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SYNTHESIS OF A G-2 MELAMINE BASED DENDRON HAVING 2-AMINO-2-METHYLPROPANOL UNITS AS PERIPHERAL GROUPS

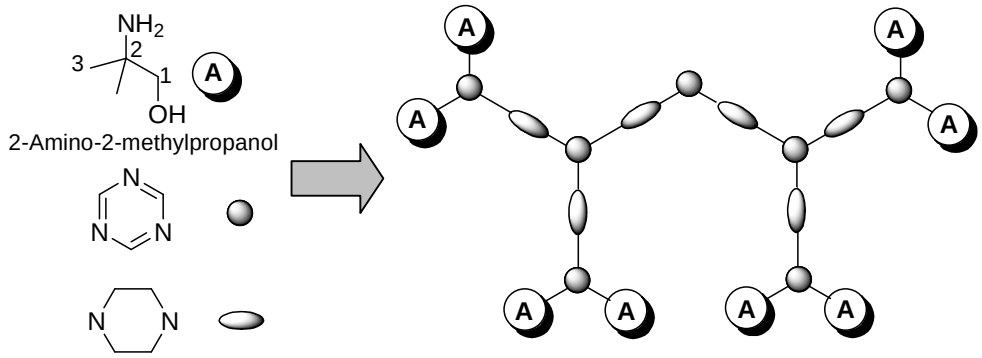
ANTAL ZOLTÁN, CARMEN BATIU, MIRCEA DARABANTU*

ABSTRACT. Starting from 2-amino-2-methylpropanol, a concise five steps iterative synthesis of a title type compound is described

Keywords: *amino alcohols, dendrons, iterative synthesis, melamines*

INTRODUCTION

In continuation of our recent findings [1] in the field of *N*-substituted-2,4,6-triaimino-*s*-triazines' (*melamines*) based dendrons and dendrimers by convergent iterative approach starting from *C*-substituted-2-aminopropane-1,3-diols (*serinols*), we report herein the preparation of a G-2 dendron having amino monoalcohol units, namely 2-amino-2-methylpropanol **A**, as peripheral groups (Scheme 1).



Scheme 1

* *"Babes-Bolyai" University, Department of Organic Chemistry, 11 Arany Janos st., 400028, Cluj-Napoca, Romania. darab@chem.ubbcluj.ro*

Indeed, we have previously described our failure, involving C-2-substituted serinols (*e.g.* 2-amino-2-methylpropane-1,3-diol, *methylserinol*) [1b], to perform iterative synthesis directed to dendritic melamines. Hence, we considered of interest to simplify our attempt by using an amino *mono*-alcohol (Scheme 1).

On the other hand, despite availability of a large variety of amino alcohols, there is just one patent referring to amination of cyanuric chloride by 2-amino-2-methylpropanol **A** [2], the resulting *N*-substituted-2-chloro-4,6-diamino-*s*-triazine being claimed as rubber-to-metal adhesion promoter.

RESULTS AND DISCUSSION

1. Synthesis

The convergent strategy we applied is resumed in Scheme 2 [3, 4] [*].

$$\mathbf{A} \xrightarrow{+\,T} \mathbf{TA_2} \xrightarrow{+\,P} \mathbf{PTA_2} \xrightarrow{+\,T} \mathbf{T(PTA_2)_2} \xrightarrow{+\,P} \mathbf{PT(PTA_2)_2} \xrightarrow{+\,T} \mathbf{T^0[PT^I(PT^{II}A_2)_2]_2}$$

A: 2-**A**mino-2-methylpropanol; **T**: cyanuric chloride (*s*-**T**riazine); **P**: **P**iperazine

Scheme 2

It consisted of five steps selective amination of cyanuric chloride (*s*-triazine as branch cell **T**) carried out firstly with the amino alcohol **A** (peripheral group) as nucleophile then with piperazine (as linker **P**). Reaction conditions and quantitative results are shown in Scheme 3.

The first step, consisting of double amination of cyanuric chloride by 2-amino-2-methylpropanol **A**, reached completion at 45 ^{o}C only[*], affording the expected *N*-substituted-chlorodiamino-*s*-triazine **1**. Although compound **1** was contaminated with two side products, presumably the mono- and triaminated *s*-triazines (TLC monitoring), pure analytical samples could be obtained efficiently by simple recrystallisation from boiling ethanol.

