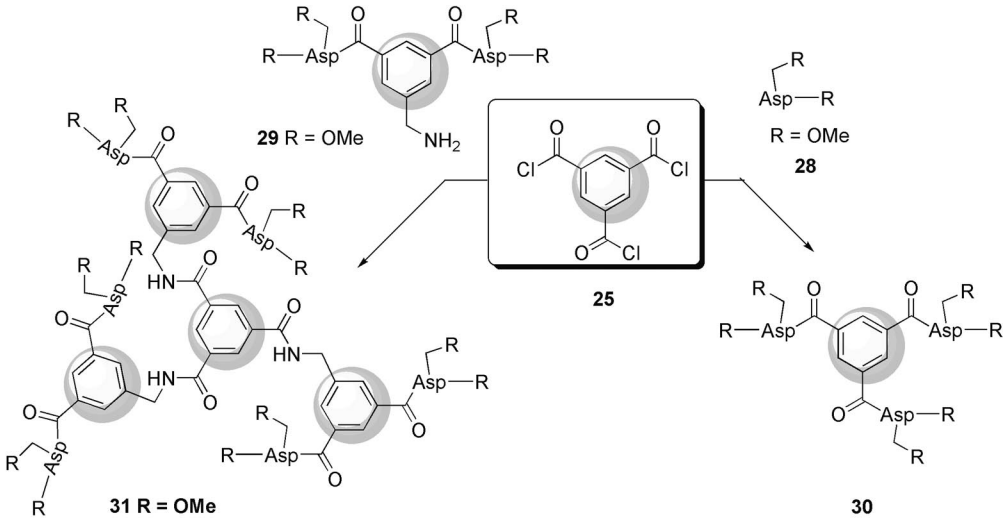
This synthesis allows us to incorporate a wide variety of amino acids into the dendrimer skeleton. The versatility of the design is illustrated by the incorporation of the hydrophobic leucine as peripheral units. Z-Asp (Z = benzyloxycarbonyl) was treated with Leu.OMe under *N*-hydroxysuccinimide/DCC coupling conditions to generate Z-Asp-(Leu.OMe)Leu.OMe in 94% yield. Deprotection of the benzyloxycarbonyl group with H_2 in the presence of Pd/C and reaction with acid chloride **12** afforded dendron **13c**, which on click reaction with Lys-dendrons provided unsymmetrical dendrimers.

The additional advantage of dendrons **13a** and **13b** with an azide unit is that it is not only suitable for click chemistry, but may also be reduced to generate amine-truncated dendrons. The amine-truncated dendrons **28** and **29** were used for the synthesis of all-amide dendrimers[19] **30** and **31** (Scheme 6). To synthesize an all-amide symmetric dendrimer, AspdiOMe was treated with 1,3,5-tris(chlorocarbonyl)benzene to yield 65% of the first-generation dendrimer **30**. To synthesize higher-generation dendrimers, the Asp-dendron **13a** was reduced with Pd/C in methanol to produce amine **29**, which on reaction with 1,3,5-tris(chlorocarbonyl)benzene yielded 83% of the all-amide dendrimer **31**. Dendrimer **31** has a central benzene core, a second tier of benzene units and surface peptide units. The second tier of benzene rings act as branching units.

The dendrimers were characterized by HPLC, NMR and mass spectrometry. The purity of all the dendrimers synthesized was checked by reversed-phase analytical HPLC (RP-HPLC) using a C-18 column and a binary gradient with the mobile phase solvents [solvent A: 0.1% trifluoroacetic acid (TFA) in water; solvent B: 0.1% TFA in acetonitrile



Scheme 5. Synthesis of tri- and hexaalkyne cores.



Scheme 6. Synthesis of all-amide dendrimers.

(see the Supporting Information)]. HPLC traces showed an increase in retention time with increasing generation of dendrimers. For example, **18** and **20** showed a retention time of 24.2 and 39.3 min in a binary gradient with the acetonitrile/water/TFA system. The NMR spectrum of dendrimer **18** indicated a very symmetrical structure with 18 α-COOMe and 18 β-COOMe units resonating at δ = 3.62 and 3.60 ppm, respectively. The five-tier dendrimer **20** showed a single peak for each of the 36 α-COOMe and 36 β-COOMe units. The molecular integrity was shown by mass spectrometry; the mass spectrometric analysis showed a strong molecular-ion peak for all dendrimers synthesized. For example, dendrimer **20** showed a mass of 3849.1419 in HRMS, compared with the theoretical molecular weight of 3849.1418 calculated for $C_{165}H_{183}N_{33}NaO_{75}$.

