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Journal of Molecular Catalysis A: Chemical 241 (2005) 166–174
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Proline-modified poly(propyleneimine) dendrimers as catalysts for asymmetric aldol reactions

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Received 20 May 2005; accepted 30 May 2005
Available online 19 August 2005

Abstract

A series of surface-functionalized poly(propyleneimine) dendrimers (five generations) based on proline were synthesized and were evaluated as catalysts for asymmetric aldol reactions. Using 6.5 mol% of the second generation modified dendrimer as catalyst, the products of the aldol reactions were obtained in yields and and ee's comparable to those observed using proline itself, in much less reaction time (2 h) in comparison to that required for proline (16–18 h). In addition, the improved solubility of dendritic catalysts in organic solvents provides completely homogeneous reaction mixtures.

Keywords: Aldol reactions; Asymmetric catalysis; Dendrimers; Organocatalysis; Proline

1. Introduction

One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes [1]. Particular emphasis has been given to nonmetallic small organic molecules termed organocatalysts. The natural amino acid L-proline is one such small molecule [2], which has given rich dividends in ee's and yields in several asymmetric transformations, such as aldol [3], Mannich [4] and Michael [5] reactions, Robinson annulation [6], synthesis of amino acids [7], α-amination of aldehydes and ketones [8], α-oxidation [9] and α-alkylation of aldehydes [10].

Dendrimers are highly branched macromolecules synthesized stepwise from a central core and leading to a well-defined number of generations and end groups. They have three architectural regions: a core, an interior, and a highly functionalized surface, and they possess a high degree of symmetry [11]. Surface functionalized dendrimers have been proposed to fill the gap between homogeneous and heterogeneous catalysis combining the advantages of both heterogeneous (recycling of the catalyst) and homogeneous (fast kinetics) catalysts [12].

The rather poor solubility of proline in organic solvents is a major drawback for its application as a catalyst. Very recently, a number of proline-modified catalysts (acyl sulfonamides [13] and tetrazoles [14]) have been reported to present improved solubility and catalytic properties. The aim of our project was to synthesize poly(propyleneimine) dendrimers modified at the surface by proline presenting improved solubility and to study their activities for the catalysis of asymmetric aldol reactions [15].

2. Results and discussion

To develop proline-based dendritic catalysts, we decided to maintain the proline backbone, since both the carboxylic acid and pyrrolidine functionalities are essential for effective asymmetric induction, and link this backbone through a glutarate spacer with commercially available poly(propyleneimine) dendrimers. L-Hydroxyproline, which has already been used successfully as a catalyst

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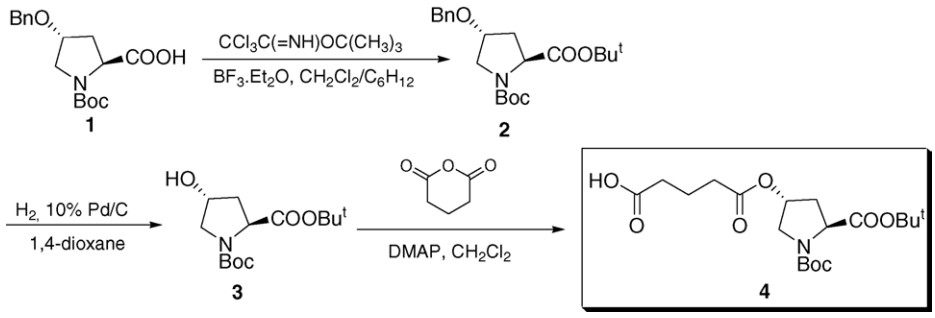
doi:10.1016/j.molcata.2005.05.047



Scheme 1. Synthesis of glutarylated 4-hydroxyproline derivative **4**.

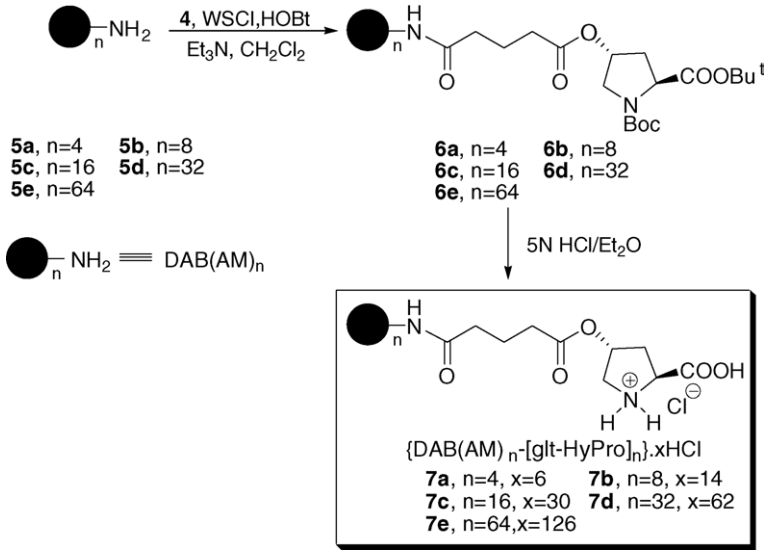
of the aldol reaction [3c], seemed an ideal template. Commercially available (2*S*,4*R*)-*N*-(*tert*-butoxycarbonyl)-4-benzyloxy-proline (**1**) was converted into compound **2** by treatment with *tert*-butyl 2,2,2-trichloroacetimidate in the presence of $BF_3{\cdot}Et_2O$ (Scheme 1). Catalytic hydrogenation of compound **2** afforded derivative **3**, which was further reacted with glutaric anhydride in the presence of catalytic amount of 4-dimethylamino-pyridine (DMAP) to give compound **4**.