We next performed the mono-anchorage of **1** on piperazine, a widely used linker in melamine dendritic chemistry, as connecting cores [4b, 4f, 4h, 5a], generations [4e, 4g, 4i, 5b] or both [4c, 4j, 5c-e]. In our hands, the

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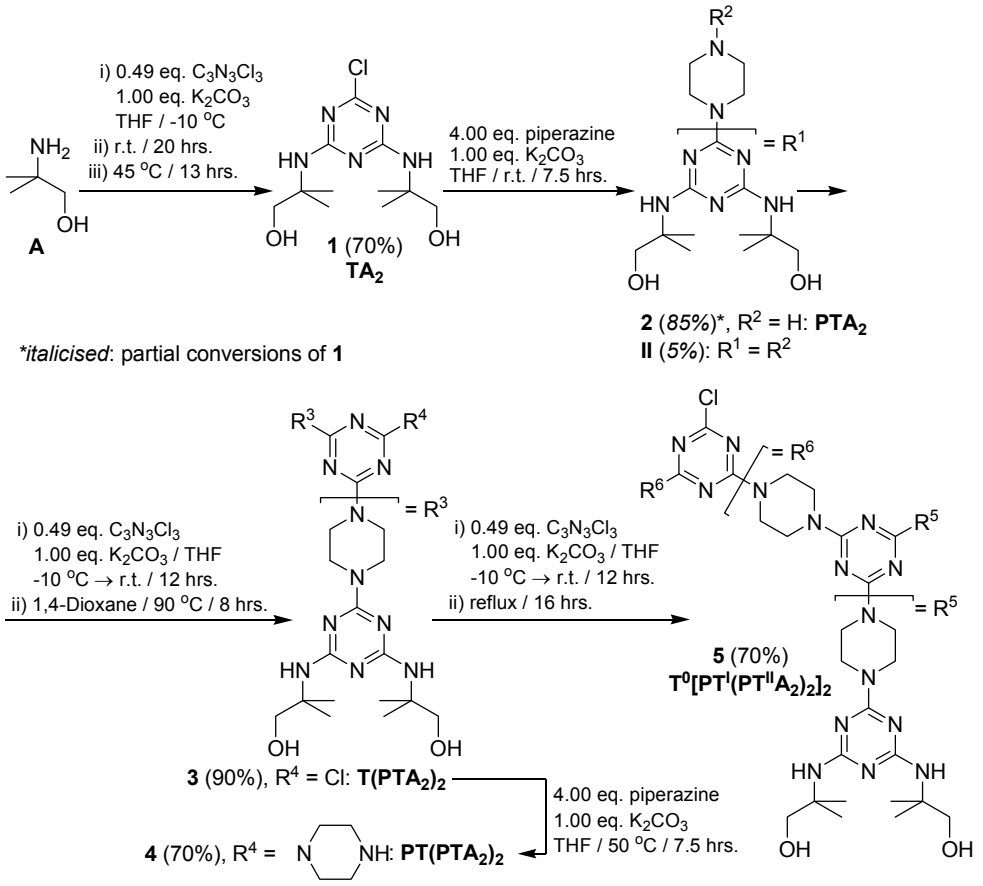
[*] In the present preliminary report nomenclature and symbols earlier recommended by Tomalia [3] and Simanek [4] are used.

[*] The same synthesis performed with a more solvated nucleophile, 2-amino-2-methylpropane-1,3-diol (*methylserinol*), produced the corresponding *N*-substituted-2-chloro-4,6-diamino-*s*-triazine in refluxing THF (24 hrs. 92% yield) with no noticeably side products (see later discussion, compound **1a**) [1b].



Scheme 3

previously reported direct methodologies [4c, 4e, 4i, 5b] (no protecting-deprotecting step), worked properly just in essentially modified conditions. Thus, selectivity (mono- *vs.* double anchorage) was ensured by adding portionwise chloro-*s*-triazines **1** (0.2 eq. each 90 min.) in THF at room temperature, to 4 equivalents of anhydrous piperazine. After each of these periods, TLC monitoring indicated the complete consumption of the starting **1**, the presence of the desired compound **2** together with significant traces of the symmetrical disubstituted piperazine derivative **II**. To our surprise, the formation of the later was observed even in the first stage of the synthesis when the initial molar ratio **1**: HN< groups was, in fact, 0.2:8. Differently than the corresponding analogous of type **2**, originating from *C*-substituted 2-aminopropane-1,3-diols [1b, 1c], compounds **2** and **II** could be eluted and successfully separated by flash column chromatography but on deactivated silica gel only (see **EXPERIMENTAL SECTION**).

No problem we encountered in the preparation of the G-1 dendron **3** obtainable in high yield. We note the harder conditions required by the complete double amination of cyanuric chloride by **2** in comparison with the synthesis of **1**.

