A new one-pot hydroformylation/Strecker synthesis as a versatile synthetic tool for polyfunctional compounds and functionalization of dendrimers

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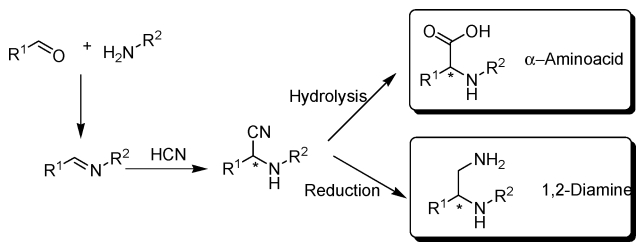
A versatile and high yielding one-pot hydroformylation/Strecker synthesis is reported for the synthesis of various α-aminonitriles. This methodology allows functionalization of dendrimers (*e.g.* polyamines **4–7**) and hyper branched polymers (*e.g.* polyallyl glycerol **12**) to give corresponding dendritic structures with α-aminonitriles and/or amino acids in the outer shell in good to excellent yields.

Efficient syntheses of α-amino acids are of considerable interest as they are not only important building blocks of peptides and proteins but also widely distributed in other natural products.[1] The non-natural α-amino acids are expected to play an important role in improving the original properties of proteins.[2] Strecker synthesis is a versatile low cost approach for the synthesis of racemic α-amino acids.[3] It was the first multicomponent reaction and several modifications of this reaction have been reported for the synthesis of racemic α-aminonitriles.[4] The Strecker product, α-aminonitrile, can be converted to α-amino acids by hydrolysis and/or 1,2-diamines by reduction of the nitrile functional group (Scheme 1).



Scheme 1 Scope of Strecker synthesis.

In recent years, significant progress has been made towards the development of an enantioselective version of this reaction for the synthesis of chiral amino acids. Several chiral organo metallic complexes[5] as well as organo catalysts[6] have been employed for this three component asymmetric Strecker synthesis. In addition some examples are also reported in which the α-aminonitriles are synthesized in the absence of catalyst, in this case the solvent itself acts as a catalyst.[7] More recently solvent free Strecker synthesis is reported for non selective α-aminonitriles.[8]

An aldehyde is one of the three components of a Strecker reaction. Hydroformylation, since its first discovery in 1938 by Roelen, has been used for industrial scale production of aldehydes worldwide.[9] Various organic compounds of great importance have been synthesized by different one-pot versions of this reaction.[10]

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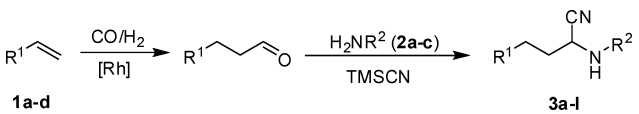
In the present study, we report the first application of a one-pot hydroformylation/Strecker synthesis for the synthesis of racemic α-aminonitriles and dendritic polyamines with α-aminonitrile terminal groups. This three component reaction consists of an initial hydroformylation of an olefin, which undergoes condensation with an amine to form an imine followed by the addition of HCN to the C–N double bond of the imine to give α-aminonitriles (Scheme 2). The method offers a convenient approach towards variation of different alkyl groups at the α-position starting with different olefins.

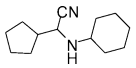
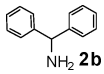
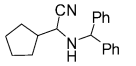
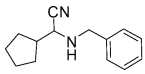
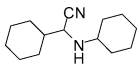
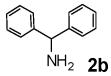
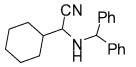
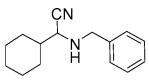
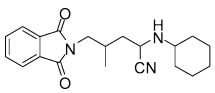
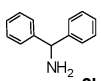
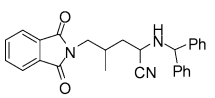
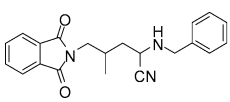
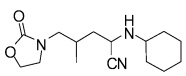
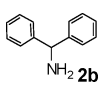
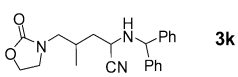
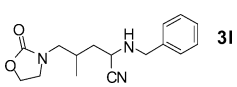


Scheme 2 One-pot hydroformylation/Strecker synthesis.

In the initial experiments various olefins **1a–d** were used which can be converted to the corresponding aldehydes by hydroformylation under standard conditions ($[Rh(COD)Cl]_2$ (0.3 mol%) as catalyst, 60 bars of CO/H_2 (1:1) and at 100 °C in dioxane). In all cases, olefins were converted to the corresponding aldehydes in full conversion in 48 h except cyclohexene **1b** that required an extended reaction time from 48 to 72 h (Table 1, entry 1). The primary amines **2a–c** were added to the aldehydes followed by the addition of TMSCN to give *N*-substituted α-aminonitriles **3a–l** in good to excellent yields (Table 1). Trimethylsilyl cyanide (TMSCN) was used as an alternative to HCN, which is a safer source of cyanide anion.[11] In our studies, cyclic olefins and methylallyl systems were chosen as model systems to avoid linear (*n*) to branched (*iso*) selectivity problems in the initial hydroformylation step.

This method also allows the synthesis of polyfunctional nitriles starting from different protected *N*-olefins **1c–d**. Starting with *N*-methylallylphthalimide **1a** (as a primary amine masked functional group), primary amines **2a–c** and TMSCN, the corresponding phthalimide-protected α-aminonitriles **3g–i** were obtained in good yields (Table 1 entry 3). Hydrazinolysis of **3j–l** by standard Ing–Manske procedure[12] can be done to get primary amine functionalized α-aminonitriles. Similarly, *N*-methylallyl oxazolidinone **1d** (as an amino alcohol masked functional group) gave oxazolidinone functionalized

Table 1 α-Aminonitriles obtained *via* one-pot hydroformylation/Strecker synthesis

Entry	Olefins	Amines	Product	Yield[%]
		 **2a**	 **3a**	69
1[a]	 **1a**	 **2b**	 **3b**	70
		 **2c**	 **3c**	74
		 **2a**	 **3d**	69
2[a]	 **1b**	 **2b**	 **3e**	75
		 **2c**	 **3f**	74
		 **2a**	 **3g**	94
3[b]	 **1c**	 **2b**	 **3h**	89
		 **2c**	 **3i**	77
		 **2a**	 **3j**	92
4[b]	 **1d**	 **2b**	 **3k**	75
		 **2c**	 **3l**	90

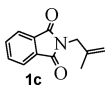
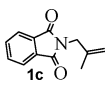
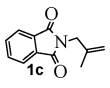
[a] CO/H_2 (1:1) 80 bar, 120 °C, 72 h. [b] CO/H_2 (1:1) 60 bar, 100 °C, 48 h.

N-substituted α-aminonitriles **3j–l** in excellent yields (Table 1, entry 4).