Conclusions

The synthetic strategy and design of dendrimers with multi-tier architecture will be useful for generating dendritic structures with the capability of trapping substrates in different tier regions, which could thus act as reaction vessels. These dendrimers could be designed to trap biologically important molecules for site-specific delivery in cells. The two synthetic approaches demonstrated herein will be useful for the future generation of dendrimers with functional properties. The orthogonality and fidelity of the click reaction will facilitate the conjugation of important chemical entities in the presence of numerous other unprotected functionalities.

The synthesis reported herein is particularly attractive because it has the potential to produce dendrimers with en-

hanced biocompatibility and biodistribution. These are desirable properties for dendrimers to find applications in biology. The dendrimers reported herein can be easily modified at their surfaces to obtain desired biological properties.

Experimental Section

Synthesis of Aryl-Anchored Dendrons

Preparation of 13a: Dry triethylamine (NEt_3; 0.76 mL, 5.5 mmol) was added to an ice-cooled solution of Asp.diOMe.HCl (**28**; 0.493 g, 2.5 mmol) in dry CH_2Cl_2 (20 mL) and the mixture was stirred for 20 min. 5-(Azidomethyl)benzene-1,3-dicarbonyl dichloride (**12**; 0.258 g, 1 mmol) dissolved in dry CH_2Cl_2 (50 mL) was added dropwise for 15 min and left to stir for 24 h. The reaction mixture was mixed with distilled CH_2Cl_2 (30 mL) and washed with aqueous 2 N H_2SO_4 followed by water and aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and evaporated to yield 0.370 g of the crude product. Chromatographic purification of the crude product yielded 0.300 g of **13a**. Yield 59%; viscous liquid. $[a]_D$ = +0.171 (c = 0.270, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.00 (dd, J = 17.1, 4.3 Hz, 2 H), 3.16 (dd, J = 17.1, 4.3 Hz, 2 H), 3.72 (s, 6 H), 3.81 (s, 6 H), 4.47 (s, 2 H), 5.08 (m, 2 H), 7.41 (d, J = 7.8 Hz, 2 H), 7.92 (s, 2 H), 8.20 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.6, 35.9, 49.1, 52.1, 52.9, 53.8, 125.4, 129.9, 134.6, 137.0, 165.6, 171.0, 171.5 ppm. IR (KBr): $\tilde{\nu}$ = 3390, 2955, 2102, 1740, 1655, 1532, 1442, 1219 cm^{-1}. HRMS: calcd. for $C_{21}H_{25}N_5NaO_{10}$ 530.1499; found 530.1499.

Preparation of 13b: Et_3N (0.5 mL, 3.52 mmol) was added to an ice-cooled solution of H_2N-Asp(Asp.diOMe)Asp.diOMe (0.591 g, 1.41 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred for 20 min. 5-(Azidomethyl)benzene-1,3-dicarbonyl dichloride (**12**; 0.182 g, 0.705 mmol) dissolved in dry CH_2Cl_2 (40 mL) was added dropwise for 15 min and left to stir for 24 h. The reaction mixture was mixed with distilled CH_2Cl_2 (20 mL) and washed with aqueous 2 N H_2SO_4 and aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and evaporated to yield 0.535 g of the crude product. This was dissolved in $CHCl_3$ and precipitated with the addition of hexane to yield 0.495 g of **13b**. Yield 69%; m.p. 194–195 °C. $[a]_D$ = +0.769 (c = 0.130, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.83–3.07 (br. m, 12 H), 3.49 (s, 6 H), 3.66 (s, 6 H), 3.75 (s, 12 H), 4.39 (s, 2 H), 4.90 (m, 4 H), 5.07 (m, 2 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.87 (s, 2 H), 8.08 (s, 1 H), 8.27 (d, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 35.7, 35.9, 37.5, 48.9, 49.0, 50.8, 52.1, 52.8, 52.9, 53.8, 125.2, 130.4, 133.9, 136.9, 165.9, 170.2, 170.9, 171.1, 171.2, 171.6, 171.8 ppm. IR (KBr): $\tilde{\nu}$ = 3296, 3070, 2955, 2103, 1741, 1649, 1536, 1440, 1220, 1000 cm^{-1}. HRMS: calcd. for $C_{41}H_{53}N_9NaO_{22}$ 1046.3203; found 1046.3204.