Furthermore, we reiterated the mono anchorage of **3** on piperazine and accessed compound **4** in satisfactory yield. The synthetic protocol we used was similar to the above one in the case of **2**, account being taken on the lower reactivity observed for the chloro-*s*-triazine derivative **3**. No significant side products we detected by TLC monitoring; hence, the G-1 dendron **4** could be purified routinely by flash column chromatography on silica gel or direct crystallisation.

The target G-2 dendron **5** was prepared in a comparable large domain of temperature required by the selective and complete double amination (75 ^{o}C) as in the case of the G-1 precursor **3** (100 ^{o}C). Compound **5** was purified simply by twice crystallisations from boiling ethanol. The MS spectrum of **5** confirmed the desired structure (Figure 1).

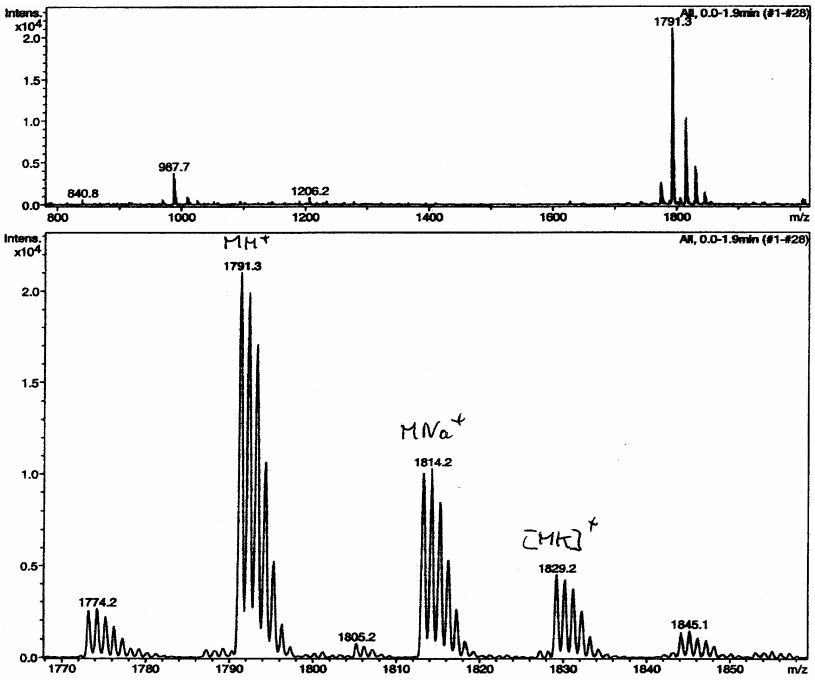


Figure 1: MS Spectrum of compound **5** (ESI+ in acetone-DMSO diluted with ACN) ($C_{77}H_{128}ClN_{41}O_8$ requires 1790.06).

To resume, the G-2 dendron **5** was conveniently obtained in five linear steps in a 26% global yield.

2. Preliminary structural assignments

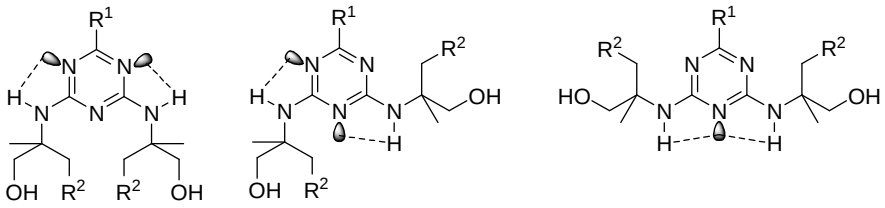
We will limit the present preliminary discussion to NMR data. Besides fully confirming the identity of all compounds **1**-**5** (Scheme 3), at room temperature, they exposed the restricted rotation about the C(*s*-triazine)-N(exocyclic) partial double bonds, caused by the lpN(exocyclic) → π(*s*-triazine) conjugation. This rotational (pro)diastereomerism [1a, 1b]] is already a well established feature as early as 1993 [6] being supported by molecular mechanics [6a], X-Ray data [6c, 6d, 6f] and DNMR techniques. They all revealed this complex type of rotamerism in *N*-substituted melamines and their chlorodiamino-*s*-triazine precursors. Actual progress in the rotational stereochemistry phenomena of dendritic melamines differentiated their *angular* vs. *linear* construction as well as *internal* vs. *peripheral* location of the involved Ar-N< partial double bonds [1b]. In the same approach, using NMR methods, it was possible, very recently, to probe the "choreography of a dendrimer's dance" following classical concepts of conformational analysis applied to *s*-triazine dendrimers [7].

In our series of compounds, the most relevant rotameric behaviour was observed in the NMR spectra of the first two terms, **1** and **2** (Table 1, Figure 2, 3).

