Synthesis of NO–NSAID dendritic prodrugs *via* Passerini reaction: new approach to the design of dendrimer-drug conjugates

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We report the synthesis of a novel class of dendritic prodrugs *via* Passerini reaction in one pot. Such dendrimers feature a simultaneous attachment of a conventional non-steroidal anti-inflammatory drug (NSAID) (such as ibuprofen and aspirin) and a nitric oxide (NO)-releasing moiety (such as an organic nitrate) onto their surface, and are therefore regarded as new drug delivery systems for NO-releasing NSAIDs (NO–NSAIDs).

Keywords: Passerini reaction, dendritic prodrugs, dendrimers, non-steroidal anti-inflammatory drugs, NO-releasing NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used groups of drugs in the world, primarily used for the treatment of pain, fever and inflammation. However, chronic ingestion of NSAIDs may cause a wide variety of adverse events, including gastrointestinal (GI) side effects (such as dyspepsia, GI bleeding, obstruction and even perforation), renal side effects, and some additional side effects such as hypersensitivity reactions and distinct salicylate intoxication,[1] thus largely limiting their use.

The potential toxicity of NSAIDs and their side effects have prompted considerable effort to search for safer alternatives with similar pharmacological properties. It was reported that patients receiving high doses of multiple NSAIDs, or NSIADs concomitant with a corticosteroid suffer an increased risk of GI complications,[2] suggesting that these therapeutic strategies may fail the treatment due to GI side effects. A fascinating strategy has been generated from the discovery of two cyclooxygenase (COX) enzyme systems controlling the production of prostanoids, *i.e.* COX-1 and COX-2. The latter is believed to regulate the production of prostaglandins involved in inflammation, pain and fever. At the beginning of this century, two new highly selective COX-2 inhibitors, known as coxibs (celecoxib and rofecoxib), emerged on the market and are claimed to have low GI side effects. However, an alarming turn of events occurred in late 2004 when rofecoxib was withdrawn from the market worldwide due to the serious cardiovascular events. Subsequently, other coxibs were shown to have the same adverse reaction, although to various degrees.[3] Thus, there remains a compelling need for developing new NSAIDs with improved safety. Considering that nitric oxide (NO) can exert some prostaglandin functions for GI tract defence,[4–6] researchers have developed a promising strategy to reduce these side effects by coupling an NO-donating moiety to a conventional NSAID molecule. A class of new chemical entities, namely, the NO-releasing NSAIDs (NO–NSAIDs) is formed, which claims the potential to improve cardiovascular safety and at the same time spare the GI tract. Del Soldato and coworkers synthesised the first NO–NSAIDs,[7] and many advances have been made in the last decade.[8–13]

Parallel to the preparation of NO–NSAIDs, a number of macromolecular drug delivery systems have been developed in order to enhance the bioavailability of the NSAIDs and reduce or eliminate their side effects.[14,15] Dendrimers represent a relatively novel class of macromolecules with salient features such as monodispersity, well-defined globular shape, and high density of peripheral functional groups. Their unique structural properties make dendrimers suitable candidates for a wide range of applications, especially as nano-devices for drug delivery.[16–20] As for NSAIDs, dendrimers have proved to be efficient carriers when compared to classical linear polymers.[21] Furthermore, dendrimers have been utilised as the scaffold for NO release.[22,23] Mutlticomponent reactions have been known for over 150 years, and in these reactions, more than two reactants combine in a sequential manner to give highly selective products that retain the majority of the atoms of the starting material. Jee and coworkers reported on the convergent synthesis of a diverse class of dendimers *via* Passerini reaction,[24] and a recent patent revealed the manufacture of peptidic, peptoidic, and chimeric peptoidic–peptidic dendrimers by Ugi and (or) Passerini multicomponent reactions starting with a multifunctional core.[25] We now describe a new method for the synthesis of a novel class of dendrimers (NO-NSAID dendrimers), onto the surface of which an NSAID molecule (*e.g.*, aspirin and ibuprofen), and NO-donating moieties are attached simultaneously. This new methodology features an efficient and straightforward one-pot Passerin reaction, a three-component reaction, involving a carboxylic acid, a carbonyl compound, and an isocyanide.