Preparation of Dendron 13c

Preparation of Z-Asp.(Leu.OMe)Leu.OMe: A solution of NH_2-Leu.OMe (2.20 g, 15.06 mmol) containing triethylamine (1.51 g, 15.00 mmol) was added to a well-stirred and ice-cooled solution of Z-aspartic acid (1.6 g, 5.99 mmol), *N*-hydroxysuccinimide (1.72 g, 14.99 mmol) and DCC (3.09 g, 14.97 mmol) in dry CH_2Cl_2 (20 mL). After stirring for 24 h at room temperature, the reaction mixture was filtered. The residue was washed with CH_2Cl_2 (4 × 20 mL) and the combined filtrates were washed sequentially with 2 N H_2SO_4, H_2O and 5% aqueous $NaHCO_3$. The organic layer was dried with Na_2SO_4, evaporated in vacuo and the crude product was purified by chromatography on a column of silica gel using EtOAc/hexane as eluent to afford 2.950 g of the peptide. Yield 94%; m.p. 143–144 °C. $[a]_D$ = –40.4 (c = 0.5, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (m, 12 H), 1.57 (m, 6 H), 2.63 (dd, J = 15.3, 7.0 Hz, 1 H), 2.87 (br. d, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 4.55 (m, 3 H), 5.11 (s, 2 H), 6.40 (d, J = 7.2 Hz, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 7.31 (m, 6 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): δ = 21.6, 21.7, 22.6, 22.7, 24.7, 33.8, 38.0, 40.7, 41.0, 50.9, 51.0, 51.4, 52.1, 52.2, 67.0, 127.9, 128.0, 128.4, 136.1, 156.0, 170.6, 170.8, 173.2, 173.5 ppm. IR (KBr): $\tilde{\nu}$ = 3298, 3076, 2956, 2878, 1740, 1702, 1653, 1542, 1441, 1362, 1257, 1141 cm^{-1}. HRMS: calcd. for $C_{26}H_{39}N_3NaO_8$ 544.2635; found 544.2636.

Preparation of NH_2-Asp.(Leu.OMe)Leu.OMe: An ice-cooled solution of Z-Asp.(Leu.OMe).Leu.OMe (0.650 g, 1.24 mmol) in dry MeOH (10 mL) was mixed with 10% Pd/C (peptide/catalyst 1:0.25, w/w) and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction (TLC), the solution was filtered and the filtrate was evaporated to yield 0.442 g of the product. Yield 92%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (m, 12 H), 1.58 (m, 6 H), 1.91 (m, 2 H), 2.51 (dd, J = 14.7, 7.5 Hz, 1 H), 2.75 (dd, J = 14.5, 4.4 Hz, 1 H), 3.73 (s, 6 H), 4.53 (m, 2 H), 4.58 (m, 1 H) 6.99 (br. d, 1 H), 7.84 (d, J = 8.4 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3324, 3188, 3077, 2960, 1752, 1679, 1525, 1443, 1375, 1313, 1242, 1204, 1164 cm^{-1}. HRMS: calcd. for $C_{18}H_{33}KN_3O_6$ 426.2006; found 426.2007.

Preparation of the Azide: Et_3N (0.26 g, 2.6 mmol) was added to an ice-cooled solution of NH_2-Asp.(Leu.OMe).Leu.OMe (0.442 g, 1.14 mmol) in dry CH_2Cl_2 (30 mL) and the mixture was stirred for 20 min. 5-(Azidomethyl)benzene-1,3-dicarbonyl dichloride (0.134 g, 0.52 mmol) dissolved in dry CH_2Cl_2 (40 mL) was added dropwise over 25 min and left to stir overnight. The reaction mixture was mixed with distilled CH_2Cl_2 (20 mL) and washed with aqueous 2 N H_2SO_4 and aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and evaporated to yield 0.5 g of the crude product. Chromatographic purification of the crude product yielded 0.480 g of **13c**. Yield 96%. $[a]_D$ = –34.0 (c = 0.2, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.81 (m, 12 H), 0.92 (m, 12 H), 1.67 (m, 12 H), 2.74 (dd, J = 14.8, 6.1 Hz, 2 H), 2.98 (dd, J = 12.1, 5.1 Hz, 2 H), 3.63 (s, 6 H), 3.69 (s, 6 H), 4.37 (s, 2 H), 4.62 (m, 4 H), 5.13 (m, 2 H), 6.98 (br. d, 2 H), 7.75 (s, 2 H), 7.90 (br. d, 2 H), 8.11 (s, 1 H), 8.41 (br. d, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.6, 22.7, 22.8, 24.7, 29.6, 37.9, 40.1, 40.8, 50.8, 51.5, 52.2, 53.7, 126.0, 129.3, 134.1, 136.5, 165.2, 170.7, 172.1, 173.6 ppm. IR (KBr): $\tilde{\nu}$ = 3288, 3066, 2984, 2096, 1743, 1646, 1536, 1441, 1376, 1243 cm^{-1}. HRMS: calcd. for $C_{45}H_{69}N_9NaO_{14}$ 982.4862; found 982.4862.