After successful synthesis of different α-aminonitriles, we extended the application of this method for the synthesis of α-aminonitrile terminated dendrimers. As can be seen in Table 1, the synthesis of α-aminonitriles by this one pot method proceed almost quantitatively, so this makes it as interesting tool for functionalization of dendrimers. Dendrimers are polyfunctional hyper branched macromolecules containing a core surrounded by a back bone and shell.[13] For dendrimer synthesis the reaction must occur in full conversion and high yields in multiple times, otherwise the branching structure will have missing repeat units. Thus the reaction for shell modification has to proceed in a quantitative way to prevent defects in the ideal dendrimer structure.

In principle, this synthetic methodology can be used for functionalization of dendritic structures having either primary amine and/or olefinic terminal groups. Following the first option, the first dendritic α-aminonitrile **7a** was obtained in 84% yield from the condensation of tris(aminoethyl)amine **4** with aldehyde obtained by hydroformylation of cyclopentene **1a** followed by the addition of TMSCN (Scheme 2). As expected, on the use of different olefins **1b–c** and **4**, the corresponding dendritic polyamines **7b–c** were obtained in good to excellent yields (Table 2, entries 2–3). For higher generation dendrimers using a divergent strategy, tris(aminoethyl)amine **4** was alkylated by Michael addition. In the

Table 2 α-Aminonitrile terminated polyamine dendrimers *via* hydroformylation/Strecker synthesis

Entry	Olefin	Polyamine	Product	*Mw*[g/mol]	Yield[%]
1	 1a	4	**7a**	467.69	84
2	 1b	4	**7b**	509.77	96
3	 1c	4	**7c**	662.77	64
4	 1a	5	**8a**	1131.71	79
5	 1b	5	**8b**	1215.87	85
6	 1c	5	**8c**	1929.34	52
7	 1a	6	**9a**	2559.76	83
8	 1b	6	**9b**	2628.08	93
9	 1c	6	**9c**	4057.02	62

next step Raney-cobalt mediated reduction of nitrile functional groups to primary amines under a hydrogen atmosphere was carried out to obtain polyamine cores with a higher degree of primary amine terminal groups (Scheme 3).[14] In this synthetic route a nitrogen atom was used as a branching point for the next generations.

As shown in Table 2, α-aminonitrile terminated dendritic polyamines **8a–c** and **9a–c** (up to generation-3.5) were obtained in high yields starting from different olefins **1a–c** and polyamine core molecules **5** and **6** (Table 2). Dialysis was used as a membrane ultrafiltration method for the purification of dendritic polyamines (Mw < 1000 g/mol).[15]

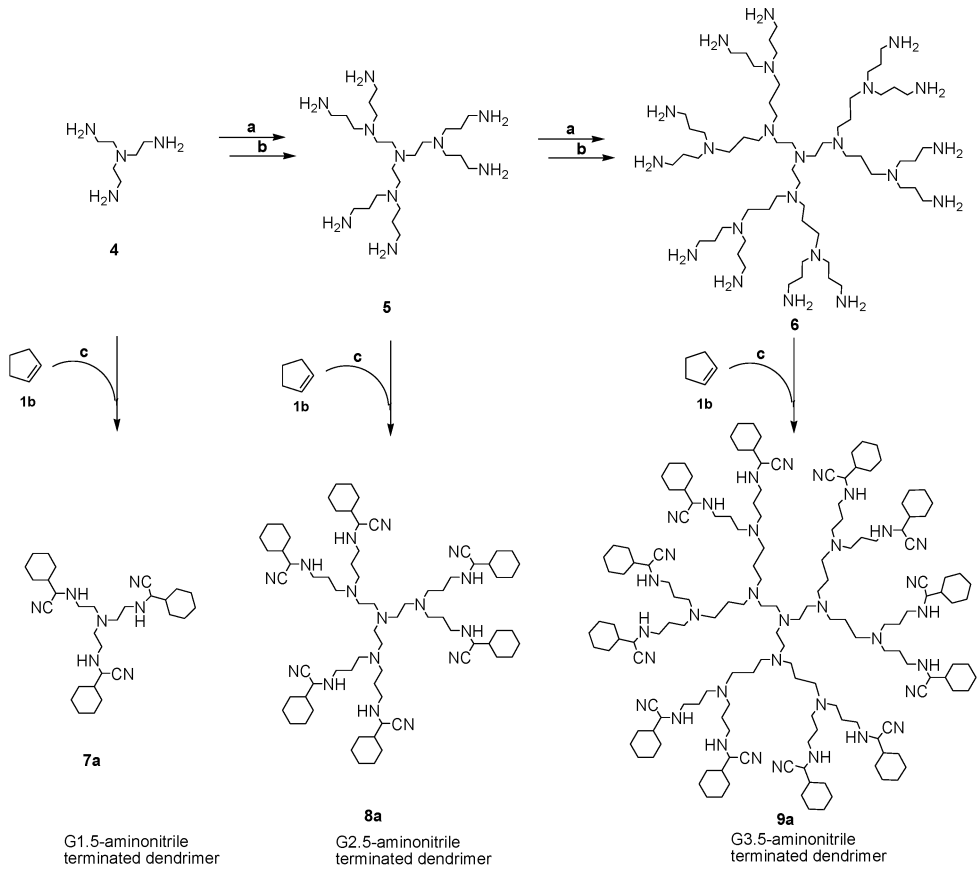
Similarly, using the second option and to extend the generality of this method further, polyallyl ether **10** obtained from polyglycerols[16,17] can also be functionalized by α-aminonitriles by this method. Polyglycerols are known to offer biocompatible cores and polyether having amino acids functional groups on the periphery might have potential for biological applications.[18] In the first step a regioselective hydroformylation was carried out in the presence of XANTHPHOS (ligand) and $Rh(acac)(CO)_2$.[19,20] The catalyst and ligand were used in 1:4 ratios. The polyaldehyde **11a** was obtained in high selectivity (*n:iso*, 96:4) with full conversion (Scheme 4). Linear to branched ratio (*n:iso*) and conversion were determined by ^{1}H NMR spectroscopy. In the second step amine was added followed by the addition of TMSCN to get polyethers with α-aminonitrile terminal groups. This reaction sequence was performed using different primary amines **12a–c** and corresponding dendritic α-aminonitriles **13a–c** were obtained in good yields (Table 3). Final products were obtained in pure form after dialysis.