In this study, L-Glutamic acid **1** was firstly reacted with benzyl alcohol to give compound **2**, which was then coupled with suberic acid to afford compound **3**. Subjected to hydrogenolysis, **3** was converted to the tetracarboxy core **4**, to which **2** (4 equiv.) was coupled again to provide compound **5**, whose benzyl protecting groups were later removed by hydrogenolysis to yield the desired octacarboxy dendrimer **6** in an overall yield of 54% (Scheme 1). This procedure is similar to that reported by Mitchell *et al*.[26,27]

The second components for Passerini reaction are isocyanides. First of all, ethylene glycol **7** was treated with concentrated HNO_3, AcOH, and Ac_2O to afford the mononitrate **8**. At the same time, starting from glycine **9**, through benzylation (to yield compound **10**), formylation (to yield compound **11**), hydrogenolysis (to yield compound **12**), esterification (to yield compound **13**), and finally dehydration, isocyanide **14** was obtained (Scheme 2). The third components in Passerini reaction, namely, aldehydes **17** and **20** (derived from ibuprofen and aspirin, respectively), were obtained *via* two oxidation reactions described in Scheme 3. Ibuprofen was treated with thionyl chloride to give compound **15**, which was then reacted with ethylene glycol to afford compound **16**. This intermediate was readily converted to aldehyde **17** by using *o*-iodoxybenzoic acid (IBX) as the oxidising agent. On the contrary, parallel oxidation reaction of the intermediate (synthesised from aspirin and ethylene glycol following the protocol employed to the preparation of compound **16**, but not shown in Scheme 3) with IBX did not provide aldehyde **20**, but gave a complicated reaction mixture where the main product was difficult to be identified, according to the TLC results. However, the reaction of asprin **18** with 3-bromopropene gave rise to the production of compound **19**, upon ozonolysis of which aldehyde **20** was successfully produced after reductive workup with triphenylphosphine.

