The discovery of a facile access to the synthesis of NSAID dendritic prodrugs

Zuyin Du, Yanhui Lu, Xuedong Dai, Daisy Zhang-Negrerie and Qingzhi Gao*

Tianjin Key Laboratory for Modern Drug Delivery and High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. China

An efficient and straightforward method for the preparation of dendritic prodrugs is reported. Based on this new approach, a class of biodegradable dendrimers has been synthesised from L-tartaric acid and one of the nonsteroidal anti-inflammatory drugs, namely, aspirin or ibuprofen.

Keywords: dendritic prodrugs, dendrimers, L-tartaric acid, nonsteroidal anti-inflammatory drugs, drug delivery

Controlled release systems can improve the effectiveness of drug therapy by sustained release of drugs over a desired period of time or specific release aimed at a particular target.[1,2] Indeed, by controlling the time and location of delivery, side effects can be minimised and drug efficacy can be significantly improved which leads to lower dosages for patients. Polymers, as well as macromolecules, have played an important role in the development of drug delivery systems possessing controlled release ability, due to the advantages they offer in comparison to conventional methods including increased water solubility, improved pharmacokinetics, reduced antigenic activity, and so on.[3] Although many polymeric materials and polymer-drug conjugates have revealed promising results as drug carriers in *in vitro* studies, a large number failed the *in vivo* testings as a consequence of either lack of improved therapeutic index or polymer-related toxicity.[4] Furthermore, low drug-carrying capacity of the polymer moledules is a crucial limiting factor in the design of polymer-drug conjugates.

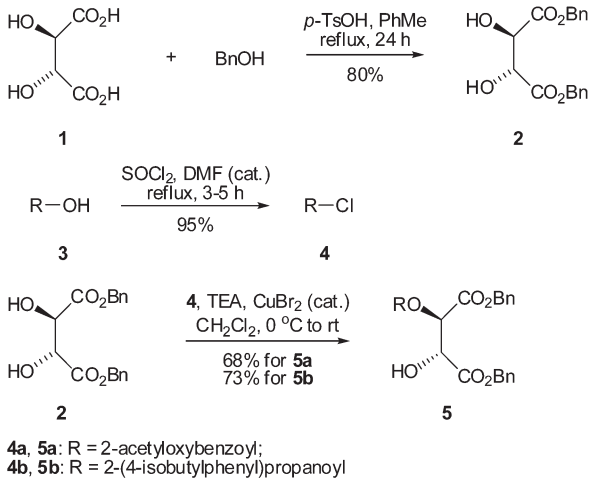
Dendrimers are highly branched, spherical, monodisperse macromolecules that have sparked significant interest in the last two decades because of their unique architectures and properties.[5–7] Such distinctive structures along with terminal surface functionalities and well-defined interior nano-voids make these macromolecules more suitable as drug carriers when compared with traditional linear polymers.[8–13] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to control pain, fever and inflammation. Based on the unique features of dendrimers, many dendrimer-NSAID conjugates have been prepared, proven to be more effective but have fewer side effects.[14–19] There are two methodologies for the preparation of dendrimer-based prodrugs. The first involves direct conjugation of drug molecules to the surface of dendrimers, while the second constructs dendrimers with drug molecules as branching units. Chai and coworkers[20–23] reported on the synthesis of L-DOPA dendrimers and salicylate dendritic prodrugs using L-DOPA and salicylic acid as branching units, respectively. Both of these dendritic prodrugs have the drug entities chemically incorporated into the dendrimer backbone, but not just attached as pendants on the surface or physically encapsulated inside the cavities. We report here the synthesis of a similar type of biodegradable dendritic prodrug which is a promising precursor to a broad range of drugs, starting from L-tartaric acid and NSAIDs such as aspirin and ibuprofen.

L-Tartaric acid is multifunctional has low toxicity, is readily available, and has been utilised as a building block to synthesise chiral dendrimers, for which chiroptical properties have been investigated.[24–29] However, there has been no report on dendritic prodrugs synthesised from L-tartaric acid.