The commercially available diaminobutane poly(propyleneimine) dendrimers DAB(AM)$_n$ (n = 4, 8, 16, 32, 64) **5a–e**, containing 4, 8, 16, 32, 64 free amino groups, were coupled with the carboxylic acid **4** using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) as a condensing agent [16] in the presence of 1-hydroxybenzotriazole (HOBt) to produce the functionalized at the periphery dendrimers **6a–e,** respectively (Scheme 2). Finally, treatment of dendrimers **6a–e** with 5 N HCl/Et_2O afforded the deprotected chiral dendrimers **7a–e** with 4, 8, 16, 32, 64 L-proline moieties at the periphery.

The structure of dendrimers was established by NMR spectroscopy and elemental analysis. The completion of acylation of the terminal primary NH_2 groups for the DAB(AM)$_{64}$ dendrimer was also confirmed by reacting the highest generation modified protected dendrimer **6e** with fluorescamine, a reagent suitable for the detection of primary amines in the picomole range [17]. In this case, 99.6% of the primary amino groups of DAB(AM)$_{64}$ dendrimer were fully reacted. It should be also noticed that in the spectra of **6a–e** no signal was observed at 40–41 ppm, where the terminal CH_2NH_2 carbons of the parent dendrimers **5a–e** resonate, indicating that all the peripheral amino groups of **5a–e** were fully acylated [18].

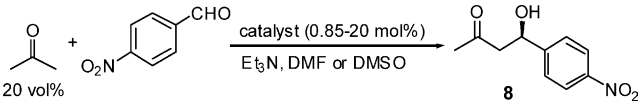
The asymmetric aldol reaction is one of the most powerful C–C bond forming reaction in organic synthesis [19] and has been thoroughly investigated by Barbas and coworkers using proline as catalyst [3c]. Therefore, the reaction of 4-nitrobenzaldehyde with acetone was used as a model reaction in our preliminary investigations and we have studied the catalytic effect of derivatives **7a–e**, L-HyPro, L-Pro and L-ProHCl on this reaction. The results of our studies are summarized in Table 1.

Under the conditions employed (see Table 1), the aldol product was obtained in 70% ee and 69% ee, when L-hydroxyproline and L-proline were used as catalysts (entries 1 and 2, respectively). Similarly, L-proline hydrochloric salt led



Scheme 2. Synthesis of dendritic catalysts **7a–e**.

Table 1
Direct asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde using hydroxyproline-modified dendrimers as catalysts



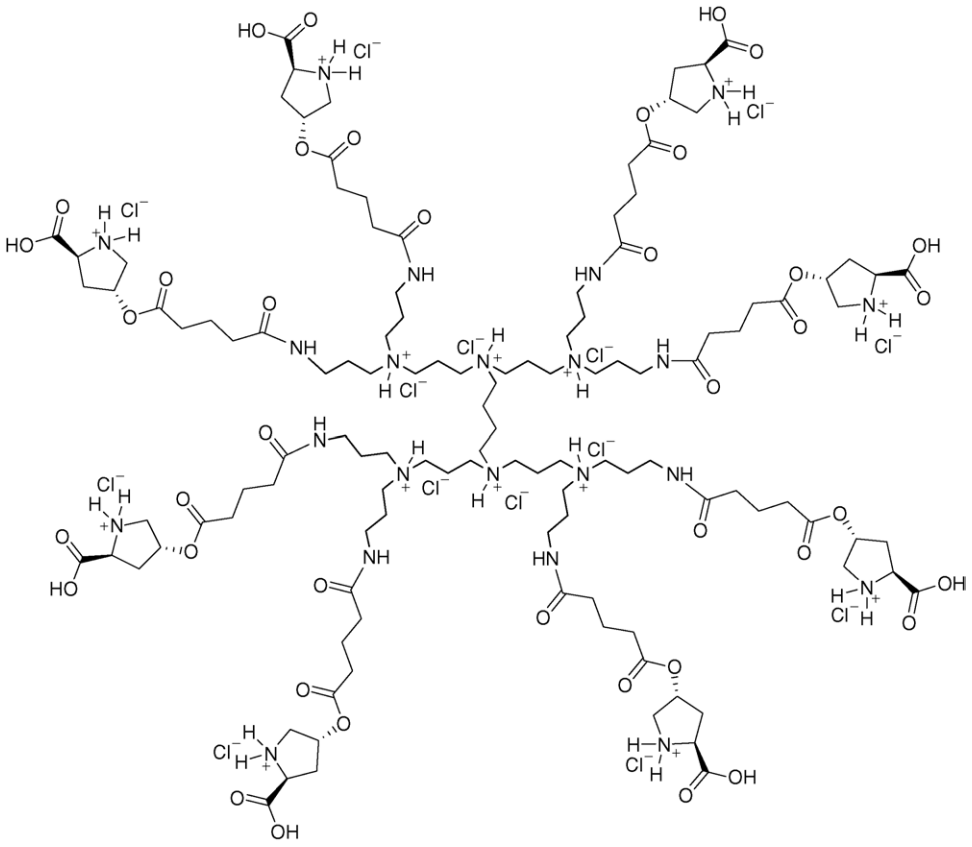
Entry	Catalyst	Catalyst loading (%)	Conditions[a]	Yield (%)[b]	ee (%)[c]
1	L-HyPro	20	DMF[d]	71	70
2	L-Pro	20	DMF[d]	63	69
3	L-ProHCl	20	DMF	60	63
4	L-ProHCl	20	DMF[d]	–	–
5	**7a**	17	DMSO	40	35
6	**7a**	17	DMF	56	33
7	**7a**	7.5	DMF	62	38
8	**7a**	7.5	DMF[e]	<5	n.d.[f]
9	**7b**	6.5	DMF	70	53
10	**7b**	6.5	DMF[e]	61	65
11	**7b**	1.0	DMF	34	36
12	**7b**	6.5	DMF/H_2O[g]	70	38
13	**7c**	17	DMSO	40	27
14	**7c**	6.5	DMF	50	39
15	**7c**	3.2	DMF	68	41
16	**7c**	3.2	DMF[e]	58	32
17	**7c**	1.6	DMF	34	28
18	**7d**	1.6	DMF	60	21
19	**7d**	1.6	DMF[e]	55	38
20	**7e**	0.85	DMF	68	33
21	**7e**	0.85	DMF[e]	59	46