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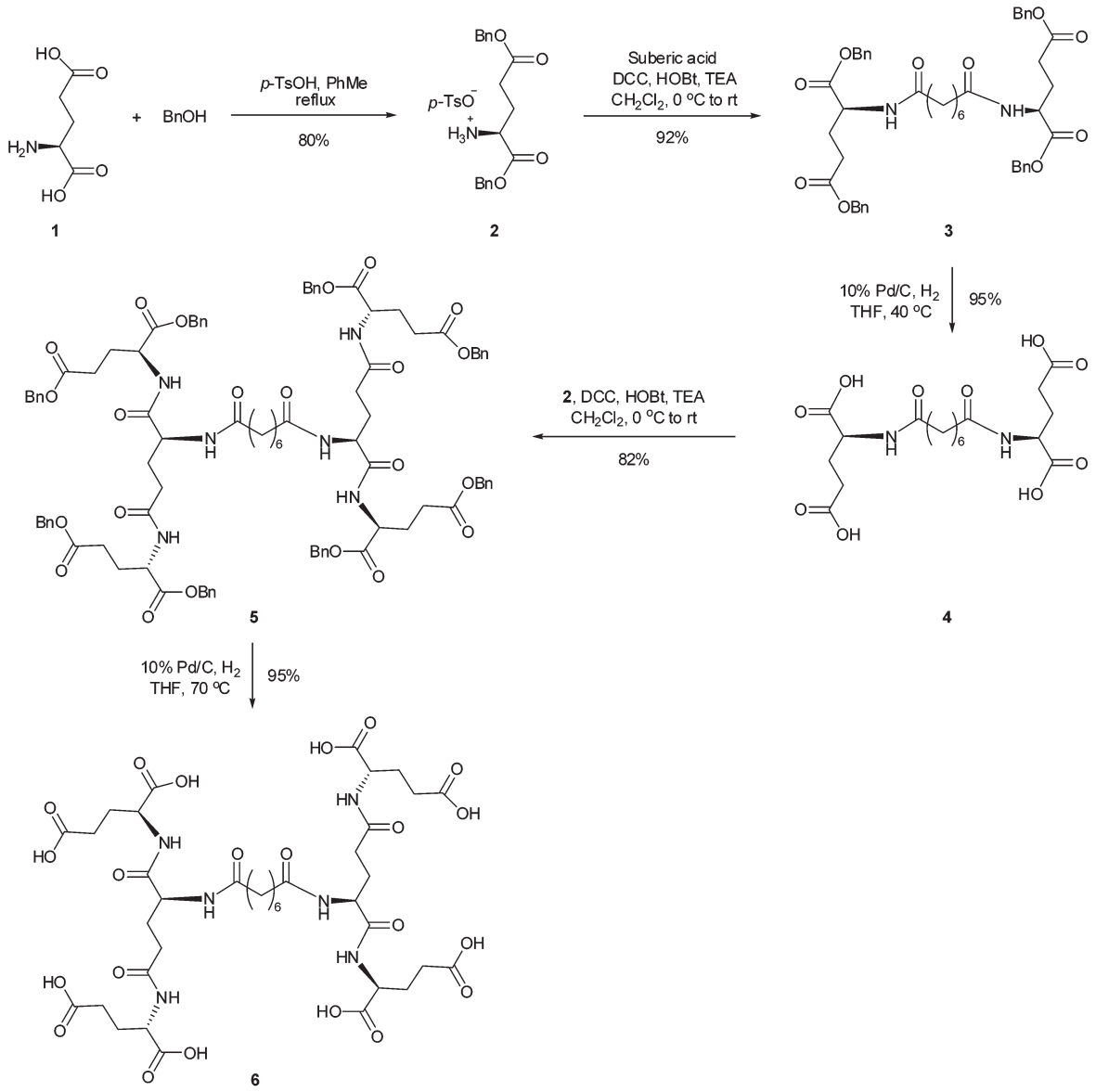
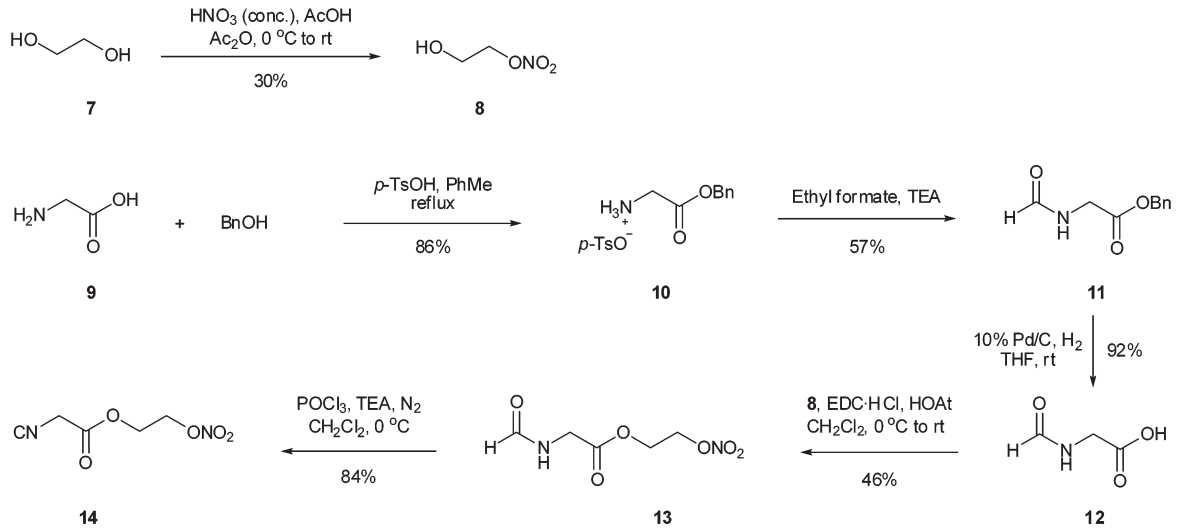
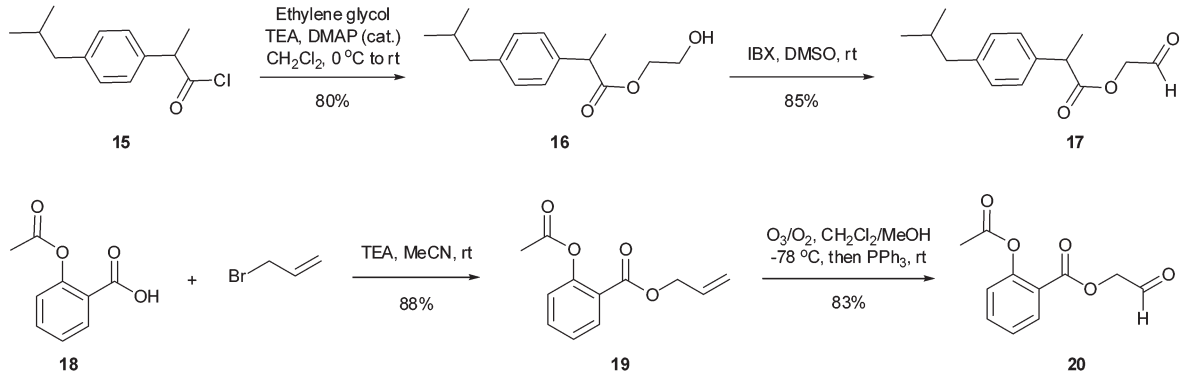