In this study, L-tartaric acid **1** was first reacted with benzyl alcohol to give L-dibenzyl tartrate **2**. Meanwhile, NSAID **3**, *i.e.*, asprin or ibuprofen, was treated with thionyl chloride to afford acid chloride **4**. Next, **2** and **4** were condensed to yield the building block **5** (Scheme 1). Starting from L-glutamic acid **6**, through benzylation (to give compund **7**), acylation with sebacic acid (to give compund **8**), and hydrogenolysis, the tetracarboxyl core **9** was prepared (Scheme 2). The yields of these conversions were good to excellent. Note that a diverse class of building blocks (branching units), can be prepared by just changing the drug molecules coupled to L-dibenzyl tartrate **2**. Therefore, it is convenient to construct a library of dendritic prodrugs in which not only can the same drug molecules be incorporated into the dendrimer scaffold, but so also can different drug molecules as long as these drugs can be administered synergistically.

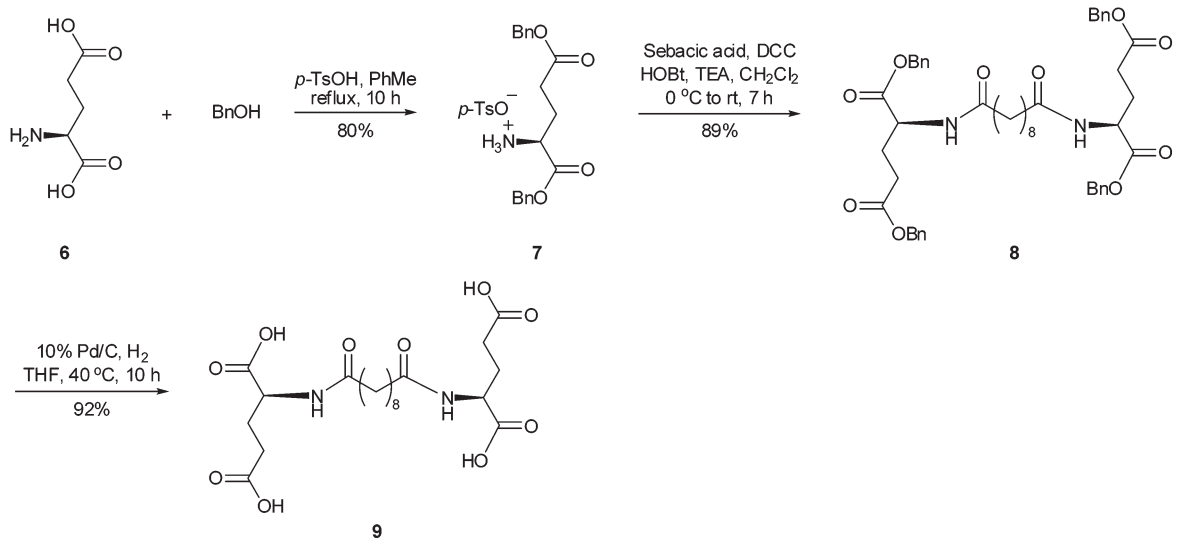
In the subsequent synthetic steps, compound **5** was coupled to the core **9** to afford compound **10**, and then all benzyl protecting groups were removed by hydrogenolysis to provide compound **11**, the first generation dendrimer, to which eight units of compound **5** were coupled by esterification to yield compound **12**. Again, hydrogenolysis afforded the second generation dendritic prodrug **13** (Scheme 3). The yields for all the esterification steps were medium to good, while all yields for hydrogenolysis were excellent. The structures of the desired dendrimers were confirmed by ^{1}H and ^{13}C NMR, and MALDI-FTICR-MS. The degradation behaviour and pharmacokinetics of these dendritic prodrugs are under investigation.

In summary, we have presented a new approach to the synthesis of dendritic prodrugs. With this approach, a broad spectrum of drugs, for example, carboxylic NSAIDs and organic nitrates, can be incorporated into a dendrimer structure layer by layer. This novel design of dendritic prodrugs may well provide a versatile platform for creating various controlled drug delivery systems.



Scheme 1 Synthesis of the building block **5**.