[a] Dried solvents and reactions carried out for 16–18 h unless stated otherwise.
[b] Isolated yields after column chromatography.
[c] The ee was determined by HPLC analysis on a Daicel Chiralpak AD-RH column.
[d] In the absence of Et_3N.
[e] Reaction carried out for 2 h.
[f] Not determined.
[g] 2.5% (v/v) H_2O.

to chemical yield and ee value comparable to those acquired by using L-hydroxyproline and L-proline, in the presence of an equivalent amount of Et_3N (entry 3). However, when the same experiment was carried out with L-ProHCl in the absence of Et_3N, no aldol product was produced (entry 4). Thus, invoking the proposed mechanism [3a,20], the secondary amine group of the pyrrolidine ring should remain free.

As shown in Table 1, the second-generation dendrimer **7b** with eight L-hydroxyproline moieties at its surface (Scheme 3) led to a chemical yield (61%) and an ee value (65%) (entry 10) comparable to those obtained for L-hydroxyproline or L-proline, whilst the first generation dendrimer **7a** as well as the higher generation derivatives **7c–e** (third, fourth and fifth generation) led to lower enantioselectivity but good chemical yields. Several loadings of the dendritic catalysts **7a–e** were used in order to investigate whether there is any proportional relationship between enantioselectivity and dendrimer generation but unfortunately such a connection was not ascertained. It is interesting to note that the loading of the catalyst, even for the same dendritic compound, significantly influenced both the chemical yield and the enantioselectivity.

The results concerning the second generation dendrimer **7b** and higher generation dendrimers **7c–e** are in agreement with those reported in the literature, where dendrimers of low generation can possibly be expected to provide enantioselelective catalytic activity higher than that of high generation dendrimers [21]. It seems that in higher-generation dendrimers **7c–e**, with crowded surfaces, the catalytically active proline moieties are not freely accessible for enantioselective reactions. Hence, the loss of enantioselectivity for dendritic catalysts **7c–e** (negative dendritic effect) might be ascribed to steric hindrance between the proline moieties at the periphery. On the other hand, according to the proposed mechanism [20], the intermediate enamine, formed by the reaction of proline and acetone, approaches the *Re*-face of the aldehyde carbonyl group, to provide the (*R*)-aldol (Fig. 1). Therefore, it seems that in higher generation surface-crowded dendrimers the previous-mentioned steric preference is partly inhibited. It is noteworthy that the negative dendritic effect (loss of enantioselectivity in comparison to monomeric proline) was curiously observed even for the first generation dendrimer **7a**, but this phenomenon was vanished in the case of the second-generation dendrimer **7b**.



Scheme 3. Dendritic catalyst **7b**.

Sakthivel et al. reported that the model reaction between acetone and 4-nitrobenzaldehyde catalyzed by simple monomeric proline tolerates a small amount of water (<4%) without affecting the enantiomeric excess of the aldol product [3c]. However, in our study, the addition of an even smaller amount of water (2.5%) greatly influenced the enantioselectivity without affecting the chemical yield of the aldol product (Table 1, entry 12 in comparison to entry 9), indicating that the presence of water severely compromises the enantioselectivity.