Preparation of Symmetrical Dendrimers 18–20

Preparation of Trialkyne Core 14: Dry NEt_3 (0.7 mL, 5 mmol) was added to an ice-cooled solution of propargylamine (**26**; 0.2 mL, 3 mmol) in dry CH_2Cl_2 (25 mL) and the mixture was stirred for 20 min. 1,3,5-Tris(chlorocarbonyl)benzene (**25**; 0.265 g, 1 mmol) dissolved in dry CH_2Cl_2 (50 mL) was added dropwise over a period of 15 min and the mixture was stirred for 24 h. The solvent was evaporated and the residue obtained was dissolved in distilled ethyl acetate (50 mL) and washed with aqueous 2 N H_2SO_4 followed by water and saturated aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and the solvent evaporated to yield 0.200 g of **14**. Yield 62%; m.p. >300 °C. ^1H NMR ([D_6]DMSO, 300 MHz): δ = 3.16 (s, 3 H), 4.08 (d, J = 2.6 Hz, 6 H), 8.44 (s, 3 H), 9.18 (br. d, 3 H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 29.2, 73.6, 81.5, 129.4, 134.9, 165.6 ppm. IR (KBr): $\tilde{\nu}$ = 3282, 3243, 3059, 2930, 1639, 1551, 1292, 1417, 1292 cm^{-1}. HRMS: calcd. for $C_{18}H_{16}N_3O_3$ 322.1192; found 322.1192.

Synthesis of Hexaalkyne Core 15: TFA (3 mL) was added to an ice-cooled solution of Boc-Asp-dipropargyl ester (0.825 g, 2.67 mmol) in dry CH_2Cl_2 (6 mL). The solution was left to stir for 2 h and completion of the reaction was monitored by TLC. The reaction mixture was subjected to a high vacuum to yield 0.558 g of the amine **27**, which was used as such without further purification. Yield 100%. ^{1}H NMR (D_2O, 300 MHz): δ = 2.83 (t, J = 2.4 Hz, 1 H), 2.86 (t, J = 2.4 Hz, 1 H), 3.06 (dd, J = 18.1, 4.6 Hz, 1 H), 3.17 (dd, J = 18.3, 5.7 Hz, 1 H), 4.44 (m, 1 H), 4.67 (d, J = 2.4 Hz, 2 H), 4.76 (dd, J = 3.3, 2.4 Hz, 2 H) ppm. IR (KBr): $\tilde{\nu}$ = 3419, 3298, 2931, 2873, 2132, 1752, 1675, 1527, 1435, 1397, 1196 cm^{-1}. HRMS: calcd. for $C_{10}H_{12}NO_4$ 210.0766; found 210.0766.

Dry NEt_3 (0.3 mL, 1.98 mmol) was added to an ice-cooled solution of **27** (0.140 g, 0.67 mmol) in 10 mL of dry CH_2Cl_2 and the mixture was stirred for 20 min. 1,3,5-Benzenetricarbonyl trichloride (**25**; 0.058 g, 0.22 mmol) dissolved in dry CH_2Cl_2 (20 mL) was added dropwise over a period of 10 min and stirred for 24 h. The reaction mixture was mixed with distilled CH_2Cl_2 (30 mL) and washed with aqueous 2 N H_2SO_4 followed by water and aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and the solvent evaporated to yield 0.120 g of **15**. Yield 71%; m.p. 150–151 °C. $[\alpha]_D$ = –12.00 (c = 0.100, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.55 (m, 6 H), 3.12 (dd, J = 17.4, 4.6 Hz, 3 H), 3.22 (dd, J = 17.4, 5.7 Hz, 3 H), 4.76 (d, J = 2.4 Hz, 6 H), 4.82 (d, J = 2.1 Hz, 6 H), 5.16 (m, 3 H), 7.55 (d, J = 7.8 Hz, 3 H), 8.29 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 35.8, 49.4, 52.7, 53.5, 75.5, 75.8, 128.9, 134.2, 165.5, 169.9 ppm. IR (KBr): $\tilde{\nu}$ = 3292, 3070, 2944, 2131, 1746, 1647, 1560, 1436, 1383, 1272, 1168 cm^{-1}. HRMS: calcd. for $C_{39}H_{33}KN_3O_{15}$ 822.1549; found 822.1547.