Scheme 1 Synthesis of the octacarboxy dendrimer **6**.



Scheme 2 Synthesis of isocyanide **14**.



Scheme 3 Synthesis of aldehydes **17** and **20**.

The one-pot reaction of the three components of **6**, **14** and **17** (**20**) which produces the dendritic prodrug **21** is described in Scheme 4. As expected, two dendritic prodrugs were obtained *via* Passerini reaction, albeit in low to medium yields. Our investigation also shows that high concentration of the substrates and nonpolar aprotic solvents (such as THF) are favourable for the Passerini reaction, which is well-established in the literature.[28] Besides the simplicity of the synthetic procedure, another attractive feature of this strategy is the room it leaves for convenient variation of the dendrimer scaffolds as well as the drug molecules attached at the periphery. This ability provides an efficient approach to construct a library of dendritic prodrugs. The structures of all newly synthesised compounds were characterised by ^{1}H and ^{13}C NMR spectroscopy, and MALDI-FTICR-MS or LRMS. Additionally, the biological and pharmaceutical activities of these NO–NSAID dendritic prodrugs are under investigation.

In conclusion, an efficient and straightforward method for the synthesis of a versatile class of NO–NSAID dendrimers has been presented. This type of dendritic prodrug is promising in having therapeutic activities of NO and NSAIDs, and sustained-release behaviour as well. The methodology is not restricted to the Passerini reaction and the substrates mentioned in this study, but is readily applied to other multicomponent reactions (such as Ugi-type four-component reaction), dendrimers (such as PAMAM dendrimers), and drugs that can be administered synergistically. Due to its efficiency and diversity in nature, we believe this approach can be considered as one of the most valuable strategies towards the design of new controlled drug-delivery systems.