In an attempt to test the efficacy of our best dendritic catalyst **7b**, we submitted 4-bromobenzaldehyde and 2-chlorobenzaldehyde as acceptor substrates to the aldol process. The results are presented in Table 2. When proline was used as catalyst in the reaction between acetone and 4-bromobenzaldehyde in 20 mol% loading, the aldol product was obtained in 62% ee value, whilst in 10 mol% proline amount practically no aldol product was acquired (entry 2). When catalyst **7b** was employed in 6.5 mol% catalyst loading, the aldol product was isolated in a chemical yield (70%) and an ee value (67%) comparable to that obtained for L-proline (entry 2). In a similar manner, in the reaction between acetone and 2-chlorobenzaldehyde, catalyst **7b** in 6.5 mol% amount led to a chemical yield (78%) and ee value (64%) also comparable to that observed by using proline itself (64% ee for 20 mol% proline and almost no aldol product for 10 mol%) (entry 3).

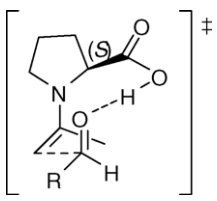
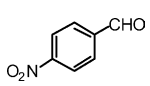
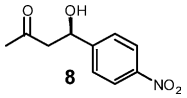
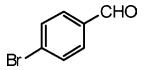
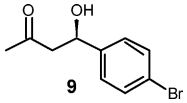
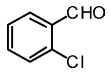
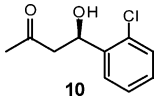


Fig. 1. Most favourable transition state for the proline catalyzed aldol reaction.

Benaglia et al. reported that poly(ethylene glycol)-supported proline (PEG-Pro) enantioselectively catalyzes aldol and imino aldol reactions [22] and also the synthesis of γ-nitroketones [23]. According to their findings, when PEG-Pro (15–30 mol%) was used as catalyst, the aldol products of the reactions between acetone and 4-nitrobenzaldehyde and also between acetone and 4-bromobenzaldehyde were obtained in chemical yields and ee's comparable to those acquired when employing non-supported proline derivatives as catalysts, but in higher reaction times (20–60 h) in the same solvent (DMF). However, the same aldol products were also obtained in yields and ee's comparable to those obtained by using proline itself, but in much less reaction time (2 h) (Table 2, entries 1 and 2), when dendritic catalyst **7b** was employed in 6.5 mol% catalyst loading, which amounts to

Table 2
The comparison between proline and catalyst **7b** in the direct asymmetric aldol reaction

Entry	Substrate	Product	Proline[a] (10 mol%)		Proline[a] (20 mol%)		**7b**[b] (6.5 mol%)	
			Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]
1		 **8**	<5	n.d.[e]	63	69	61	65
2		 **9**	<5	n.d.[e]	71	62	70	67
3		 **10**	<5	n.d.[e]	80	64	78	64

[a] Reactions carried out for 16–18 h.
[b] Reactions carried out for 2 h.
[c] Isolated yields after column chromatography.
[d] The ee was determined by HPLC on a Daicel Chiralpak AD-RH column.
[e] Not determined.

52 mol% regarding catalytic proline sites, since dendrimer **7b** contains eight proline residues at its periphery. It is worth noting that the improved solubility of dendritic catalysts provides completely homogeneous reaction mixtures (homogeneous catalysis).

3. Conclusions

In conclusion, a series of functionalized at the periphery poly(propyleneimine) dendrimers (five generations) based on proline were synthesized and were evaluated as metal-free catalysts for asymmetric aldol reactions. In particular, employing 6.5 mol% of the second generation modified dendrimer **7b** as catalyst, the products of the aldol reactions were obtained in yields and and ee's comparable to those observed using proline itself and also in much less reaction time (2 h) in comparison to that required for proline (16–18 h). In addition, these new catalysts offer improved solubility in organic solvents.

4. Experimental

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded on 200 and 300 MHz Varian spectrometers. Where applicable, structural assignments were based on COSY experiments. In accordance to the literature [24], the number of signals in ^{13}C NMR spectra is higher than the expected because of the existence of rotamers. Where these rotamers are apparent, peaks for major and minor rotamers are reported, when resolved. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Visualisation of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin both in ethanol stain. THF and 1,4-dioxane were freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere and immediately prior to use. Et_2O was treated with calcium chloride and stored over Na. DMF was stirred in the presence of P_2O_5 for 15 h and distilled under reduced pressure. Acetone was dried overnight over 3 Å activated molecular sieves (10%, w/v) and then distilled. All other solvents and chemicals were of reagent grade and used without further purification. Elemental analyses were obtained in a Perkin-Elmer 2400 instrument from vacuum dried samples (over P_2O_5 at 1–2 mmHg, 48 h at r.t.) and were within ±0.4% of theoretical values.

*4.1. (2S,4R)-di-tert-butyl 4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (**2**)*

To a stirred solution of Boc-L-Pro(Bn)-OH (322 mg, 1.00 mmol) in CH_2Cl_2 (1 mL), a solution of *tert*-butyl-2,2,2-trichloroacetimidate (440 mg, 2.00 mmol) in C_6H_{12} (2 mL) was added, followed by $BF_3{\cdot}Et_2O$ (20 μL). The stirring was continued for 24 h at room temperature. Work-up involved filtration of the reaction mixture through a pad of Celite to remove trichloroacetamide and removal of the solvent under reduced pressure. The residue was purified by column chromatography using a mixture of $CHCl_3$:MeOH 95:5 as eluent to afford **2**. Yellowish oil (315 mg, 84%); $[\alpha]_D$ −23.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (br, 18H), 2.05 (m, 1H), 2.35 (m, 1H), 3.45–3.75 (m, 2H), 4.10–4.38 (m, 2H), 4.42–4.60 (m, 2H), 7.25–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 28.3, 35.4, 36.7, 51.2, 51.8, 58.6, 71.1, 75.7, 76.7, 79.7, 79.9, 81.0, 127.6, 127.7, 128.4, 137.7, 154.0, 172.1; Anal. Calcd. for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.59; H, 8.38; N, 3.68.