Table 3 α-Aminonitrile terminated PG *via* hydroformylation/Strecker synthesis

Entry	R-NH_2 (**12a–c**)	Product	*Mw* [kDa]	Yield [%]
1	Cyclohexanamine	**13a**	16.4	64
2	Cyclopentanamine	**13b**	15.5	67
3	Benzylamine	**13c**	17.4	71

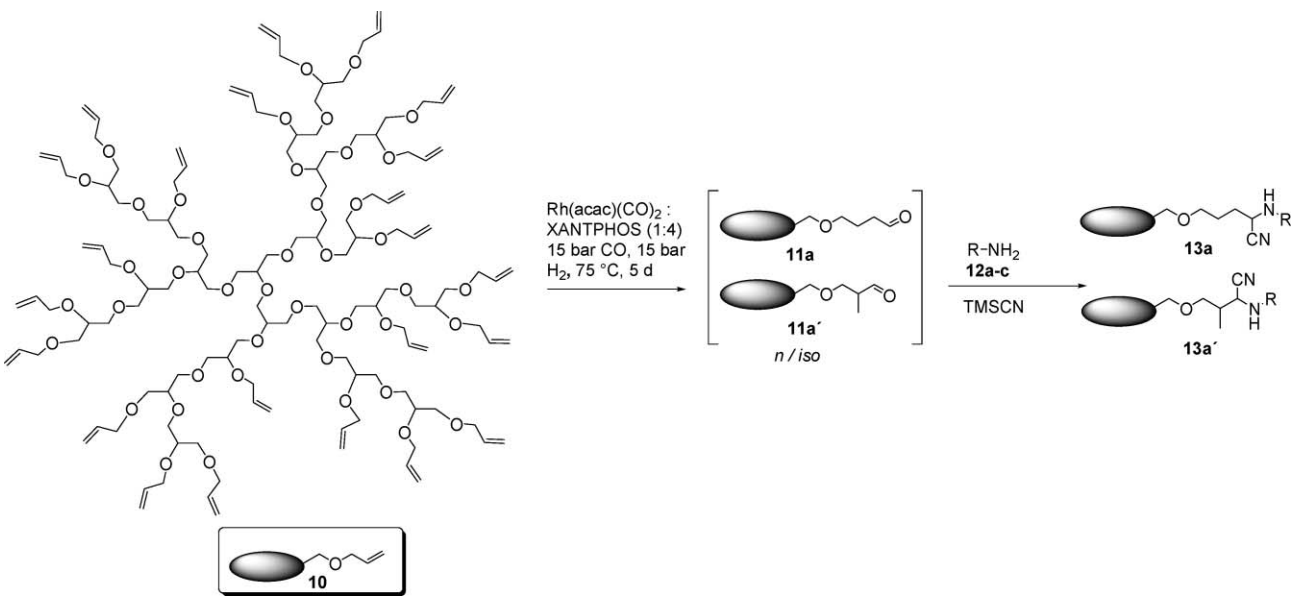
Thus, this method allows the modification of hyperbranched polyallyl ethers **10** with *N*-substituted α-aminonitriles in one step. A remarkable increase in the molecular weight (*Mw* ~17400) of the polymer backbone was observed, which is another advantage that makes these nanoparticles attractive for separation by membrane filtration techniques.

As described earlier, α-amino acids and/or 1,2-diamines can be obtained on hydrolysis or reduction of nitrile groups in the Strecker product (Scheme 1). To show this exemplarily, **7a** was hydrolyzed to give a dendritic polyamine molecule **14** with 3 α-amino acid groups in 85% overall yield (for two step hydroformylation/Strecker synthesis and hydrolysis). The nitrile groups in Strecker product **7** were reduced by Raney-cobalt (200 wt%) under a hydrogen atmosphere (40 bars) in 2 h to get polyamine **15** in 83% yield (Scheme 5). Thus starting from an olefin, amine and TMSCN, the desired racemic α-amino acids and/or 1,2-diamines can be synthesized by employing this one-pot synthetic methodology.

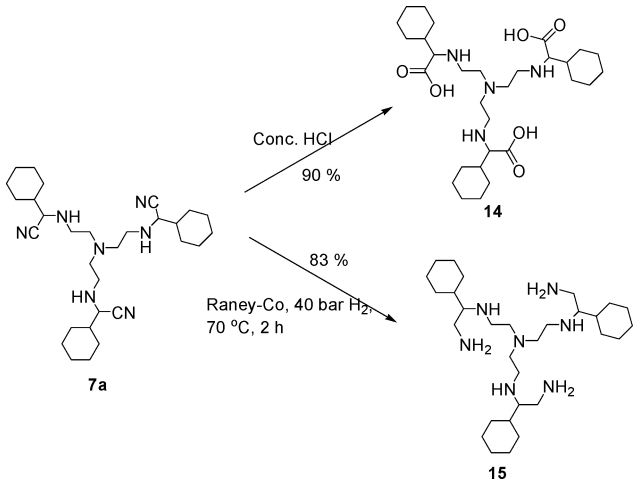


[a] Acrylnitrile, H_2O, 3h, Reflux. [b] Raney-Co (200 wt %) 40bar H_2, 70 °C, 3h. [c] *1)*[Rh(COD)Cl]$_2$, CO/H_2(40/40bar),48h, 100 °C. *2)* TMSCN, 12h, r.t

Scheme 3 α-Aminonitrile terminated dendrimers *via* hydroformylation/Strecker synthesis.



Scheme 4 α-Aminonitrile terminated polyglycerols *via* one-pot hydroformylation/Strecker synthesis.



Scheme 5 Transformation of α-aminonitriles to α-amino acids and/or to 1,2-diamine surface groups.

Conclusions

In conclusion, we have developed a new method for an efficient synthesis of α-aminonitriles in good to excellent yields. Our one-pot approach relies on hydroformylation of olefins to aldehydes in the first step. In the following step aldehyde condenses with amine followed by addition of TMSCN to give respective α-aminonitriles. This method allows variation of different alkyl groups at the α position of aminonitriles and synthesis of polyfunctional compounds. We have also shown that this method provides a facile route for the functionalization of dendritic molecules either starting from a polyamine core molecule with primary amine terminal groups and/or polyether with olefinic terminal groups. The resulting α-aminonitrile terminated dendrimers have good solubility properties and might provide potential for pharmaceutical applications. Thus this procedure is a powerful tool for the synthesis of α-aminonitriles and functionalization of dendritic structures.

Experimental section

All general chemicals were purchased and used as such. ^{1}H and ^{13}C NMR spectra were recorded at room temperature with Bruker DRX 400 and DRX 500 spectrometers using $CDCl_3$ as solvent and TMS as internal standard. Infrared spectroscopy was performed on a Nicolet Impact 400 D spectrometer using KBr pallets or as disks with KBr. High resolution mass analyses were performed on a JEOL JMS-SX 102A. ESI-MS was done on Finnigan ThermoQuest TSQ (ESI). Reactions under pressure were carried out in a magnetically stirred BERGHOF type A (250 ml, 4 glass vials at 20 ml) pressure vessel, a comparable house made autoclave (100 ml) or in a PARR autoclave.