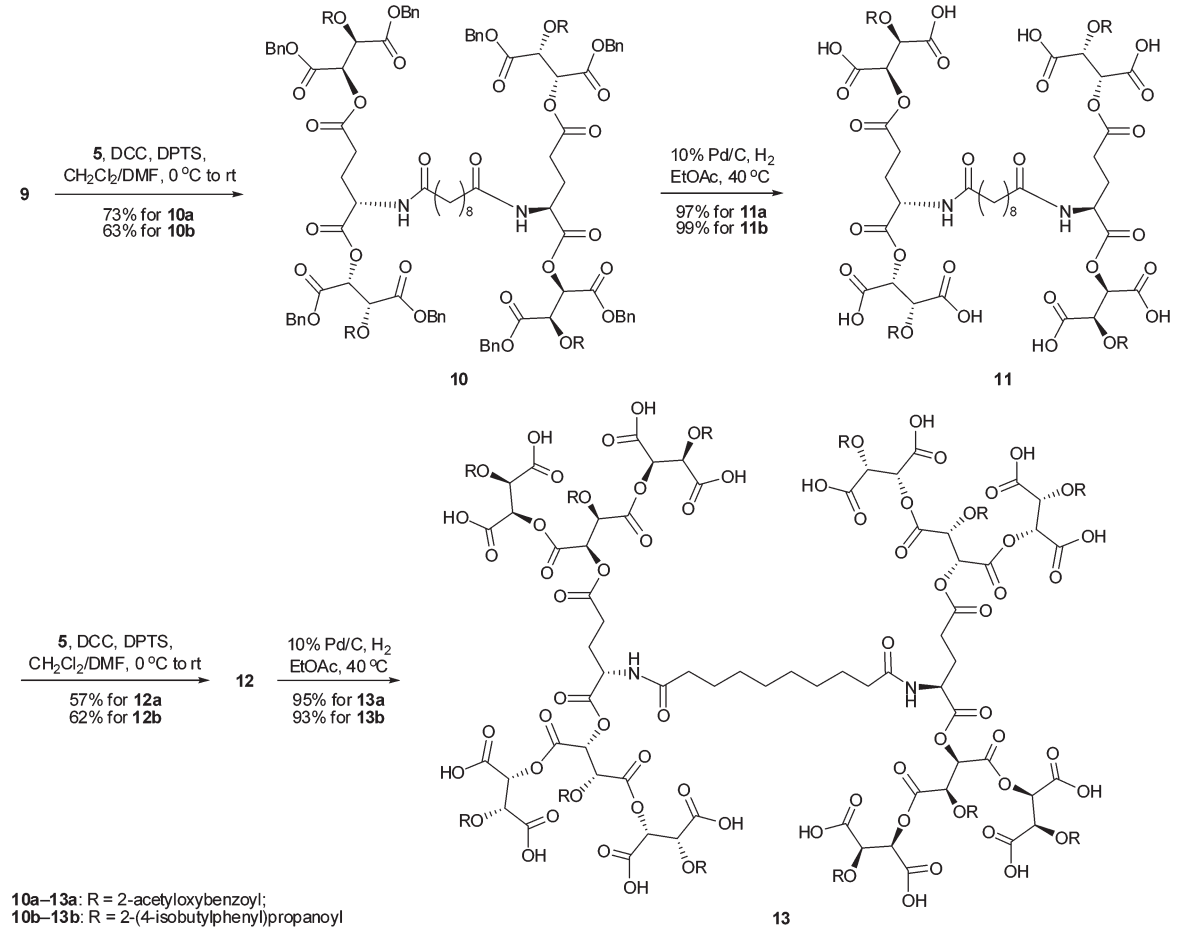
* Correspondent. E-mail: qingzhi@gmail.com



Scheme 2 Synthesis of the core **9**.

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.



Scheme 3 Synthesis of the dendritic prodrug **13**.

Synthesis of **5a**; *general procedure*
$CuBr_2$ (1.1 g, 5 mmol) and triethyl amine (13.9 mL, 100 mmol) were added to a solution of L-dibenzyl tartrate **2** (33.0 g, 100 mmol) in CH_2Cl_2 (200 mL). The flask was then placed in an ice-water bath, followed by adding dropwise the solution of **4a** (19.9 g, 100 mmol) in CH_2Cl_2 (120 mL) within 2 h. After completing the addition, the ice-water bath was removed and the reaction mixture was stirred at room temperature for another 4 h. The reaction mixture was washed with 1N HCl (3 × 100 mL), saturated brine (2 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL) and saturated brine (2 × 100 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and finally purified by column chromatography on silica gel using petroleum ether/CH_2Cl_2 as eluent to afford **5a** as a colourless viscous oil (33.4 g, yield 68%).