4.2. (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (**3**)

To a stirred solution of (2*S*,4*R*)-di-*tert*-butyl 4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (**2**) (380 mg, 1.00 mmol) in anhydrous 1,4-dioxane (10 mL), 10% Pd/C (40 mg) was added. The reaction mixture was stirred under H_2 for 24 h at room temperature. After filtration through a pad of Celite, the solvent was removed and the residue was purified by column chromatography using EtOAc as eluent to give **3**. Colourless oil (240 mg, 84%); $[\alpha]_D$ −68.0 (ca. 1.0, MeOH); [Lit. [25] $[\alpha]^{21}_D$ −68.9 (*c* 1.06, MeOH)]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (br, 18H), 2.01 (m, 1H), 2.25 (m, 1H), 2.92 (br, 1H), 3.33–3.68 (m, 2H), 4.28 (m, 1H), 4.45 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 28.3, 38.3, 39.1, 54.5, 58.5, 69.1, 70.0, 79.9, 80.2, 81.1, 154.3, 172.2; Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.65; H, 7.69; N, 4.88.

4.3. 5-((3R,5S)-1,5-bis(tert-butoxycarbonyl)pyrrolidin-3-yloxy)-5-oxopentanoic acid (**4**)

To a stirred solution of (2*S*,4*R*)-di-*tert*-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (**3**) (287 mg, 1.00 mmol) in CH_2Cl_2 (7 mL), a solution of glutaric anhydride (224 mg, 2.00 mmol) in CH_2Cl_2 (3 mL) was added, followed by DMAP (16 mg, 0.13 mmol). The stirring was continued for 36 h at room temperature. The solvent was then removed under reduced pressure, water (8 mL) was added and the product was extracted with EtOAc (3× 8 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ (1× 20 mL) and H_2O (1× 25 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography using EtOAc as eluent to give **4**. Light yellowish oil (300 mg, 75%); $[\alpha]_D$ −37.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (br, 18H), 1.92–2.08 (m, 2H), 2.17 (m, 1H), 2.27–2.51 (m, 5H), 3.40–3.78 (m, 2H), 4.25 (m, 1H), 5.27 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 27.8, 27.9, 28.2, 29.6, 32.8, 33.1, 35.5, 36.5, 51.9, 52.1, 58.4, 71.9, 72.8, 80.3, 80.5, 81.5, 153.9, 171.6, 172.3, 177.9; FAB-MS: *m*/*z* (%): 402 (10) $[M + H^+]$, 424 (2.5) $[M + Na^+]$; Anal. Calcd. for $C_{19}H_{31}NO_8$: C, 56.84; H, 7.78; N, 3.49. Found: C, 56.65; H, 7.69; N, 3.48.

4.4. General procedure for the preparation of modified dendrimers **6a**–**e**

To a stirred solution of 5-((3*R*,5*S*)-1,5-bis(*tert*-butoxycarbonyl)pyrrolidin-3-yloxy)-5-oxopentanoic acid (**4**) (0.060 × *n* mmol, *n* = 4, 8, 16, 32, 64) in CH_2Cl_2 (5–10 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.070 × *n* mmol, *n* = 4, 8, 16, 32, 64), 1-hydroxybenzotriazole (0.060 × *n* mmol, *n* = 4, 8, 16, 32, 64), Et_3N (0.075 × *n* mmol, *n* = 4, 8, 16, 32, 64) and $DAB(AM)_n$ (**5a**–**e**) (0.040 mmol, *n* = 4, 8, 16, 32, 64). The reaction mixture was stirred for 1 h at 0 °C and for 24–72 h at room temperature. The solvent was removed, water (12 mL) was added and the product was extracted with EtOAc (3× 15 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ (1× 25 mL), H_2O (1× 25 mL), 5% aqueous $NaHCO_3$ (1× 25 mL), H_2O (1× 30 mL), dried (Na_2SO_4), and the solvent was evaporated to give the modified dendrimers **6a**–**e**.

4.4.1. Dendrimer **6a** (*n* = 4)

Green, viscous oil (65 mg, 88%); $[\alpha]_D$ −26.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 [br, 72H, 8 × C$(CH_3)_3$], 1.56–2.05 (m, 20H, 6 × C$H_2$$CH_2$N, 4 × CH_2C$H_2$$CH_2$), 2.10–2.58 (m, 32H, 4 × CH_2CHN, 6 × CH_2N, 4 × C$H_2$$CH_2CH_2$), 3.16–3.40 (m, 8H, 4 × CH_2NH), 3.42–3.79 (m, 8H, 4 × OCHCH_2N), 4.16–4.35 (m, 4H, 4 × CHN), 5.15–5.35 (m, 4H, 4 × OCH), 6.70–6.95 (m, 4H, 4 × NHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 24.7, 26.7, 27.9, 28.2, 29.5, 33.3, 34.1, 35.1, 35.4, 36.3, 38.1, 44.3, 51.9, 54.4, 58.2, 58.5, 71.7, 72.5, 80.3, 81.3, 153.8, 153.9, 171.5, 172.1, 172.3, 172.6; FAB-MS: *m*/*z* (%): 1851 (70) $[M + H^+]$; Anal. Calcd. for $C_{92}H_{156}N_{10}O_{28}$: C, 59.72; H, 8.50; N, 7.57. Found: C, 59.78; H, 8.69; N, 4.78.