General procedure A: hydroformylation/Strecker synthesis

An olefin (10 mmol) and $[Rh(cod)Cl]_2$ (15 mg, 0.3 mol%) were dissolved in 8 mL of dioxane in a glass vessel and placed in an autoclave. The autoclave was pressurized with 60–80 bars of CO/H_2 (1:1) and heated at 100–120 °C for 48–72 hours. After cooling, the pressure was released and amine (10 mmol) was added and the reaction mixture was stirred for 5 min. Then TMS-CN (10 mmol) was added and reaction mixture was stirred for 12 hours. Solvent was removed under reduced pressure and the crude product was purified by column chromatography.

General procedure B: synthesis of α-aminonitrile terminated polyamine dendrimers

An olefin (1.6 equiv. to each NH_2-group present in polyamine core) and $[Rh(cod)Cl]_2$ (0.3 mol%) were dissolved in 8 mL of dioxane in a glass vessel and placed in an autoclave. The autoclave was pressurized with 60–80 bars of CO/H_2 (1:1) and heated at 100–120 °C for 48–72 hours. The polyamine core was dissolved in 5 mL of methanol and added slowly to the aldehyde solution. After 30 min of stirring at room temprature TMSCN was added slowly and the reaction mixture was stirred for another 12 h at room temperature. Solvent was removed under reduced pressure and the crude product was purified by dialysis in chloroform or methanol.

General procedure C: functionalization of PG with α-aminonitrile terminated shell

Polyallyl ether **10**, $Rh(acac)(CO)_2$ (0.5 mol%), and xanthphos (2 mol%) were dissolved in dry toluene in a glass vessel and placed in an autoclave. The autoclave was pressurized with 30 bars of CO/H_2 (1:1) and heated at 75 °C for 3 days. After cooling, amine was added to the crude PG-aldehyde (^{1}H-NMR was used to confirm full conversion) and stirred for 1 hour at room temperature. Then, TMS-CN was added and the reaction mixture was stirred for 12 hours. Solvent was removed under reduced pressure. The crude product was purified by running dialysis in methanol/chloroform overnight.

Cyclohexylamino-cyclopentyl-acetonitrile (3a)

The general procedure **A** was followed with cyclopentene (102 mg, 1.5 mmol), cyclohexylamine (149 mg, 1.5 mmol) and TMSCN (149 mg, 1.5 mmol) to give cyclohexylamino-cyclopentyl-acetonitrile (**3a**) (216 mg, 1.05 mmol, 70%) as yellow oil.^{1}H-NMR ($CDCl_3$): δ[ppm] = 0.93–1.86 (19H, m), 2.15 (1H, m), 2.69 (1H, m), 3.50 (1H, d, ^3J = 6.99 Hz). ^{13}C-NMR ($CDCl_3$, δ): 24.53, 25.06, 25.08, 25.23, 25.83, 28.88, 29.67, 31.76, 33.90, 42.89, 52.33, 54.60, 120.28. FTIR (neat): 3319, 2929, 2854, 2224, 1464, 1450, 1375, 1350, 1132, 891, 721. LR-MS (FAB): 207.1 [M^++H^+]. HR-MS (FAB): for $C_{13}H_{22}N_2$ Calculated: 207.1783 [M^++H^+], found: 207.1766 [M^++H^+].

(Benzhydryl-amino)-cyclopentyl-acetonitrile (3b)

The general procedure **A** was followed with cyclopentene (400 mg, 5.93 mmol), diphenylmethanamine (860 mg, 4.69 mmol) and TMSCN (728 mg, 7.35 mmol) to give **3b** (1.301 mg, 4.50 mmol, 96%) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.35–2.01 (8H, m), 2.19–2.36 (2H, m), 3.32–3.34 (1H, d, CH, J = 6.72 Hz), 5.16 (1H, s), 7.18–7.59 (10H, m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 25.3, 29.2, 30.0, 43.0, 54.2 (CH_2) 65.6, 120.0, 127.0, 127.7, 128.6, 141.4 (C). IR: (Film, KBr) ν [cm^{-1}] = 761, 893, 1027, 1122, 1305, 1452, 1598, 1700, 1953, 2038, 2225, 2867, 3027, 3313. HR-MS (FAB): for $C_{20}H_{22}N_2$ Calculated: 291.1783 [M^++H^+], found: 291.1798 [M^++H^+].

Benzylamino-cyclopentyl-acetonitrile (3c)

The general procedure **A** was followed with cyclopentene (102 mg, 1.5 mmol), benzylamine (161 mg, 1.5 mmol) and TMSCN (149 mg, 1.5 mmol) to give benzylamino-cyclopentyl-acetonitrile (**3c**) (237 mg, 1.11 mmol, 74%) as yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.25–1.92 (m, 8H,) 2.15–2.25 (m, 1H), 3.37 (d, $J = 7.28$ Hz, 1H), 3.81 (d, $J = 13.05$ Hz, 1H), 4.07 (d, $J = 13.05$ Hz 1H), 7.23–7.28 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 25.0, 25.2, 28.9, 29.6, 42.5, 51.5, 54.4, 119.7, 127.3, 128.2, 128.4, 138.3. FTIR (neat): 3330, 2954, 2868, 1454, 1126, 739, 698. LR-MS (FAB): 215.1 [M^++H^+]. HR-MS (FAB): for $C_{14}H_{18}N_2$ Calculated: 215.147 [M^++H^+], found: 215.1485 [M^++H^+].

Cyclohexyl-cyclohexylamino-acetonitrile (3d)

The general procedure **A** was followed with cyclohexene (124 mg, 1.5 mmol), cyclohexylamine (149 mg, 1.5 mmol) and TMSCN (149 mg, 1.5 mmol) to give cyclohexyl-cyclohexylamino-acetonitrile (**3d**) (228 mg, 1.03 mmol, 69%) as yellow oil.^{1}H-NMR ($CDCl_3$): δ[ppm] = 0.93–1.35 (9H), 1.55–1.84 (11H), 2.68 (m, 1H), 3.42 (1H, d, ^{3}J = 5.98 Hz). ^{13}C-NMR ($CDCl_3$, δ): 24.15, 24.64, 25.58, 25.70, 25.92, 26.02, 28.65, 29.82, 31.85, 33.99, 41.04, 53.28, 54.69, 120.13. FTIR (neat): 3321, 2927, 2850, 2222, 1488, 1452, 1377, 1147, 1128, 906, 849, 835, 789, 758, 696, 625. LR-MS (FAB): 221.1 [M^++H^+]. HR-MS (FAB): for $C_{14}H_{24}N_2$ Calculated: 221.1939 [M^++H^+], found: 221.1956 [M^++H^+].