5a: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.32 (3H, s), 3.33 (1H, br), 4.92 (1H, d, *J* = 2.5 Hz), 5.20 (2H, m), 5.27 (2H, m), 5.76 (1H, d, *J* = 2.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 7.25 (6H, m), 7.36 (5H, br), 7.59 (1H, dt, *J* = 8.0 Hz and 1.5 Hz), 7.90 (1H, dd, *J* = 8.0 Hz and 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 68.0, 68.7, 70.9, 73.5, 122.0, 124.2, 126.3, 128.4, 128.7, 128.8, 128.9, 129.0, 132.2, 134.7, 135.2, 151.3, 163.1, 166.5, 169.9, 170.8. LRMS observed: $[M + H]^+$ 493.2; Calcd for $C_{27}H_{24}O_9H^+$: 493.1.

Synthesis of **5b**
Following the similar procedure for **5a**, **5b** was prepared and purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent.

5b: Colourless oil; yield 73%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.86 (6H, m), 1.44 (3H, dd, *J* = 13.0 Hz and 8.0 Hz), 1.79 (1H, m), 2.39 (2H, m), 3.15 (1H, br), 3.64 and 3.78 (1H, m), 4.51 and 4.92 (1H, m), 4.75 (1H, d, *J* = 23.0 Hz), 4.97 and 5.09 (1H, m), 5.15–5.27 (2H, m), 5.47 (1H, dd, *J* = 18.5 Hz and 2.5 Hz), 7.05 (2H, t, *J* = 7.5 Hz), 7.08–7.10 (1H, m), 7.16 (2H, q, *J* = 8.0 Hz), 7.21–7.23 (1H, m), 7.26–7.30 (3H, m), 7.31–7.35 (5H, m). LRMS observed: $[M + H]^+$ 519.2; Calcd for $C_{31}H_{34}O_7H^+$: 519.2.

Synthesis of **8**
Sebacic acid (3.3 g, 16.3 mmol), **7** (11.0 g, 33.6 mmol), triethyl amine (5.1 mL, 37.0 mmol) and HOBt (5.0 g, 37.0 mmol) were added to CH_2Cl_2 (50 mL). Then the flask was placed in an ice-water bath, and DCC (9.0 g, 43.6 mmol) was dissolved in CH_2Cl_2 (50 mL) and added dropwise to the aforementioned solution within 50 min. After completing the addition, the reaction mixture was stirred at the same temperature for another 2 h, and then the ice-water bath was removed and the reaction temperature was warmed to room temperature, maintained for about 5 h. Subsequently, the reaction mixture was concentrated under reduced pressure to remove most of the solvent, and the residue was redissolved in EtOAc (100 mL), filtered to remove the byproduct DCU and washed with a small amount of cold EtOAc. The filtrate was then washed with saturated citric acid solution (4 × 30 mL), saturated brine (2 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL) and saturated brine (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the residue obtained was further purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/25 to 50/50) to give **8** as a white solid (11.9 g, yield 89%).

8: M.p. 81–82 °C. LRMS observed: $[M + H]^+$ 821.4; Calcd for $C_{48}H_{56}O_{10}N_2H^+$: 821.4.

Synthesis of **9**
10% Pd/C (1.0 g) was added to a solution of **8** (10.5 g, 12.8 mmol) in THF (120 mL). Then the flask was flushed with dry nitrogen twice and charged with hydrogen (in a balloon, *ca* 3 atm). The reaction mixture was stirred at 40 °C for 10 h and filtered. The filtrate was concentrated under reduced pressure to provide the desired compound **9** as a colourless and crystalline powder (5.4 g, yield 92%).

9: M.p. 124–125 °C. LRMS observed: $[M + H]^+$ 461.2; Calcd for $C_{20}H_{32}O_{10}N_2H^+$: 461.2.

Synthesis of **10a**; *general procedure*
One portion of **9** (763 mg, 1.66 mmol) was dissolved in DMF (3.5 mL), to which CH_2Cl_2 (35 mL), DPTS (489 mg, 1.66 mmol) and **5a** (4903 mg, 9.96 mmol) were added consecutively. Subsequently, the reaction mixture was cooled to 0 °C in an ice-water bath and DCC (2055 mg, 9.96 mmol) was added. Then the ice-water bath was removed to allow the reaction temperature to be warmed to room temperature. After being stirred for 16 h at room temperature the reaction mixture was concentrated *in vacuo* to remove most of the solvents, and the residue was redissolved in EtOAc (50 mL), filtered to remove the byproduct DCU and washed with a small amount of cold EtOAc. The filtrate was then washed with saturated citric acid solution (4 × 30 mL), saturated brine (2 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL) and saturated brine (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the residue obtained was further purified by column chromatography on silica gel (petroleum ether/EtOAc/MeOH, 75/25/5) to afford **10a** as a white solid (2855 mg, yield 73%).