Preparation of 16: TFA (10 mL, 130 mmol) was added to an ice-cooled solution of **17** (0.252 g, 0.30 mmol) in dry CH_2Cl_2 (4 mL) and the mixture was stirred at room temp. for 3 h. The reaction mixture was then subjected to a vacuum to remove CH_2Cl_2 and TFA to afford 0.132 g of **16**. Yield 100%. ^{1}H NMR (D_2O, 300 MHz): δ = 1.20–1.90 (m, 18 H), 2.52 (m, 1 H), 2.90 (m, 4 H), 3.13 (m, 2 H), 3.82–3.93 (m, 4 H), 4.16 (t, J = 7.0 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3277, 3083, 2922, 2833, 1772, 1675, 1548, 1434, 1196 cm^{-1}. HRMS: calcd. for $C_{21}H_{42}N_7O_3$ 440.3349; found 440.3352.

Preparation of 18: The propargyl derivative **14** (0.041 g, 0.129 mmol) was dissolved in dry CH_3CN by heating. N_2 was bubbled through the homogeneous solution for 30 min and after that DIEA (0.07 mL, 0.386 mmol) was added followed by the azide **13a** (0.196 g, 0.386 mmol) and Cu^I (0.008 g, 0.042 mmol). The reaction mixture was stirred under N_2 for 24 h. The solvent was evaporated and subjected to a high vacuum. The solid obtained was washed several times in ethyl acetate to remove unreacted starting materials. The ethyl acetate insoluble part was dissolved in $CHCl_3$ (30 mL) and washed with an aqueous NH_4Cl/NH_4OH (9:1) solution followed by 0.5 N H_2SO_4. The organic layer was dried with Na_2SO_4 and evaporated to yield 0.095 g of the pure product **18**. Yield 40%; m.p. 160–161 °C. $[\alpha]_D$ = –4.667 (c = 0.150, MeOH). ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 2.85 (dd, J = 16.5, 7.8 Hz, 6 H), 2.97 (dd, J = 16.5, 5.8 Hz, 6 H), 3.61 (s, 18 H), 3.64 (s, 18 H), 4.54 (br. s, 6 H), 4.85 (m, 6 H), 5.69 (s, 6 H), 7.99 (s, 6 H), 8.12 (s, 3 H), 8.29 (s, 3 H), 8.46 (s, 3 H), 9.17 (br. d, J = 7.5 Hz, 9 H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 34.7, 48.9, 51.3, 51.8, 122.9, 129.9, 134.1, 136.2, 164.8, 164.9, 170.0, 170.6 ppm. IR (KBr): $\tilde{\nu}$ = 3426, 2955, 1739, 1656, 1538, 1439, 1286, 1222 cm^{-1}. HRMS: calcd. for $C_{81}H_{90}N_{18}NaO_{33}$ 1865.5815; found 1865.5812.

Preparation of 19: The propargyl derivative **14** (0.029 g, 0.090 mmol) was dissolved in dry CH_3CN (10 mL) by heating. DIEA (0.05 mL, 0.273 mmol) was added followed by the azide **13b** (0.256 g, 0.25 mmol) and Cu^I (0.008 g, 0.042 mmol). The reaction mixture was stirred under N_2 for 24 h. The reaction mixture was evaporated and subjected to high vacuum. The solid obtained was washed several times in ethyl acetate to remove unreacted starting materials. The ethyl acetate insoluble part was obtained in 0.132 g yield and was confirmed to be the product **19**. Yield 43%; m.p. >250 °C. ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 2.68 (m, 36 H), 3.50 (s, 18 H), 3.56 (s, 36 H), 3.60 (s, 18 H), 4.61 (br. s, 18 H), 4.80 (br. s, 6 H), 5.67 (br. s, 6 H), 7.98 (br. s, 6 H), 8.16 (br. s, 3 H), 8.28 (br. s, 3 H), 8.45 (br. s, 15 H), 8.68 (br. s, 6 H), 9.21 (br. s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 3288, 2954, 1737, 1653, 1533, 1438, 1372, 1285, 1224 cm^{-1}. HRMS: calcd. for $C_{141}H_{174}KN_{30}O_{69}$ 3430.0666; found 3430.0694.