(Benzhydryl-amino)-cyclohexyl-acetonitrile (3e)

The general procedure **A** was followed with cyclohexene (365 mg, 4.45 mmol), diphenylmethanamine (817 mg, 5.56 mmol) and TMSCN (551 mg, 5.56 mmol) to give (benzhydryl-amino)-cyclohexyl-acetonitrile (**3e**) (1.241 mg, 4.09 mmol, 92%) as white crystalline solid. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.10–1.39 (4H, m), 1.65–2.06 (8H, m, CH_2), 3.25–3.26 (1H, d, CH, J = 5.34 Hz), 5.15 (1H, s), 7.18–7.59 (10H, m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 24.8, 26.1, 29.2, 29.8, 41.2, 54.2 (CH_2), 65.6, 119.8, 127.0, 127.7, 128.6, 141.4 (C). IR: (Film, KBr) ν [cm^{-1}] = 761, 893, 1027, 1122, 1305, 1452, 1598, 1700, 1953, 2038, 2225, 2867, 3027, 3313. HR-MS (FAB): for $C_{21}H_{24}N_2$ Calculated: 304.1939 [M^++H^+] found: 304.1967 [M^++H^+].

Benzylamino-cyclohexyl-acetonitrile (3f)

The general procedure **A** was followed with cyclohexene (124 mg, 1.5 mmol), benzylamine (161 mg, 1.5 mmol) and TMSCN (149 mg, 1.5 mmol) to give benzylamino-cyclohexyl-acetonitrile (**3f**) (253 mg, 1.11 mmol, 74%) as yellow oil. ^{1}H-NMR ($CDCl_3$): δ[ppm] = 1.26–1.47 (4H, m), 1.54–1.73 (4H, m), 1.80–1.92 (2H, m), 2.20 (2H, m), 3.37 (1H, d, ^{3}J = 7.28 Hz), 3.81 (1H, m), 4.06 (1H, m), 7.24–7.37 (5H). ^{13}C-NMR ($CDCl_3$, δ): 25.1, 25.2, 29.0, 29.6, 42.5, 51.6, 54.5, 119.8, 127.4, 128.2, 128.4, 138.4. FTIR (neat): 3330, 3086, 3062, 3030, 2954, 2868, 2224, 1604, 1496, 1454, 1363, 1321, 1126, 1076, 1028, 887, 739, 698. LR-MS (FAB): 229.1 [M^++H^+]. HR-MS (FAB): for $C_{15}H_{20}N_2$ Calculated: 229.1626 [M^++H^+], found: 229.1647 [M^++H^+].

2-Cyclohexylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (3g)

The general procedure **A** was followed with methylallylphthalimide (301 mg, 1.5 mmol), cyclohexylamine (148 mg, 1.5 mmol) and TMSCN (148 mg, 1.5 mmol) to give 2-cyclohexylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (**3g**) (468 mg, 1.38 mmol, 92%) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.96 (3H, d, $^3J = 6.78$ Hz), 1.13–1.14 (4H, m), 1.53–1.74 (H, m), 1.82–1.86 (1H, m), 2.25–2.39 (2H, m), 2.65–2.71 (2H, m), 3.58–3.68 (2H, m), 3.73–3.88 (1H, m), 7.71–7.74 (2H, m), 7.82–7.85 (2H, m). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 17.6, 24.3, 26.0, 30.1, 31.8, 38.6, 45.7, 54.6, 120.5, 123.4, 131.9, 134.1, 168.7. IR: (Film, KBr) ν [cm^{-1}] = 794, 873, 1051, 1189, 1253, 1336, 1398, 1436, 1467, 1720, 1772, 2223, 2854, 2929, 3316, 3467. LR-MS (FAB): 340.33 [M^++H^+]. HR-MS (FAB): for $C_{20}H_{25}N_3O_2$ Calculated: 340.1947 [M^++H^+], found: 340.1966 [M^++H^+].

2-(Benzhydryl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (3h)

The general procedure **A** was followed with methylallylphthalimide ((500 mg, 2.48 mmol), diphenylmethanamine (517 mg, 2.73 mmol) and TMSCN (271 mg, 2.73 mmol) to give **3h** (988 mg, 2.33 mmol, 95%) as solid. mp = 79 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.89–1.00 (3H, d, CH_3, $J = 6.53$ Hz), 1.25–1.48 (1H, m), 1.59–1.75 (1H, m), 2.06–2.28 (3H, m), 3.51–3.69 (2H, m), 5.22 (1H, s), 7.1–7.42 (10H, m), 7.67–7.73 (2H, m), 7.81–7.87 (2H, m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 17.9, 30.0, 37.5, 44.0, 60.1, 60.7, 123.5, 127.3, 128.8, 134.3, 45.7, 169.0. IR: (Film, KBr) ν [cm^{-1}] = 700, 761, 842, 900, 1058, 1261, 1452, 1492, 1758, 2123, 2925, 2958, 3307, 3372. ESI-MS = 424.2 [M + H]$^+$. HR-MS (FAB): for $C_{27}H_{25}N_3O_2$ Calculated: 424.1947 [M^++H^+]. found: 424.1979 [M^++H^+].

2-Benzylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (3i)

The general procedure **A** was followed with methylallylphthalimide (301 mg, 1.5 mmol), benzylamine (160 mg, 1.5 mmol) and TMSCN (148 mg, 1.5 mmol) to give 2-benzylamino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (**3i**) (400 mg, 1.15 mmol, 77%) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.85–0.97 (3H, d, $^3J = 6.78$ Hz), 1.62 (1H, m), 1.82–1.93 (1H, m), 2.34–2.41 (1H, m), 3.56–3.68 (4H, m), 3.76–3.88 (1H, m), 4.09–4.14 (1H, m), 7.26–7.29 (5H, m), 7.71–7.74 (2H, m), 7.82–7.85 (2H, m). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 17.1, 29.7, 37.8, 43.1, 47.9, 51.6, 119.8, 123.3, 127.5, 128.3, 131.8, 134.0, 168.5. IR: (Film, KBr) ν [cm^{-1}] = 725, 912, 1052, 1124, 1359, 1398, 1614, 1716, 1772, 2223, 2933, 2964, 3324. LR-MS (FAB): 348.25 [M^++H^+]. HR-MS (FAB): for $C_{21}H_{21}N_3O_2$ Calculated: 348.1634 [M^++H^+] found: 348.1647 [M^++H^+].