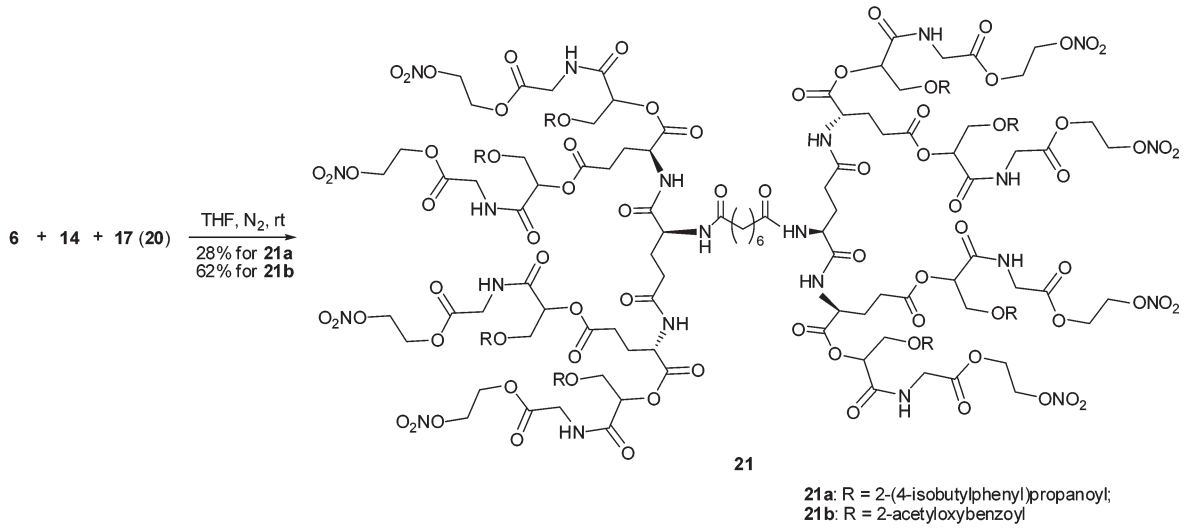
Experimental

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz Inova Varian spectrometer at 25 °C. Chemical shift values are given in ppm with the internal reference given by TMS set at 0.0 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; qui, quintuplet; m, multiplet; dd, doublet of doublets; and br, broad singlet. The coupling constants *J* are reported in Hz. Low-resolution mass spectra (LRMS) were obtained on an ion trap (Agilent 6310) spectrometer using electrospray ionisation (ESI) in positive or negative mode. High-resolution mass spectra (HRMS) were obtained on a Varian 7.0T FTMS in positive or negative mode. Melting points were determined with an X-4 micromelting point apparatus (Beijing, China) without corrections. IR spectra were recorded on a Nicolet IR200. TLC plates were visualised by exposure to UV light or stains. All reagents and solvents were purchased as reagent grade and used without further purification.

Synthesis of **6**

10% Pd/C (1.0 g) was added to a solution of **5** (5.0 g, 3.0 mmol) in THF (100 mL), and then the flask was flushed with dry nitrogen twice and charged with hydrogen (in a balloon, *ca* 3 atm), heated to 70 °C and stirred for 24 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the desired compound **6** as a white solid (2.7 g, yield 95%).

6: M.p. 66–69 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.23 (4H, br), 1.47 (4H, br), 1.69–1.77 (6H, br), 1.87 (2H, m), 1.95–1.99 (4H, br), 2.09–2.18 (8H, br), 2.23–2.29 (8H, br), 4.20 and 4.30 (6H, m), 7.93 (2H, dd, *J* = 20.0 Hz and 8.0 Hz), 8.13 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.8, 26.9, 27.0, 28.7, 29.1, 30.6, 30.7, 32.3, 35.8, 51.7, 51.8, 52.6, 172.3, 172.5, 173.0, 174.0, 174.3, 174.4. LRMS observed: $[M + Na]^+$ 971.2; calculated for $C_{38}H_{56}O_{22}N_6Na^+$: 971.3.



Scheme 4 Synthesis of the NO-NSAID dendritic prodrug **21**.

Synthesis of **13**

Ethylene glycol mononitrate **8** (2.27 g, 22 mmol), **12** (2.14 g, 20 mmol) and HOAt (2.86 g, 21 mmol) were added to CH_2Cl_2 (40 mL). Then the flask was placed in an ice-water bath, to which EDC•HCl (4.98 g, 26 mmol) was added in portions. After completing addition, the reaction mixture was stirred at 0 °C for 2 h, and then warmed to room temperature and stirred for another 22 h. The reaction mixture was washed with H_2O (40 mL), and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and the residue was finally purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20 to 40/60) to afford **13** as a yellowish oil (1.7 g, yield 46%).

13: LRMS observed: $[M + H]^+$ 192.9; calculated for $C_5H_8O_6N_2H^+$: 193.0.

Synthesis of **14**

Phosphoryl chloride (0.88 mL, 9.4 mmol) and **13** (1.62 g, 8.5 mmol) were added to CH_2Cl_2 (40 mL) at 0 °C, to which triethyl amine (3.9 mL, 28 mmol) was added dropwise under N_2 within 15 min. After completing the addition, the reaction mixture was stirred for another 2 h at the same temperature. Then saturated $NaHCO_3$ solution (40 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and finally purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to afford **14** as a yellowish-brown oil (1.24 g, yield 84%).