Preparation of 20: The propargyl derivative **15** (0.040 g, 0.051 mmol) was dissolved in dry CH_3CN (10 mL). N_2 was bubbled through the solution for 30 min and after that DIEA (0.026 mL, 0.153 mmol) was added followed by the azide **13a** (0.155 g, 0.306 mmol) and Cu^I (0.008 g, 0.042 mmol). N_2 bubbling was continued for an additional 2–3 h and then the reaction mixture was stirred under N_2 for 24 h. The reaction mixture was evaporated and subjected to high vacuum. The solid thus obtained was washed several times in ethyl acetate to remove the unreacted starting materials. The ethyl acetate insoluble part was dissolved in $CHCl_3$, washed with an aqueous NH_4Cl/NH_4OH (9:1) solution followed by 0.5 N H_2SO_4. The organic layer was dried with Na_2SO_4 and evaporated to yield 0.147 g of **20**. Yield 75%. $[\alpha]_D$ = –0.006 (c = 0.130, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.04 (m, 30 H), 3.68 (s, 36 H), 3.77 (s, 36 H), 4.95–5.51 (m, 39 H), 7.60–8.45 (m, 42 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.7, 35.8, 49.4, 52.1, 52.9, 57.9, 58.9, 125.1, 125.7, 128.5, 129.7, 130.0, 134.4, 135.8, 142.6, 165.8, 170.5, 171.3 ppm. IR (KBr): $\tilde{\nu}$ = 3428, 2927, 1735, 1650, 1534, 1446, 1347, 1220 cm^{-1}. HRMS: calcd. for $C_{165}H_{183}N_{33}NaO_{75}$ 3849.1418; found 3849.1419.

Preparation of Unsymmetrical Dendrimers 21–24

Preparation of 21: The propargyl derivative **16** (0.132 g, 0.30 mmol) was dissolved in dry CH_3CN (20 mL). N_2 was bubbled through the reaction mixture for 30 min and after that DIEA (0.3 mL, 1.8 mmol) was added followed by the azide **13a** (0.150 g, 0.3 mmol) and Cu^I (0.012 g, 0.063 mmol). N_2 bubbling was continued for an additional 2–3 h and then the reaction mixture was stirred under N_2 for 24 h. The CH_3CN was evaporated and subjected to high vacuum. It was washed several times with a 1:1 mixture of EtOAc/hexane to remove all other impurities. The product **21** was obtained in 0.143 g yield. Yield 51%. $[\alpha]_D$ = +1.33 (c = 0.300, $CHCl_3$). ^{1}H NMR (D_2O, 300 MHz): δ = 0.90–1.85 (br. m, 18 H), 2.65–3.10 (br. m, 10 H), 3.56 (s, 6 H), 3.63 (s, 6 H), 3.80 (m, 3 H), 4.06 (m, 2 H), 4.88 (s, 2 H), 5.59 (s, 2 H), 7.74 (s, 2 H), 7.86 (s, 1 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 22.2, 26.3, 27.7, 30.4, 35.3, 39.0, 49.8, 52.6, 53.3, 126.4, 130.5, 134.3, 136.4, 161.3, 162.0, 162.5, 162.9, 168.7, 169.4, 172.4, 172.9, 173.2 ppm. IR (KBr): $\tilde{\nu}$ = 3435 (br), 3272 (br), 3077 (br), 2954 (br), 1739, 1677, 1547, 1437, 1202, 1133, 1004 cm^{-1}. HRMS: calcd. for $C_{42}H_{67}N_{12}O_{13}$ 947.4951; found 947.4951.

Preparation of 22: The propargyl derivative **17** (0.084 g, 0.1 mmol) was dissolved in dry CH_3CN (30 mL) and N_2 was bubbled through the liquid for 30 min and after that DIEA (0.05 mL, 0.3 mmol) was added followed by the azide **13b** (0.102 g, 0.1 mmol) and Cu^I (0.008 g, 0.042 mmol). N_2 bubbling was continued for an additional 2–3 h and then the reaction mixture was stirred under N_2 for 24 h. The reaction mixture was evaporated and subjected to high vacuum. The solid thus obtained was washed several times with ethyl