10a: M.p. 58–62 °C; ^{1}H NMR ($CDCl_3$, 500 M): δ 1.21 (8H, t, *J* = 8 Hz), 1.55 (4H, br), 1.92 (4H, m), 2.12 (6H, br), 2.16–2.27 (4H, m), 2.29 (12H, s), 2.34–2.44 (2H, br), 4.54 (1H, br), 4.66 (1H, m), 5.07–5.17 (12H, m), 5.23–5.28 (4H, m), 5.83–5.85 (4H, m), 5.92–5.95 (4H, m), 6.04 (1H, d, *J* = 7.5 Hz), 6.19 (1H, d, *J* = 7.5 Hz), 7.09 (4H, m), 7.18–7.22 (24H, m), 7.29–7.31 (20H, m), 7.52–7.57 (4H, m), 7.88 (4H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 M): δ 21.0, 25.2, 25.3, 26.4, 26.5, 29.2, 29.3, 29.5, 29.7, 36.0, 36.1, 51.2, 51.6, 67.9, 68.0, 68.1, 68.2, 70.9, 71.0, 71.4, 71.6, 121.3, 121.4, 123.9, 126.1, 126.2, 126.3, 128.3, 128.4, 128.5, 128.6, 128.7, 132.0, 132.1, 132.2, 134.3, 134.4, 134.5, 134.6, 134.7, 134.8, 151.1, 151.2, 162.4, 162.5, 162.6, 165.0, 165.1, 165.3, 165.4, 165.6, 169.4, 170.3, 170.7, 171.3, 171.6, 173.1, 173.2. MALDI-FTICR-MS observed: $[M + Na]^+$ 2379.7181; Calcd for $C_{128}H_{120}O_{42}N_2Na^+$: 2379.7213.

Synthesis of **10b**
Following the similar procedure for **10a**, **10b** was prepared and purified by column chromatography on silica gel (petroleum ether/EtOAc, 85/15).

10b: Colourless oil; yield 63%; ^{1}H NMR ($CDCl_3$, 500 M): δ 0.84 (24H, m), 1.29 (8H, br), 1.43 (12H, m), 1.59 (4H, br), 1.77 (4H, m), 1.87 (4H, m), 2.15 (6H, br), 2.38 (10H, m), 3.63–3.80 (4H, m), 4.42–4.53 (2H, m), 4.63 (2H, m), 4.84 (2H, m), 4.94 (2H, m), 5.03–5.30 (10H, m), 5.68–5.79 (7H, m), 6.07 (1H, m), 7.04 (12H, br), 7.15–7.21 (16H, br), 7.27–7.32 (28H, br); ^{13}C NMR ($CDCl_3$, 125 M): δ 18.1, 18.2, 18.3, 22.3, 22.4, 25.3, 25.4, 26.5, 29.3, 29.4, 29.6, 29.7, 30.1, 36.0, 36.1, 44.2, 44.3, 44.6, 44.9, 45.0, 51.5, 51.6, 67.7, 67.8, 67.9, 68.0, 68.1, 70.6, 70.7, 70.8, 70.9, 71.3, 71.4, 127.3, 127.4, 128.1, 128.2, 128.4, 128.6, 128.7, 129.2, 129.4, 134.3, 134.4, 134.5, 134.6, 134.7, 134.8, 136.3, 136.4, 136.8, 140.7, 140.8, 164.5, 164.9, 165.1, 165.2, 165.3, 165.4, 165.5, 165.6, 170.2, 170.7, 171.2, 171.3, 171.4, 173.0, 173.1, 173.2, 173.3, 173.4. MALDI-FTICR-MS observed: $[M + Na]^+$ 2484.0692; Calcd for $C_{144}H_{160}O_{34}N_2Na^+$: 2484.0750.