14: FT-IR (film, cm^{-1}): *v* 2970, 2905, 2168, 1766, 1652, 1424, 1376, 1288, 1197, 1051, 998, 904, 861, 705, 577; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.30 (2H, s), 4.53 (2H, t, *J* = 2.0 Hz), 4.72 (2H, t, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 43.6, 62.4, 70.1, 161.6, 164.2. LRMS observed: $[M + H]^+$ 175.1; calculated for $C_5H_7O_5N_2H^+$: 175.0.

Synthesis of **17**

16 (1.5 g, 6.0 mmol) was addedd to the solution of IBX (2.5 g, 9.0 mmol) in DMSO (10 mL), and the reaction mixture was stirred at room temperature for *ca* 16 h. Then H_2O (30 mL) and EtOAc (30 mL) were added, and the reaction mixture was stirred for 5 min, filtered. The filtrate was washed with saturated $NaHCO_3$ solution (3 × 10 mL) and saturated brine (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure, and finally purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5) to afford **17** as a colourless oil (1.3 g, yield 85%).

17: ^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (6H, d, *J* = 6.5 Hz), 1.56 (3H, d, *J* = 7.0 Hz), 1.85 (1H, m), 2.46 (2H, d, *J* = 7.5 Hz), 3.85 (1H, q, *J* = 7.5 Hz), 4.63 (2H, AB, *J* = 37.5 Hz and 17.5 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 9.54 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.5, 22.3, 30.1, 44.7, 45.0, 68.7, 127.097, 129.4, 137.0, 140.8, 174.2, 195.9. LRMS observed: $[M + H]^+$ 249.1; calculated for $C_{15}H_{20}O_3H^+$: 249.1.

Synthesis of **19**

Aspirin (8.0 g, 44.4 mmol), 3-bromopropene (4.2 mL, 48.8 mmol) and triethyl amine (6.8 mL, 48.8 mmol) were added to acetonitrile (45 mL) and stirred for 2 h at room temperature. Then the reaction mixture was concentrated under reduced pressure, and the residue was redissolved in EtOAc (80 mL), washed with a small amount of water, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and finally purified by column chromatography on silica gel (petroleum ether/EtOAc, 85/15) to afford **19** as a colourless oil (8.6 g, yield 88%).

19: ^1H NMR ($CDCl_3$, 500 MHz): δ 2.31 (3H, s), 4.75 (2H, d, *J* = 5.5 Hz), 5.27 (1H, dd, *J* = 10.5 Hz and 1.0 Hz), 5.98 (1H, m), 7.08 (1H, d, *J* = 8.0 Hz), 7.29 (1H, t, *J* = 8.0 Hz), 7.53 (1H, dt, *J* = 8.0 Hz and 1.5 Hz), 8.02 (1H, dd, *J* = 8.0 Hz and 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 66.0, 119.0, 123.5, 124.0, 126.3, 132.0, 132.1, 134.2, 150.9, 164.4, 169.9. LRMS observed: $[M + H]^+$ 221.2; calculated for $C_{12}H_{12}O_4H^+$: 221.1.

Synthesis of **20**

Compound **19** (5.0 g, 22.7 mmol) was dissolved in CH_2Cl_2/MeOH (4/1, v/v, 50 mL). After cooling to –78 °C, O_3/O_2 was passed through the solution and about 2 h later, the starting material disappeared, according to the TLC results. Upon completion, the flask was flushed with N_2 for 5 min, and PPh_3 (6.6 g, 25.0 mmol) was added. Then the reaction mixture was warmed to room temperature, stirred for approximate 24 h, concentrated under reduced pressure, and finally purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5 to 85/15) to afford **20** as a colourless oil (4.2 g, yield 83%).

20: ^1H NMR ($CDCl_3$, 500 MHz): δ 2.33 (3H, s), 4.83 (2H, s), 7.13 (1H, d, *J* = 8.0 Hz), 7.34 (1H, t, *J* = 8.0 Hz), 7.60 (1H, t, *J* = 8.0 Hz), 8.09 (1H, d, *J* = 8.0 Hz), 9.65 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.2, 69.2, 122.2, 124, 2, 126.4, 132.103, 134.8, 151.2, 164.0, 169.9, 195.9. LRMS observed: $[M + H]^+$ 223.0; calculated for $C_{11}H_{10}O_5H^+$: 223.1.