4.4.2. Dendrimer **6b** (*n* = 8)

Green, viscous oil (115 mg, 75%); $[\alpha]_D$ −22.6 (*c* 0.60, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 [br, 144H, 16 × C$(CH_3)_3$], 1.55–2.05 (m, 44H, 14 × C$H_2$$CH_2$N, 8 × CH_2C$H_2$$CH_2$), 2.10–2.55 (m, 84H, 8 × CH_2CHN, 18 × CH_2N, 8 × C$H_2$$CH_2CH_2$), 3.15–3.38 (m, 16H, 8 × CH_2NH), 3.45–3.79 (m, 16H, 8 × OCHCH_2N), 4.15–4.35 (m, 8H, 8 × CHN), 5.19–5.34 (m, 8H, 8 × OCH), 7.00–7.20 (m, 8H, 8 × NHCO). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 24.5, 24.8, 26.8, 27.8, 28.2, 30.2, 33.3, 33.8, 34.8, 35.0, 36.3, 37.8, 48.7, 51.4, 51.9, 55.6, 58.2, 71.7, 72.5, 80.0, 80.3, 81.3, 153.8, 154.0, 171.5, 172.3, 172.5; Anal. Calcd. for $C_{192}H_{328}N_{22}O_{56}$: C, 60.04; H, 8.61; N, 8.02. Found: C, 59.89; H, 8.69; N, 8.18.

4.4.3. Dendrimer **6c** (*n* = 16)

Pale yellow, viscous oil (244 mg, 78%); $[\alpha]_D$ −20.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 [br, 288H, 32 × C$(CH_3)_3$], 1.50–2.07 (m, 92H, 30 × C$H_2$$CH_2$N, 16 × CH_2C$H_2$$CH_2$), 2.08–2.60 (m, 180H, 16 × CH_2CHN, 16 × C$H_2$$CH_2CH_2$, 42 × CH_2N), 3.10–3.38 (m, 32H, 16 × CH_2NH), 3.40–3.78 (m, 32H, 16 × OCHCH_2N), 4.16–4.40 (m, 16H, 16 × CHN), 5.18–5.32 (m, 16H, 16 × OCH), 7.10–7.37 (m, 16H, 16 × NHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 24.6, 24.9, 25.4, 26.9, 27.9, 28.3, 30.2, 33.4, 34.9, 35.1, 36.4, 37.8, 48.9, 51.4, 52.0, 55.7, 58.4, 71.8, 72.6, 80.1, 80.3, 81.4, 153.9, 154.1, 156.8, 171.5, 172.4, 172.6; Anal. Calcd. for $C_{392}H_{672}N_{46}O_{112}$: C, 60.19; H, 8.66; N, 8.24. Found: C, 59.95; H, 8.61; N, 8.28.

4.4.4. Dendrimer **6d** (*n* = 32)

Pale yellow, viscous oil (474 mg, 75%); $[\alpha]_D$ −24.1 (*c* 0.60, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 [br, 576H,

64 × C(CH$_3$)$_3$], 1.53–2.04 (m, 188H, 62 × C*H*$_2$CH$_2$N, 32 × CH$_2$C*H*$_2$CH$_2$), 2.04–2.65 (m, 372H, 32 × C*H*$_2$CHN, 90 × CH$_2$N, 32 × C*H*$_2$CH$_2$CH$_2$), 3.12–3.36 (m, 64H, 32 × C*H*$_2$NH), 3.36–3.78 (m, 64H, 32 × OCHC*H*$_2$N), 4.15–4.35 (m, 32H, 32 × CHN), 5.18–5.32 (m, 32H, 32 × OCH), 7.30–7.60 (m, 32H, 32 × NHCO); ^{13}C NMR (50 MHz, CDCl$_3$) δ 20.6, 24.2, 24.8, 26.8, 27.7, 28.1, 29.4, 33.2, 34.9, 35.3, 36.2, 37.5, 48.5, 51.1, 51.8, 54.3, 58.1, 71.6, 72.4, 79.9, 80.1, 81.2, 153.6, 153.9, 157.0, 171.2, 171.4, 172.4; Anal. Calcd. for $C_{792}H_{1360}N_{94}O_{224}$: C, 60.27; H, 8.68; N, 8.34. Found: C, 60.20; H, 8.71; N, 8.50.