Synthesis of **11a**; *general procedure*
To a solution of **10a** (949 mg, 0.4 mmol) in EtOAc (40 mL) was added 10% Pd/C (190 mg). Then the flask was flushed with dry nitrogen twice and charged with hydrogen (in a balloon, *ca* 3 atm). The reaction mixture was stirred at 40 °C for 15 h and filtered. The filtrate was concentrated under reduced pressure to provide the desired compound **11a** as a white solid (633 mg, yield 97%).

11a: M.p. 129–132 °C. MALDI-FTICR-MS observed: $[M + Na]^+$ 1659.3403; Calcd for $C_{72}H_{72}O_{42}N_2Na^+$: 1659.3457.

Synthesis of **11b**
Following the similar procedure for **11a**, **11b** was prepared.

11b: White solid; yield 99%; m.p. 99–103 °C. MALDI-FTICR-MS observed: $[M + Na]^+$ 1763.6918; Calcd for $C_{88}H_{112}O_{34}N_2Na^+$: 1763.6994.

Synthesis of **12a**; *general procedure*
One portion of **11a** (491 mg, 0.3 mmol) was dissolved in DMF (5 mL), to which CH_2Cl_2 (30 mL), DPTS (883 mg, 3 mmol) and **5a** (1772 mg, 3.6 mmol) were added consecutively. Subsequently, the reaction mixture was cooled to 0 °C in an ice-water bath and DCC (743 mg, 3.6 mmol) was added. Then the ice-water bath was removed to allow the reaction temperature to be warmed to room temperature. After being stirred for 20 h at room temperature the reaction mixture was concentrated *in vacuo* to remove most of the solvents, and the residue was redissolved in EtOAc (100 mL), filtered to remove the byproduct DCU and washed with a small amount of cold EtOAc. The filtrate was then washed with saturated citric acid solution (4 × 30 mL), saturated brine (2 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL) and saturated brine (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the residue obtained

was further purified by column chromatography on silica gel (petroleum ether/EtOAc/MeOH, 70/30/5) to afford **12a** as a white solid (932 mg, yield 57%).

12a: M.p. 69–73 °C; FT-IR (KBr, cm^{-1}): ν 3402, 3036, 2946, 1768, 1682, 1607, 1487, 1454, 1370, 1195, 1131, 1074, 915, 752, 698; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.97 (8H, br), 1.40 (4H, br), 1.97 (7H, br), 2.14 (3H, br), 2.17 (7H, br), 2.26–2.35 (27H, br), 2.44 (1H, br), 2.66 (3H, br), 4.80–4.98 (12H, m), 5.03–5.29 (22H, m), 5.89–6.20 (24H, m), 7.02–7.13 (53H, m), 7.17–7.28 (52H, m), 7.45 (12H, m), 7.78 (7H, m), 8.05 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.8, 20.9, 25.3, 27.1, 29.2, 29.3, 29.4, 30.0, 36.1, 36.2, 50.7, 51.4, 68.1, 68.2, 68.3, 68.4, 68.6, 70.1, 70.2, 70.3, 70.4, 70.6, 70.7, 70.9, 71.7, 71.8, 71.9, 121.0, 121.1, 121.2, 121.5, 121.6, 121.8, 121.9, 123.8, 123.9, 126.0, 126.2, 126.3, 126.4, 128.3, 128.4, 128.5, 128.6, 128.7, 132.1, 132.2, 132.4, 132.5, 134.3, 134.4, 134.5, 134.6, 151.0, 151.1, 151.3, 162.3, 162.4, 162.5, 162.7, 163.9, 164.0, 164.1, 164.2, 164.3, 164.5, 164.6, 164.7, 164.8, 164.9, 165.0, 165.1, 169.3, 170.1, 170.6, 171.5, 172.8, 172.9. MALDI-FTICR-MS observed: $[M + Na]^+$ 5455.3902; Calcd for $C_{288}H_{248}O_{106}N_2Na^+$: 5455.4068.

Synthesis of **12b**

Following the similar procedure for **12a**, **12b** was prepared and purified by column chromatography on silica gel (petroleum ether/EtOAc/MeOH, 80/20/3).