2-Cyclohexylamino-4-methyl-5-(2-oxo-oxazolidin-3-yl)-pentanenitrile (3j)

The general procedure **A** was followed with methylallyloxazolidinone (500 mg, 3.54 mmol), cyclohexylamine (380 mg, 3.54 mmol) and TMSCN (351 mg, 3.54 mmol) to give 2-cyclohexylamino-4-methyl-5-(2-oxo-oxazolidin-3-yl)-pentanenitrile (**3j**) (910 mg,

3.25 mmol, 92%) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.93–0.99 (3H, dd, CH_3, J = 7.03 Hz, J = 7.03), 1.10–1.38 (6H, m), 1.51–1.63 (2H, m), 1.64–1.80 (4H, m), 1.82–1.90 (1H, m), 1.98–2.17 (2H, m), 2.63–2.76 (1H, m), 3.05–3.22 (2H, m), 3.48–3.65 (2H, m), 3.66–3.76 (2H, m), 4.25–4.38 (2H, m). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 17.2, 24.4, 25.6, 28.4, 33.7, 38.2, 45.6, 49.9, 54.5, 61.5, 120.2, 158.7. IR: (Film, KBr) ν [cm^{-1}] = 762, 893, 1133, 1376, 1468, 1766, 2222, 2661, 2843, 3311, 3469. LR-MS (FAB): 280.1. HR-MS (FAB): for $C_{15}H_{25}N_3O_2$ Calculated: 280.1947 [M^++H^+] found: 280.2003 [M^++H^+].

2-(Benzhydryl-amino)-4-methyl-5-(2-oxo-oxazolidin-3-yl)-pentanenitrile (3k)

The general procedure **A** (hydroformylation/Strecker synthesis) was followed with methylallyloxazolidinone ((500 mg, 3.54 mmol), diphenylmethanamine (714 mg, 3.89 mmol) and TMSCN (386 mg, 3.89 mmol) to give **3k** (1.268 g, 4.48 mmol, 98%) as oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.83–1.03 (3H, m), 1.22–1.52 (1H, m), 1.56–1.78 (1H, m), 1.94 (2H, m), 2.98–3.26 (2H, m), 3.44–3.78 (3H, m), 4.21–4.39 (2H, m), 5.23 (1H, s), 7.18–7.49 (10H, m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 17.5, 28.2, 37.1, 45.5, 51.0, 60.4, 62.0, 127.3, 128.8, 145.7, 159.3 (CO). IR: (Film, KBr) ν [cm^{-1}] = 700, 761, 842, 900, 1058, 1261, 1452, 1492, 1758, 2123, 2925, 2958, 3307, 3372 (m). ESI-MS = 364.4 [M + H]$^+$. HR-MS (FAB): for $C_{22}H_{25}N_3O_2$ Calculated: 364.1947 [M + H]$^+$ found: 364.1974 [M + H]$^+$.

2-Benzylamino-4-methyl-5-(2-oxo-oxazolidin-3-yl)-pentanenitrile (3l)

The general procedure **A** was followed with methylallyloxazolidinone (500 mg, 3.54 mmol), benzylamine (379 mg, 3.54 mmol) and TMSCN (351 mg, 3.54 mmol) to give 2-benzylamino-4-methyl-5-(2-oxo-oxazolidin-3-yl)-pentanenitrile (**3l**) (913 mg, 3.18 mmol, 89%) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.89–0.99 (3H, dd, CH_3, J = 7.03 Hz, J = 6.53), 1.56–1.68 (1H, m), 1.81–1.90 (1H, m), 2.00–2.18 (2H, m), 3.04–3.24 (2H, m), 3.50–366 (3H, m), 3.79–3.87 (1H, dd, CH_2, J = 5.02 Hz, J = 5.52 Hz), 4.03–4.12 (1H, dd, CH_2, J = 3.51 Hz), 4.26–4.38 (2H, m), 7.33–7.39 (5H, m). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 17.2, 28.5, 37.4, 45.2, 48.0, 50.2, 51.5, 61.6, 120.1, 127.4, 128.2, 138.1, 158.8. IR: (Film, KBr) ν [cm^{-1}] = 754, 1056, 1254, 1372, 1483, 1766, 2226, 2922, 3072, 3060, 3303. HR-MS (FAB): for $C_{16}H_{21}N_3O_2$ Calculated: 288.1634 [M + H]$^+$ found: 288.1699 [M + H]$^+$.

[2-(Bis-{2-[(cyano-cyclopentyl-methyl)-amino]-ethyl}-amino)-ethylamino]-cyclopentyl-acetonitrile (7a)

Polyamine **7a** was synthesized according to the general procedure **B** from cyclopentene (150 mg, 1.53 mmol) and TMSCN (167 mg, 1.69 mmol) and tris(aminoethyl)amine (64 mg, 0.44 mmol) as amine core. The product, **7a**, was obtained as brown oil (163 mg, 79%) without any further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.40–1.92 (26H, m), 2.51–2.77 (16H, m), 3.45 (3H, d, CH, J = 8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 25.5, 25.7, 29.6, 30.2, 53.3, 53.7, 56.2, 67.4, 120.5. IR (Film, KBr): ν [cm^{-1}] = 613, 746, 873, 888, 1048, 1082, 1122, 1253, 1453, 1712, 2222, 2866, 2955, 3312. ESI-MS: m/z = 468.38 (M + H$^+$). LR-MS (FAB): 468.3. HR-MS (FAB): for $C_{27}H_{45}N_7$ Calculated: 468.3738 [M^++H^+] found: 468.3763 [M^++H^+].

[2-(Bis-{2-[(cyano-cyclohexyl-methyl)-amino]-ethyl}-amino)-ethylamino]-cyclohexyl-acetonitrile (7b)

Polyamine **7b** was synthesized according to the general procedure **B** from cyclohexene (410 mg, 5 mmol) and TMSCN (496 mg, 5 mmol) and tris(aminoethyl)amine (224 mg, 1.53 mmol) as amine core. The product, **7b**, was obtained as brown oil (670 mg, 86%) without any further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.06–1.86 (33H, m), 2.44–2.66 (12H, m), 3.32–3.35 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 25.8, 26.1, 26.4, 28.2, 28.5, 29.2, 30.3, 53.1, 53.6, 57.2, 66.3, 120.1. IR (Film, KBr): ν [cm^{-1}] = 613, 751, 841, 873, 1047, 1082, 1122, 1254, 1451, 1668, 2223, 2853, 2930, 3318. ESI-MS: m/z = 510.43 [M^++H^+]. HR-MS (FAB): for $C_{30}H_{51}N_7$ Calculated: 510.4206 [M^++H^+] found: 510.4225 [M^++H^+].