*4.4.5. Dendrimer **6e** (n = 64)*

Yellowish, viscous oil (888 mg, 70%); [α]$_D$ −21.8 (*c* 0.67, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.44 [br, 1152H, 128 × C(CH$_3$)$_3$], 1.52–2.05 (m, 380H, 126 × C*H*$_2$CH$_2$N, 64 × CH$_2$C*H*$_2$CH$_2$), 2.05–2.85 (m, 756H, 64 × C*H*$_2$CHN, 186 × CH$_2$N, 64 × C*H*$_2$CH$_2$C*H*$_2$), 3.05–3.35 (m, 128H, 64 × C*H*$_2$NH), 3.35–4.08 (m, 128H, 64 × OCHC*H*$_2$N), 4.13–4.40 (m, 64H, 64 × CHN), 5.15–5.33 (m, 64H, 64 × OCH), 7.48–7.79 (m, 64H, 64 × NHCO); ^{13}C NMR (50 MHz, CDCl$_3$) δ 20.8, 24.9, 25.5, 26.2, 27.9, 28.3, 30.2, 33.4, 33.8, 35.1, 36.4, 37.5, 49.1, 51.0, 51.9, 54.0, 58.3, 71.7, 72.6, 80.0, 80.2, 81.3, 153.8, 154.0, 156.9, 171.4, 171.6, 172.6, 172.8; Anal. Calcd. for $C_{1592}H_{2736}N_{190}O_{448}$: C, 60.30; H, 8.70; N, 8.39. Found: C, 60.31; H, 8.78; N, 8.51.

4.5. General procedure for the removal of Boc and Bu^t protecting groups

Boc and Bu^t groups of **6a–e** (0.035 mmol) were removed by treatment with 5 N HCl in Et$_2$O (3.50 × *n* mmol, *n* = 4, 8, 16, 32, 64) for 5 h at room temperature. After evaporation under reduced pressure to a small volume (2–5 mL), anhydrous Et$_2$O was added (5 mL) and the precipitated products **7a–e** were afforded through decantation.

*4.5.1. Dendrimer **7a** (n = 4)*

White solid (48 mg, 95%); [α]$_D$ −14.3 (*c* 0.90, H$_2$O); ^{1}H NMR (200 MHz, D$_2$O) δ 1.60–1.91 (m, 20H, 6 × C*H*$_2$CH$_2$N, 4 × CH$_2$C*H*$_2$CH$_2$), 2.10–2.25 (m, 8H, 4 × C*H*$_2$CH$_2$CH$_2$), 2.25–2.45 (m, 12H, 4 × CH$_2$CH$_2$C*H*$_2$, 4 × C*H*HCHN), 2.45–2.62 (m, 4H, 4 × CH*H*CHN), 2.98–3.22 (m, 20H, 4 × C*H*$_2$NH, 6 × CH$_2$N), 3.38–3.65 (m, 8H, 4 × OCHC*H*$_2$N), 4.40–4.54 (m, 4H, 4 × CHN), 5.31–5.44 (m, 4H, 4 × OCH); ^{13}C NMR (50 MHz, D$_2$O) δ 22.0, 23.1, 23.2, 26.0, 26.4, 32.2, 35.4, 35.5, 37.1, 37.4, 38.8, 39.1, 39.5, 40.8, 53.1, 53.7, 54.7, 56.0, 57.6, 60.9, 61.1, 72.2, 75.9, 173.7, 176.9, 178.8; Anal. Calcd. for $C_{56}H_{98}Cl_6N_{10}O_{20}$: C, 46.57; H, 6.84; N, 9.70. Found: C, 46.31; H, 7.15; N, 9.50.

*4.5.2. Dendrimer **7b** (n = 8)*

White solid (103 mg, 95%); [α]$_D$ −15.8 (*c* 0.40, H$_2$O); ^{1}H NMR (200 MHz, D$_2$O) δ 1.75–2.50 (series of m, 84H, 8 × CH$_2$CH$_2$CH$_2$, 14 × C*H*$_2$CH$_2$N, 8 × C*H*HCHN), 2.50–2.68 (m, 8H, 8 × CH*H*CHN), 3.10–3.39 (m, 52H, 8 × C*H*$_2$NH, 18 × CH$_2$N), 3.40–3.72 (m, 16H, 8 × OCHC*H*$_2$N), 4.37–4.57 (m, 8H, 8 × CHN), 5.39–5.50 (m, 8H, 8 × OCH); ^{13}C NMR (50 MHz, D$_2$O) δ 21.4, 23.0, 23.3, 25.9, 32.2, 35.5, 37.1, 37.4, 38.8, 39.5, 52.3, 53.2, 53.6, 55.9, 56.5, 60.8, 61.1, 72.2, 75.7, 75.9, 173.7, 176.9, 178.7; Anal. Calcd. for $C_{120}H_{214}Cl_{14}N_{22}O_{40}$: C, 46.47; H, 6.95; N, 9.94. Found: C, 46.50; H, 7.26; N, 9.80.