Synthesis of **21a**

Compound **6** (95 mg, 0.1 mmol) was dissolved in THF (3 mL), and the solution was then concentrated under reduced pressure until the volume decreased to approximate 1.5 mL, to which isocyanide **14** (209 mg, 1.2 mmol) and aldehyde **17** (298 mg, 1.2 mmol) were added. The reaction mixture was stirred at room temperature for 6 days under N_2, and immediately purified by silica gel chromatography (petroleum ether/EtOAc/MeOH, 30/30/1 to 30/70/1) to give the dendrimer **21a** as a white powder (121 mg, yield 28%).

21a: M.p. 55–57 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88 (48H, d, *J* = 6.5 Hz), 1.28 (4H, br), 1.46 (24H, br), 1.57 (4H, br), 1.82 (8H, m), 1.94 (4H, br), 2.06 (2H, br), 2.18–2.43 (38H, br), 3.71 (8H, br), 3.96 (16H, br), 4.22 (2H, br), 4.38 (24H, br), 4.53 (10H, br), 4.64 (18H, br), 5.41 (8H, br), 7.08 (16H, br), 7.16 (16H, br); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3, 18.4, 22.4, 25.2, 26.2, 28.6, 29.5, 29.7, 30.2, 31.9, 35.9, 40.8, 41.0, 44.8, 44.9, 52.1, 61.1, 61.4, 63.0, 69.7, 70.3, 72.0, 72.1, 72.2, 72.9, 73.0, 73.1, 127.2, 129.3, 137.2, 140.8, 166.8, 166.9, 167.0, 167.4, 167.5, 169.1, 169.2, 171.4, 174.3, 174.4, 174.5. MALDI-FTICR-MS observed: $[M+Na]^+$ 4348.6755; calculated for $C_{198}H_{264}O_{86}N_{22}\ Na^+$: 4348.6859.

Synthesis of **21b**

Compound **6** (95 mg, 0.1 mmol) was dissolved in THF (5 mL), and the solution was then concentrated under reduced pressure until the volume decreased to approximate 2 mL, to which isocyanide **14** (209 mg, 1.2 mmol) and aldehyde **20** (267 mg, 1.2 mmol) were added. The reaction mixture was stirred at room temperature for 6 days under N_2, and immediately purified by silica gel chromatography (petroleum ether/EtOAc/MeOH, 60/40/2) to afford the dendrimer **21b** as a white powder (255 mg, yield 62%).

21b: M.p. 68–71 °C; FT-IR (KBr, cm^{-1}): *v* 3369, 3079, 2957, 1759, 1683, 1637, 1537, 1373, 1283, 1195, 1082, 916, 856, 755, 704; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (4H, br), 1.48 (4H, br), 1.80 (4H, br), 2.09 (8H, br), 2.17 (4H, br), 2.30 (24H, br), 2.47 (12H, br), 4.01 (14H, br), 4.18–4.34 (20H, br), 4.60 (28H, br), 4.76 (8H, br), 5.46–5.50 (8H, br), 7.07 (8H, br), 7.29 (8H, br), 7.56 (8H, br), 8.01 (8H, br); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.9, 21.0, 22.7, 25.1, 25.2, 25.5, 28.4, 29.4, 29.6, 29.7, 29.9, 31.1, 31.9, 35.7, 35.8, 40.9, 52.1, 58.8, 61.0, 63.1, 70.3, 71.9, 72.7, 122.3, 123.9, 126.2, 126.3, 132.0, 134.4, 134.5, 134.6, 150.8, 150.9, 163.6, 163.7, 163.8, 167.1, 167.5, 169.2, 169.3, 169.9, 170.0, 170.1, 171.4, 171.5. MALDI-FTICR-MS observed: $[M+Na]^+$ 4139.9705; calculated for $C_{166}H_{184}O_{102}N_{22}Na^+$: 4139.9785.

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