12b: White solid; yield 62%; m.p. 46–49 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.83 (72H, br), 1.11 (8H, br), 1.35–1.48 (40H, br), 1.76 (12H, br), 1.95 (4H, br), 2.03 (4H, br), 2.37 (26H, br), 2.57 (2H, br), 3.50–3.78 (12H, br), 4.28 (2H, br), 4.44 (2H, br), 4.78–5.20 (30H, br), 5.67–5.82 (24H, br), 7.01 (32H, br), 7.25 (96H, br); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.8, 18.1, 18.4, 18.5, 18.7, 18.9, 22.3, 24.7, 25.2, 25.3, 27.3, 29.5, 30.0, 35.9, 36.1, 44.1, 44.3, 44.9, 51.3, 68.0, 68.2, 69.9, 70.2, 70.5, 70.6, 71.2, 71.5, 127.3, 128.1, 128.5, 129.1, 129.3, 134.1, 134.3, 136.1, 136.6, 136.8, 140.2, 140.6, 140.7, 163.6, 164.1, 164.2, 164.5, 165.0, 172.9, 173.0, 173.1, 173.2, 173.3. MALDI-FTICR-MS observed: $[M + Na]^+$ 5765.4525; Calcd for $C_{336}H_{368}O_{82}N_2Na^+$: 5765.4585.

Synthesis of **13a**; *general procedure*

To a solution of **12a** (674 mg, 0.124 mmol) in EtOAc (50 mL) was added 10% Pd/C (100 mg). Then the flask was flushed with dry nitrogen twice and charged with hydrogen (in a balloon, *ca* 3 atm). The reaction mixture was stirred at 40 °C for 24 h and filtered. The filtrate was concentrated under reduced pressure to provide the desired compound **13a** as a white solid (472 mg, yield 95%).

13a: M.p. 152–157 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.02–1.12 (8H, br), 1.46 (4H, br), 1.92 (4H, s), 2.11 (8H, br), 2.26 (34H, br), 2.55–2.63 (2H, br), 4.62 and 4.76 (2H, br), 5.80–6.03 (24H, br), 7.20–7.25 (12H, br), 7.36–7.41 (12H, m), 7.68 (12H, br), 7.92 (12H, br), 8.16 (2H, br); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.8, 20.9, 25.3, 28.9, 29.0, 35.2, 35.3, 70.3, 71.0, 72.2, 72.6, 121.6, 121.7, 121.8, 121.9, 124.4, 124.5, 124.6, 126.3, 126.6, 131.5, 131.6, 132.0, 134.8, 135.0, 135.2, 150.6, 150.7, 150.8, 150.9, 162.2, 162.3, 162.4, 162.5, 162.6, 164.0, 164.1, 164.2, 164.4, 166.2, 166.3, 166.4, 166.7, 166.8, 167.0, 167.5, 169.1, 169.2, 170.5, 172.2. MALDI-FTICR-MS observed: $[M + Na]^+$ 4011.6401; Calcd for $C_{176}H_{152}O_{106}N_2Na^+$: 4011.6463.

Synthesis of **13b**

Following the similar procedure for **13a**, **13b** was prepared.

13b: White solid; yield 93%; m.p. 130–134 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.83 (72H, br), 1.22 (8H, br), 1.41 (40H, br), 1.78 (12H, br), 1.90 (4H, s), 2.13 (4H, br), 2.39 (24H, br), 2.45–2.54 (4H, br), 3.84 (12H, br), 4.59 (2H, br), 5.52–5.68 (24H, br), 7.07 (24H, br), 7.20 (24H, br); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.5, 18.7, 18.8, 19.0, 19.1, 19.3, 22.3, 24.6, 25.3, 29.1, 29.7, 35.3, 43.7, 43.8, 44.0, 44.4, 50.2, 70.0, 70.6, 72.2, 127.1, 127.5, 129.1, 137.1, 139.9, 164.5, 166.5, 167.0, 172.5, 173.0, 173.2. MALDI-FTICR-MS observed: $[M + Na]^+$ 4324.7011; Calcd for $C_{224}H_{272}O_{82}N_2Na^+$: 4324.7073.

We are grateful to the Tianjin Municipal Applied Basic Research and Cutting-Edge Technology Research Scheme of China (11JCYBJC14400) for financial support.