acetate to remove unreacted starting materials. The ethyl acetate insoluble part was obtained in 0.169 g yield and was confirmed to be the product **22**. Yield 90%. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.95–1.70 (s + m, 54 H), 2.59–2.95 (m, 18 H), 3.45 (s, 12H merged with solvent residual peak), 3.51 (s, 12 H), 3.75–4.85 (br. m, 11 H), 5.63 (br. s, 2 H), 6.68 (br. m, 3 H), 6.84 (br. m, 1 H), 7.68 (br. m, 2 H), 7.92 (br. m, 2 H), 8.23 (br. m, 2 H), 8.39 (br. m, 5 H), 8.63 (br. m, 2 H) ppm. IR (KBr): $\tilde{\nu}$ = 3138, 1739, 1650, 1532, 1401, 1279, 1171 cm^{-1}. HRMS: calcd. for $C_{82}H_{126}N_{16}NaO_{33}$ 1885.8571; found 1885.8588.

Preparation of Dendrimer 23: DIEA (0.022 mL, 0.13 mmol), **13c** (0.115 g, 0.12 mmol) and Cu^{I} (0.003 g, 0.015 mmol) were added to an ice-cooled solution of **17** (0.100 g, 0.12 mmol) in dry acetonitrile (25 mL) under nitrogen. The reaction mixture was stirred under N_2 for 16 h. The reaction mixture was evaporated and the residue was washed sequentially with EtOAc (3 × 15 mL) and chloroform (3 × 15 mL). The combined filtrates were evaporated, dissolved in EtOAc (60 mL) and washed sequentially with 0.2 N H_2SO_4, water, 5% aqueous $NaHCO_3$ solution, aqueous NH_4CI/NH_4OH (9:1) solution and finally with water. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to yield 0.180 g of dendrimer **23**. Yield 83%. $[a]_D$ = –20.4 (c = 0.25, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.81 (m, 12 H), 0.97 (m, 12 H), 1.25–1.55 (s + m, 48 H), 1.55–1.85 (m, 18 H), 2.40 (m, 6 H), 2.83 (m, 2 H), 3.09 (m, 2 H), 3.72 (s, 12 H), 4.15 (m, 2 H), 4.57 (m, 7 H), 5.20 (m, 6 H), 5.90 (m, 2 H), 7.15 (br. m, 3 H), 7.70 (br. m, 4 H), 8.10 (br. m, 4 H), 8.85 (br. d, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.64, 21.75, 22.53, 22.72, 22.80, 24.73, 24.88, 28.34, 28.41, 28.45, 29.36, 29.48, 29.56, 29.65, 30.65, 38.65, 39.78, 40.05, 40.23, 40.76, 49.42, 50.78, 51.11, 51.81, 52.21, 52.34, 54.24, 78.83, 79.67, 122.89, 126.16, 129.65, 133.79, 135.73, 145.00, 156.23, 165.23, 170.44, 172.13, 172.69, 173.57, 175.09 ppm. IR (KBr): $\tilde{\nu}$ = 3314, 3075, 2959, 2870, 1741, 1657, 1533, 1446, 1368, 1248, 1169 cm^{-1}. HRMS: calcd. for $C_{86}H_{142}N_{16}NaO_{25}$ 1822.0230; found 1822.0225.

Preparation of Dendrimer 24: DIEA (0.061 mL, 0.36 mmol), **13c** (0.115 g, 0.12 mmol) and Cu^{I} (0.003 g, 0.015 mmol) were added to an ice-cooled solution of **16** (0.052 g, 0.12 mmol) in dry acetonitrile (25 mL) under nitrogen. The reaction mixture was stirred under N_2 for 16 h. The reaction mixture was evaporated and the residue was washed with ethyl acetate and dichloromethane to remove all impurities. The dendrimer **24** was obtained in 0.120 g yield (72%). ^{1}H NMR (D_2O, 300 MHz): δ = 0.46 (br. m, 12 H), 0.77 (br. m, 12 H), 1.10–1.90 (m, 30 H), 2.85 (m, 4 H), 2.93 (m, 4 H), 3.08 (m, 2 H), 3.63 (s, 6 H), 3.69 (s, 6 H), 3.88 (m, 1 H), 3.96 (m, 1 H), 4.20 (m, 1 H), 4.35 (m, 6 H), 4.95 (s, 2 H), 5.69 (s, 2 H), 7.97 (m, 3 H), 8.20 (s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3382, 3078, 2957, 1737, 1665, 1443, 1378, 1197 cm^{-1}. HRMS: calcd. for $C_{66}H_{110}N_{16}NaO_{17}$ 1421.8133; found 1421.8136.