2-[2-(Bis-{2-[1-cyano-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-methyl-butylamino]-ethyl}-amino)-ethylamino]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-methyl-pentanenitrile (7c)

Polyamine **7c** was synthesized according to the general procedure **B** from methylallylphthalimide (1.006 g, 5 mmol) and TMSCN (496 mg, 5 mmol) and tris(aminoethyl)amine (224 mg, 1.53 mmol) as amine core. After dialysis in methanol, the product (689 mg, 52%) was obtained as dark brown oil. ^{1}H NMR: (500 MHz, CD_3OD): δ[ppm] = 0.87–1.10 (m), 1.57–1.99 (m), 2.33–2.99 (m), 3.54–3.78 (m), 7.43–7.65 (m), 7.73–7.93 (m). ^{13}C NMR: (100 MHz, CD_3OD): δ[ppm] 29.9, 30.5, 37.2, 44.1, 46.0, 59.9, 123.1, 127,9, 134.4, 136.1, 170.4. IR (Film, KBr): ν [cm^{-1}] = 1058, 1120, 1311, 1380, 1448, 1560, 1633, 1710, 2211, 2489, 2871, 2931, 3378. ESI-MS: m/z = 867.4 [M + H]$^+$ HR-MS (FAB): for $C_{48}H_{54}N_{10}O_6$ Calculated: 867.4228 [M^++H^+] found: 867.4251 [M^++H^+].

[3-((2-{Bis-[2-(bis-{3-[(cyano-cyclopentyl-methyl)-amino]-propyl}-amino)-ethyl]-amino}-ethyl)-{3-[(cyano-cyclopentyl-methyl)-amino]-propyl}-amino)-propylamino]-cyclopentyl-acetonitrile (8a)

Polyamine dendrimer **8a** was synthesized according to the procedure **B** from cyclopentene (278 mg, 4.09 mmol) and TMSCN (405 mg, 4.09 mmol) and polyamine (200 mg, 0.409 mmol) as amine core. After dialysis in chloroform, the product was obtained as brown oil (0.347 g, 81%).^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.33–1.91 (66H, m), 2.43–2.74 (36H, m), 3.32–3.46 (6H, d, J = 6.53 Hz). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 25.6, 25.8, 27.3, 29.6, 43.0, 47.2, 52.5, 53.2, 56.2, 120.5. IR (Film, KBr): ν [cm^{-1}] = 755, 873, 1124, 1373, 1450, 1679, 2015, 2221, 2852, 2933, 3324. ESI-MS: m/z = 1131.9 [M + H]$^+$ HR-MS (ES): for $C_{66}H_{114}N_{16}$ Calculated: 1131.9412 [M + H]$^+$, found: 1131.9427 [M + H]$^+$.

[3-((2-{Bis-[2-(bis-{3-[(cyano-cyclohexyl-methyl)-amino]-propyl}-amino)-ethyl]-amino}-ethyl)-{3-[(cyano-cyclohexyl-methyl)-amino]-propyl}-amino)-propylamino]-cyclohexyl-acetonitrile (8b)

Polyamine dendrimer **8b** was synthesized according to the general procedure **B** from cyclohexene (821 mg, 10 mmol) and TMSCN (992 mg, 10 mmol) and polyamine (489 mg, 1 mmol) as amine core.

After dialysis in chloroform, the product **8b** was obtained as brown oil (1.035 g, 85%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.07–1.34 (36H, m), 1.55–1.93 (48H, m), 2.62 (36H, m), 3.33 (6H, d, J = 4.52 Hz). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 25.6, 26.0, 28.8, 29.7, 36.5, 40.6, 46.5, 56.76, 119.81. IR (Film, KBr): ν [cm^{-1}] = 755, 856, 873, 1124, 1373, 1450, 2221, 2852, 2927, 3257, 3320. ESI-MS: m/z = 1216.1 [M + H]$^+$. HR-MS (ES): for $C_{72}H_{126}N_{16}$ Calculated: 1216.0351 [M + H]$^+$, found: 1216.0374 [M + H]$^+$.

Polyamine dendrimer (8c)

Polyamine dendrimer **8c** was synthesized according to the general procedure **B** from methylallylphthalimide (823 mg, 4.09 mmol) and TMSCN (405.7 mg, 5 mmol) and polyamine (200 mg, 0.409 mmol) as amine core. After dialysis in methanol, the product was obtained as brown oil (410 mg, 52%). ^{1}H NMR: (500 MHz, CD_3OD): δ[ppm] = 0.87–1.10 (m), 1.57–1.99 (m), 2.33–2.99 (m), 3.54–3.78 (m), 7.43–7.65 (m), 7.73–7.93 (m). ^{13}C NMR: (100 MHz, CD_3OD): δ[ppm] 29.9, 30.5, 37.2, 44.1, 46.0, 59.9, 123.1, 127,9, 134.4, 136.1, 170.4. IR (Film, KBr): ν [cm^{-1}] = 1058, 1120, 1311, 1380, 1448, 1560, 1633, 1710, 2211, 2489, 2871, 2931, 3378. ESI-MS: m/z = 1919.0 [M + H]$^+$. HR-MS (ES): for $C_{108}H_{135}N_{21}O_{12}$ Calculated: 1919.0599 [M + H]$^+$, found: 1919.0651 [M + H]$^+$.

Polyamine dendrimer (9a)

Polyamine dendrimer **9a** was synthesized according to the general procedure **B** from cyclopentene (231 mg, 3.4 mmol) and TMSCN (337 mg, 3.4 mmol) and polyamine (200 mg, 0.170 mmol) as amine core. After dialysis in chloroform, the product was obtained as brown oil (0.360 g, 83%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.46–1.92 (m), 2.51–2.86 (m), 3.49 (m). ^{13}C NMR: (400 MHz, $CDCl_3$): δ[ppm] = 25.6, 26.0, 28.8, 29.7, 36.5, 40.6, 46.5, 56.76, 119.81. IR (Film, KBr): ν [cm^{-1}] = 755, 873, 1124, 1373, 1450, 1679, 2015, 2221, 2852, 2933, 3324. HR-MS (ES): for $C_{144}H_{252}N_{34}$ Calculated: 1229.5382 [M + H]$^{+2}$, found: 1229.5373 [M + H]$^{+2}$.

Polyamine dendrimer (9b)

Polyamine dendrimer **9b** was synthesized according to the general procedure **B** from cyclohexene (410 mg, 5 mmol) and TMSCN (496 mg, 5 mmol) and polyamine (293 mg, 0.25 mmol) as amine core. After dialysis in chloroform, the product was obtained as brown oil (0.615 g, 93%). ^{1}H NMR: (500 MHz, $CDCl_3$): δ[ppm] = 1.03–1.34 (m), 1.44–1.91 (m), 2.27–2.67 (m), 2.78–2.94 (m) 3.19–3.35 (d, 12H, CH, J = 4.74 Hz). ^{13}C NMR: (500 MHz, $CDCl_3$): δ[ppm] = 27.1, 27.2, 27.5, 28.5, 30.3, 31.2, 42.2, 48.4, 53.7, 58.2, 121.2. IR (Film, KBr): ν [cm^{-1}] = 755, 840 (m), 873, 1049, 1124, 1373, 1450, 1654, 2021, 2852, 2944, 3320. HR-MS (ES): for $C_{156}H_{276}N_{34}$ Calculated: 1313.6321 [M + H]$^{+2}$, found: 1313.6309 [M + H]$^{+2}$.