*4.5.3. Dendrimer **7c** (n = 16)*

White solid (213 mg, 95%); [α]$_D$ −22.4 (*c* 0.40, H$_2$O); ^{1}H NMR (200 MHz, D$_2$O) δ 1.70–2.45 (m, 172H, 16 × CH$_2$CH$_2$CH$_2$, 30 × C*H*$_2$CH$_2$N, 16 × C*H*HCHN), 2.45–2.67 (m, 16H, 16 × CH*H*CHN), 3.08–3.69 (m, 148H, 16 × C*H*$_2$NH, 42 × CH$_2$N, 16 × OCHC*H*$_2$N), 4.32–4.56 (m, 16H, 16 × CHN), 5.36–5.49 (m, 16H, 16 × OCH);^{13}C NMR (50 MHz, D$_2$O) δ 21.5, 23.0, 25.9, 27.1, 32.9, 35.5, 37.1, 37.3, 38.8, 39.4, 52.3, 53.2, 53.6, 54.5, 55.9, 61.2, 72.1, 75.9, 173.8, 176.8, 178.6; Anal. Calcd. for $C_{248}H_{446}Cl_{30}N_{46}O_{80}$: C, 46.43; H, 7.01; N, 10.04. Found: C, 46.63; H, 7.33; N, 9.72.

*4.5.4. Dendrimer **7d** (n = 32)*

White solid (424 mg, 93%); [α]$_D$ −12.0 (*c* 0.64, H$_2$O); ^{1}H NMR (200 MHz, D$_2$O) δ 1.75–2.45 (series of m, 348H, 32×CH$_2$CH$_2$CH$_2$, 62 × C*H*$_2$CH$_2$N, 32 × C*H*HCHN), 2.45–2.63 (m, 32H, 32 × CH*H*CHN), 3.14–3.71 (m, 308H, 32 × C*H*$_2$NH, 90 × CH$_2$N, 32 × OCHC*H*$_2$N), 4.29–4.41 (m, 32H, 32 × CHN), 5.39–5.47 (m, 32H, 32 × OCH); ^{13}C NMR (50 MHz, D$_2$O) δ 23.0, 25.9, 32.1, 35.4, 37.0, 37.3, 38.8, 39.3, 52.2, 53.1, 53.5, 55.8, 60.7, 61.1, 72.1, 75.8, 173.7, 176.7, 178.5; Anal. Calcd. for $C_{504}H_{910}Cl_{62}N_{94}O_{160}$: C, 46.40; H, 7.03; N, 10.09. Found: C, 46.62; H, 7.38; N, 9.89.

*4.5.5. Dendrimer **7e** (n = 64)*

White solid (868 mg, 94%); [α]$_D$ −15.8 (*c* 0.60, H$_2$O); ^{1}H NMR (200 MHz, D$_2$O) δ 1.70–2.68 (series of m, 764H, 64 × CH$_2$CH$_2$CH$_2$, 126 × C*H*$_2$CH$_2$N, 64 × C*H*$_2$CHN), 3.08–3.75 (m, 628H, 64 × C*H*$_2$NH, 186 × CH$_2$N, 64 × OCHC*H*$_2$N), 4.29–4.55 (m, 64H, 64 × CHN), 5.39–5.54 (m, 64H, 64 × OCH); ^{13}C NMR (50 MHz, D$_2$O) δ 23.0, 25.9, 32.0, 35.6, 37.1, 37.4, 38.9, 39.4, 52.3, 53.2, 53.7, 55.9, 61.1, 72.1, 75.8, 173.5, 176.6, 176.8, 178.4; Anal. Calcd. for $C_{1016}H_{1902}Cl_{126}N_{190}O_{320}$: C, 46.28; H, 7.27; N, 10.09. Found: C, 46.52; H, 7.58; N, 9.95.

4.6. General procedure for the preparation of aldol products

To a mixture of anhydrous DMF (1.60 mL) and anhydrous acetone (0.40 mL) was added the corresponding aldehyde (0.20 mmol) followed by the catalysts **7a–e** or L-Pro or L-HyPro or L-ProHCl (0.85–34 mol%) and an equivalent amount of Et$_3$N. The resulting mixture was stirred at room

temperature for 2–15 h. Following aqueous workup with saturated ammonium chloride solution and extraction several times with EtOAc, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The pure aldol products were obtained by column chromatography using a mixture of EtOAc:petroleum ether 40–60 1:1 as eluent.

4.6.1. (4R)-(4-Nitrophenyl)-4-hydroxy-2-butanone ***(8)*** *[3c]*

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.83 (m, 2H), 3.56 (d, J = 3.2 Hz, 1H), 5.25 (m, 1H), 7.52 (d, J = 7.0 Hz, 2H), 8.20 (d, J = 7.0 Hz, 2H); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30/70, flow rate 0.5 mL/min, λ = 254 nm): t_R (major) = 16.58 min; t_R (minor) = 20.26 min.

4.6.2. (4R)-(4-Bromophenyl)-4-hydroxy-2-butanone ***(9)*** *[3c]*

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.82 (m, 2H), 3.40 (d, J = 3.0 Hz, 1H), 5.12 (m, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30/70, flow rate 0.5 mL/min, λ = 254 nm): t_R (major) = 27.31 min; t_R (minor) = 30.77 min.

4.6.3. (4R)-(2-Chlorophenyl)-4-hydroxy-2-butanone ***(10)*** *[3c].*

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.64–3.03 (m, 2H), 3.61 (br, 1H), 5.56 (m, 1H), 7.19–7.34 (m, 3H), 7.64 (d, J = 7.7 Hz, 1H); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30/70, flow rate 0.5 mL/min, λ = 254 nm): t_R (major) = 15.63 min; t_R (minor) = 18.07 min.

Acknowledgement

This research was supported by “Herakleitos” EPEAEK programme.

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