Received 9 December 2012; accepted 8 January 2013
Paper 1201667 doi: 10.3184/174751913X13602443643042
Published online: 12 March 2013

References

1 R.S. Langer, *Nature*, 1998, **392** (6679 Suppl.), 5.
2 K.E. Uhrich, S.M. Cannizzaro, R.S. Langer, and K.M. Shakesheff, *Chem. Rev.*, 1999, **99**, 3181.
3 J. Khandare, and T. Minko, *Prog. Polym. Sci.*, 2006, **31**, 359.
4 F. Aulenta, W. Hayes, and S. Rannard, *Eur. Polym. J.*, 2003, **39**, 1741.
5 F. Zeng, and S.C. Zimmerman, *Chem. Rev.*, 1997, **97**, 1681.
6 B. Helms, and E.W. Meijer, *Science*, 2006, **313**, 929.
7 A.-M. Caminade, C.-O. Turrin, R. Laurent, A. Ouali, and B. Delavaux-Nicot, *Dendrimers: towards catalytic*, *material and biomedical uses*, John Wiley & Sons: West Sussex, England, 2011.
8 A.R. Menjoge, R.M. Kannan, and D.A. Tomalia, *Drug Discovery Today*, 2010, **15**, 171.
9 M. Calderon, P. Welker, K. Licha, I. Fichtner, R. Graeser, R. Haag, and F. Kratz, *J. Controlled Release*, 2011, **151**, 295.
10 J.R. Baker Jr., Y. Zhang, T.P. Thomas, and A.M. Desai, *PCT Int. Appl. WO 2011011384*, 2011.
11 M. Grinda, J. Clarhaut, B. Renoux, I. Tranoy-Opalinski and S. Papot, *Med. Chem. Commun.*, 2012, **3**, 68.
12 Y. Cheng, *Dendrimer-based drug delivery systems: from theory to practice*. John Wiley & Sons: Hoboken, NJ, United States of America, 2012.
13 B.B. Ward, B. Huang, **A**. Desai, X.**-M**. Cheng, M. Vartanian, H. Zong, X. Shi, T.P. Thomas, A.E. Kotlyar, A. Van Der Spek, P.R. Leroueil, and J.R. Baker Jr, *Pharm. Res*., 2013, **30**, 247.
14 Y. Cheng, and T. Xu, *Eur. J. Med. Chem.*, 2005, **40**, 1188.
15 Y. Cheng, and T. Xu, *Eur. J. Med. Chem.*, 2008, **43**, 2291.
16 M. Chai, and D.R. Holycross, *244th ACS National Meeting & Exposition*, Philadelphia, PA, United States, August 19–23, 2012, CARB-4.
17 J. Pan, L. Ma, B. Li, Y. Li, and L. Guo, *Synth. Commun.*, 2012, **42**, 3441.
18 E. Oledzka, D. Kaliszewska, M. Sobczak, A. Raczak, P. Nickel and W. Kolodziejski, *J. Biomater. Sci., Polym. Ed.*, 2012, **23**, 2039.
19 G. Lamanna, J. Russier, H. Dumortier, and A. Bianco, *Biomaterials*, 2012, **33**, 5610.
20 S. Tang, L.J. Martinez, A. Sharma, and M. Chai, *Org. Lett.*, 2006, **8**, 4421.
21 S. Tang, S.M. June, B.A. Howell, and M. Chai, *Tetrahedron Lett.*, 2006, **47**, 7671.
22 D. Cater, M. Chai, and G. Lu, *240th ACS National Meeting*, Boston, MA, 22–26 August 2010, MEDI-455.
23 M. Chai, D.R. Holycross, D.B. MacHue, S. Tang, and C.-H. Ho, *242nd ACS National Meeting*, 28 August –1 September 2011 Denver, CO, COLL-392.
24 H.-F. Chow, L.F. Fok, and C.C. Mak, *Tetrahedron Lett.*, 1994, **35**, 3547.
25 H.-F. Chow, and C.C. Mak, *Tetrahedron Lett.*, 1996, **37**, 5935.
26 H.-F. Chow, and C.C. Mak, *Pure Appl. Chem.*, 1997, **69**, 483.
27 B. Buschhaus, W. Bauer, and A. Hirsch, *Tetrahedron*, 2003, **59**, 3899.
28 K. Hager, A. Franz, and A. Hirsch, *Chem.-Eur. J.*, 2006, **12**, 2663.
29 J.-F. Gnichwitz, M. Wielopolski, K. Hartnagel, U. Hartnagel, D.M. Guldi, and A. Hirsch, *J. Am. Chem. Soc.*, 2008, **130**, 84.