Polyamine dendrimer (9c)

Polyamine dendrimer **9c** was synthesized according to the general procedure **B** from methylallylphthalimide (685 mg, 3.4 mmol) and TMSCN (337 mg, 3.4 mmol) and polyamine (200 mg, 0.170 mmol) as amine core. After dialysis in methanol, the product was obtained as brown oil (430 mg, 62%). ^{1}H NMR: (500 MHz, CD_3OD): δ[ppm] = 0.87–1.10 (m), 1.57–1.99 (m), 2.33–2.99 (m), 3.54–3.78 (m), 7.43–7.65 (m), 7.73–7.93 (m). ^{13}C NMR: (100 MHz, CD_3OD): δ[ppm] 29.9, 30.5, 37.2, 44.1, 46.0, 59.9, 123.1, 127,9, 134.4, 136.1, 170.4. IR (Film, KBr): ν [cm^{-1}] = 1058, 1120, 1311, 1380, 1448, 1560, 1633, 1710, 2211, 2489, 2871, 2931, 3378. Elemental analysis (%) calculated for $C_{228}H_{288}N_{46}O_{24}$: C: 67.5; H: 7.1; N: 15.8. found: C: 67.3; H: 7.3, N: 15.2.

PG with α-amino nitrile shell (13a)

According to the general procedure **C**, PG with α-amino nitrile shell **13a** was synthesized from 500 mg (13.5 mmol/g allyl group), cyclopentylamine 646 mg (7.59 mmol) and TMSCN 752 mg (7.59 mmol) as yellow solid (920 mg, 84%). mp = 93 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.69–1.80 (m), 3.37–3.51 (m), 5.08 (s), 7.21–7.38 (m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 26.1, 30.8, 36.5, 48.4, 59.8, 65.6, 120.3, 127.2, 128.6, 129.0, 141.5. IR: (Film, KBr) ν [cm^{-1}] = 800, 1106, 1259, 1454, 2354, 2867, 2923, 3405. Elemental analysis (%) calculated: C: 66.9; H: 9.6; N: 11.3. found: C: 66.5; H: 9.1; N: 11.6.

PG with α-amino nitrile shell (13b)

According to the general procedure **C**, PG with α-amino nitrile shell **13b** was synthesized from 500 mg (13.5 mmol/g allyl group), cyclohexylamine 753 mg (7.59 mmol) and TMSCN 752 mg (7.59 mmol) as yellow solid (905 mg, 84%). mp = 99 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 0.95–0.98 (m), 1.13–1.31 (m), 1.58–1.86 (m), 2.6 (m), 3.53–3.63. ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 25.7, 26.1, 27.3, 32.4, 33.3, 35.4, 48.8, 51.9, 56.2, 71.0, 72.1, 122.1. IR (Film, KBr): ν [cm^{-1}] = 746, 1106, 1259, 1454, 2354, 2867, 2923, 3409. Elemental analysis (%) calculated: C: 65.8; H: 9.3; N: 11.9. found: C: 65.5; H: 9.1; N: 11.4.

PG with α-amino nitrile shell (13c)

According to the general procedure **C**, PG with α-amino nitrile shell **13c** was synthesized from 500 mg (13.5 mmol/g allyl group), benzylamine 753 mg (7.59 mmol) and TMSCN 752 mg (7.59 mmol) as off-white semi solid (924 mg, 88%). mp = 103 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ[ppm] = 1.66–1.82 (m), 3.44–3.57 (m), 3.37 (m), 4.01 (m), 7.16–7.32 (m). ^{13}C NMR: (100 MHz, $CDCl_3$): δ[ppm] = 22.9, 27.8, 31.9, 51.0, 53.0, 70.9, 71.0, 121.8, 128.9, 130.0, 130.5. IR (Film, KBr): ν [cm^{-1}] = 800, 1106, 1259, 1454, 2354, 2867, 2923, 3405. Elemental analysis (%) calculated: C: 69.5; H: 7.7; N: 11.2; found: C: 69.2; H: 7.3; N: 10.8.

[2-(Bis-{2-[(carboxy-cyclohexyl-methyl)-amino]-ethyl}-amino)-ethylamino]-cyclohexyl-acetic acid (14)

Polyamine **7a** (300 mg, 0.58 mmol) was dissolved in a small amount of concentrated HCl and heated at reflux temperature for 3 h. To the reaction mixture, 5 g of sodium sulfate were added. Later the solid was washed with methanol (50 mL × 3). Solvent was removed under reduced pressure to get **14** (298 mg, 90%).^{1}H-NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.11–1.79 (33H, m), 2.32–2.63 (12H, m), 3.20 (3H, br), 3.45–3.51 (3H, m), 9.64 (3H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 24.9, 26.3, 26.4, 28.4, 28.9, 29.2, 30.3, 53.4, 53.1, 57.2, 62.1, 229.1. IR (Film, KBr): ν [cm^{-1}] = 755, 844, 873, 1047, 1082, 1122, 1254, 1451, 1706, 2853, 2931, 3434.

ESI-MS: $m/z = 567.4$ $[M + H]^+$ HR-MS (FAB): for $C_{30}H_{54}N_4O_6$ Calculated: 567.4043 $[M + H]^+$, found: 567.4069 $[M + H]^+$.

N1-(2-{Bis-[2-(2-amino-1-cyclohexyl-ethylamino)-ethyl]-amino}-ethyl)-1-cyclohexyl-ethane-1,2-diamine (15)

Polyamine **7a** (500, 0.98 mmol) was dissolved in 50 mL of H_2O:MeOH (95:5) and poured in an autoclave. Raney-cobalt (1 g, 200 wt%) was added to the reaction mixture and the autoclave was set under reduction conditions (40 bar H_2, 70 °C, and 3 h). Then autoclave was cooled down to room temperature and the catalyst was filtered on a sintered glass filter. Solvent was removed under reduced pressure to get polyamine **15** (425 mg, 83%) without any further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.98–1.75 (36H, m), 2.10 (br), 2.44–2.66 (21H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 23.7, 26.8, 27.3, 28.2, 28.4, 29.2, 31.4, 39.4, 53.4, 53.1, 57.2, 60.6. IR (Film, KBr): ν [cm^{-1}] = 944, 1103, 1307, 1384, 1465, 1600, 2821, 2857, 2935, 3355. ESI-MS: $m/z = 567.4$ $[M + H]^+$ HR-MS (FAB): for $C_{30}H_{63}N_7O_6$ Calculated: 522.5145 $[M + H]^+$, found: 522.5172 $[M + H]^+$.

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Notes and references

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