Synthesis of All-Amide Dendrimers 30 and 31

Preparation of 29: The catalyst, 5% Pd/C (Degussa type, peptide/catalyst, 1:0.4, w/w), was added to an ice-cooled solution of **13a** (0.261 g, 0.515 mmol) in dry MeOH (10 mL) and H_2 was bubbled through the reaction mixture for 2 h. The completion of the reaction was monitored by TLC. The solution was filtered through a sintered funnel and evaporated to yield 0.247 g of **29**. Yield 100%. ^{1}H NMR (D_2O, 300 MHz): δ = 2.90 (m, 4 H), 3.63 (s, 6 H), 3.70 (s, 6 H), 4.23 (s, 2 H), 4.96 (t, J = 6.0 Hz, 2 H), 7.93 (s, 2 H), 8.06 (s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3434 (br), 2956, 1735, 1650, 1542, 1445, 1367, 1286, 1225 cm^{-1}. HRMS: calcd. for $C_{21}H_{28}N_3O_{10}$ 482.1775; found 482.1775.

Preparation of 30: Dry NEt_3 (1.1 mL, 8 mmol) was added to an ice-cooled solution of Asp.diOMe.HCl (**28**; 0.710 g, 3.6 mmol) in dry CH_2Cl_2 (20 mL) and the mixture was stirred for 20 min at 0 °C. The acid chloride **25** (0.265 g, 1 mmol) dissolved in 15 mL of dry $CH_2Cl_2$was added dropwise over a period of 30 min. The reaction mixture was left to stir for 24 h. The reaction mixture was mixed with CH_2Cl_2 (50 mL) and washed with aqueous 2 N H_2SO_4 followed by aqueous $NaHCO_3$ solution and water. The organic layer was dried with anhydrous Na_2SO_4 and evaporated to give 0.350 g of **30**. Yield 55%; m.p. 205–206 °C. $[a]_D$ = +59.25 (c = 0.400, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.09 (m, 6 H), 3.74 (s, 9 H), 3.82 (s, 9 H), 5.13 (m, 3 H), 7.68 (d, J = 7.8 Hz, 3 H), 8.26 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 35.8, 49.4, 52.1, 52.9, 128.9, 134.5, 165.4, 171.3 ppm. IR (KBr): $\tilde{\nu}$ = 3249, 3065, 2958, 2854, 1746, 1645, 1555, 1440, 1364, 1310, 1227, 1169 cm^{-1}. HRMS: calcd. for $C_{27}H_{33}N_3NaO_{15}$ 662.1809; found 662.1810.

Preparation of 31: Dry NEt_3 (0.2 mL, 1.36 mmol) was added to an ice-cooled solution of **29** (0.246 g, 0.51 mmol) in dry CH_2Cl_2 (50 mL) and the mixture was stirred for 20 min. Compound **25** (0.045 g, 0.17 mmol) dissolved in dry CH_2Cl_2 (20 mL) was added dropwise to this solution over a period of 20 min. The reaction mixture was left to stir for 24 h. The reaction mixture was mixed with distilled CH_2Cl_2 (20 mL) and treated with aqueous 2 N H_2SO_4 followed by aqueous $NaHCO_3$ solution and water. The organic extract was dried with anhydrous Na_2SO_4 and evaporated to provide 0.225 g of **31**. Yield 83%. $[a]_D$ = –10.833 (c = 0.120, MeOH). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 2.79–3.05 (m, 12 H), 3.61 (s, 18 H), 3.64 (s, 18 H), 4.59 (br. s, 6 H), 4.85 (m, 6 H), 7.99 (s, 6 H), 8.22 (s, 3 H), 8.58 (s, 3 H), 9.15 (d, J = 7.2 Hz, 6 H), 9.46 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 35.3, 42.8, 49.4, 51.8, 52.3, 125.2, 129.1, 129.7, 133.9, 134.7, 140.1, 165.5, 165.8, 170.6, 171.2 ppm. IR (KBr): $\tilde{\nu}$ = 3421 (br), 2958, 1738, 1657, 1540, 1439, 1270, 1222 cm^{-1}. HRMS: calcd. for $C_{72}H_{81}N_9NaO_{33}$ 1622.4834; found 1622.4834.

Supporting Information (see also the footnote on the first page of this article): The ^{1}H and ^{13}C NMR and mass spectra of all new compounds. The HPLC chromatograms of compounds **18**, **20** and **30**.

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