Table 1. ^{1}H NMR data (DMSO-d_6, 300 and 500 MHz) of the rotameric behaviour of compounds **1** and **2** in comparison with the chloro-*s*-triazine derivative **1a** of 2-amino-2-methylpropane-1,3-diol (*methylserinol* [1b])

No.	Indicative protons	Discriminating δ (ppm) values				Content of blocked rotamers (%)**		
		(*a*-*a*)*	(*a*-*s*) ≡ (*s*-*a*)		(*s*-*s*)*	(*a*-*a*)	(*a*-*s*) ≡ (*s*-*a*)	(*s*-*s*)
1a**	N(')H	6.41	6.66	6.74	6.78	4	46	50
	O(')H	5.19	4.82	4.65	4.65	*Frozen rotamerism*		
1	N(')H	7.13	7.01	6.94	6.61	66	31	3
	O(')H	4.82	4.82, 4.96			*Frozen rotamerism*		
2	N(')H	5.64 (303 K) → 5.45 (353 K)				*Free rotating structure*		
	O(')H	5.00 (303 K) → 4.75 (353 K)						

*substituent R^1 and propan(di)olic chains as references for descriptors *anti* (*a*) and *syn* (*s*) [6g, 7b]; **percentages calculated by using the best separated ^{1}H NMR signals ("indicative protons"): N(')H only (in **1**), averaged values using signals of N(')H, O(')H (in **1a**); ***compound previously reported by us [1b].



1, **1a**, **2**
anti-anti (*a-a*)

1, **1a**, **2**
anti-syn (*a-s*)

1, **1a**, **2**
syn-syn (*s-s*)

1: R^1 = Cl, R^2 = H; **1a**: R^1 = Cl, R^2 = OH; **2**: R^1 = piperazin-1-yl, R^2 = H

Thus, the withdrawing chlorine substituent in compound **1**, determined the highest π-deficiency of the *s*-triazine ring with respect to all series **1**-**5**, hence the highest C(*s*-triazine)-N(exocyclic) bond order. Accordingly, at room temperature (Table 1), **1** was clearly detected to be a mixture of three blocked rotamers (four anisochronous sites *anti/syn*, frozen rotamerism, [6g]).

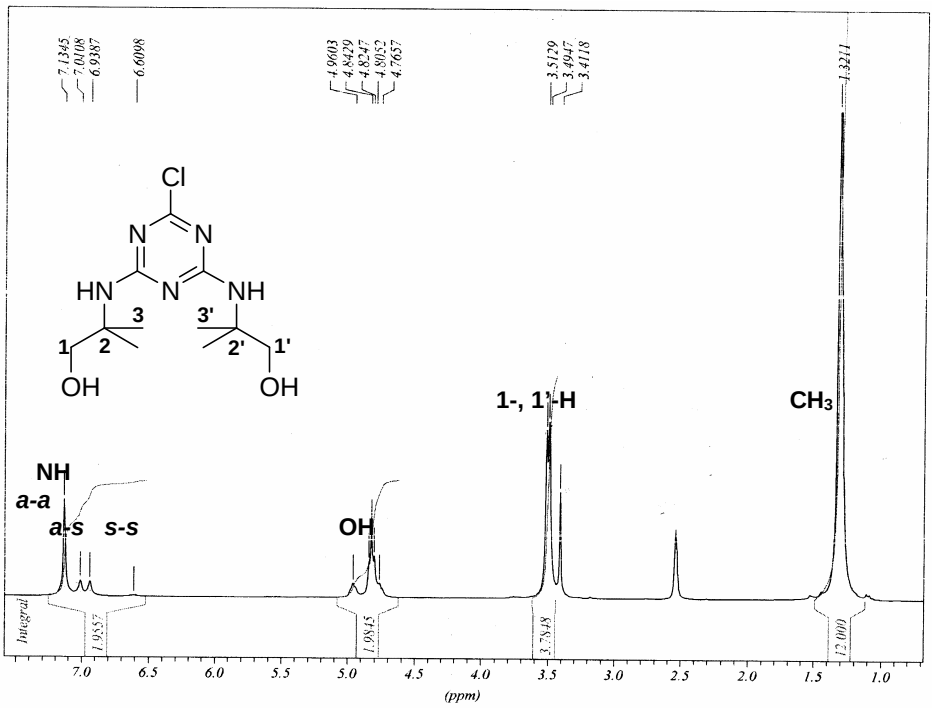


Figure 2. ^{1}H NMR spectrum of compound **1** (DMSO-d_6, 300 MHz, 25 ^{o}C)

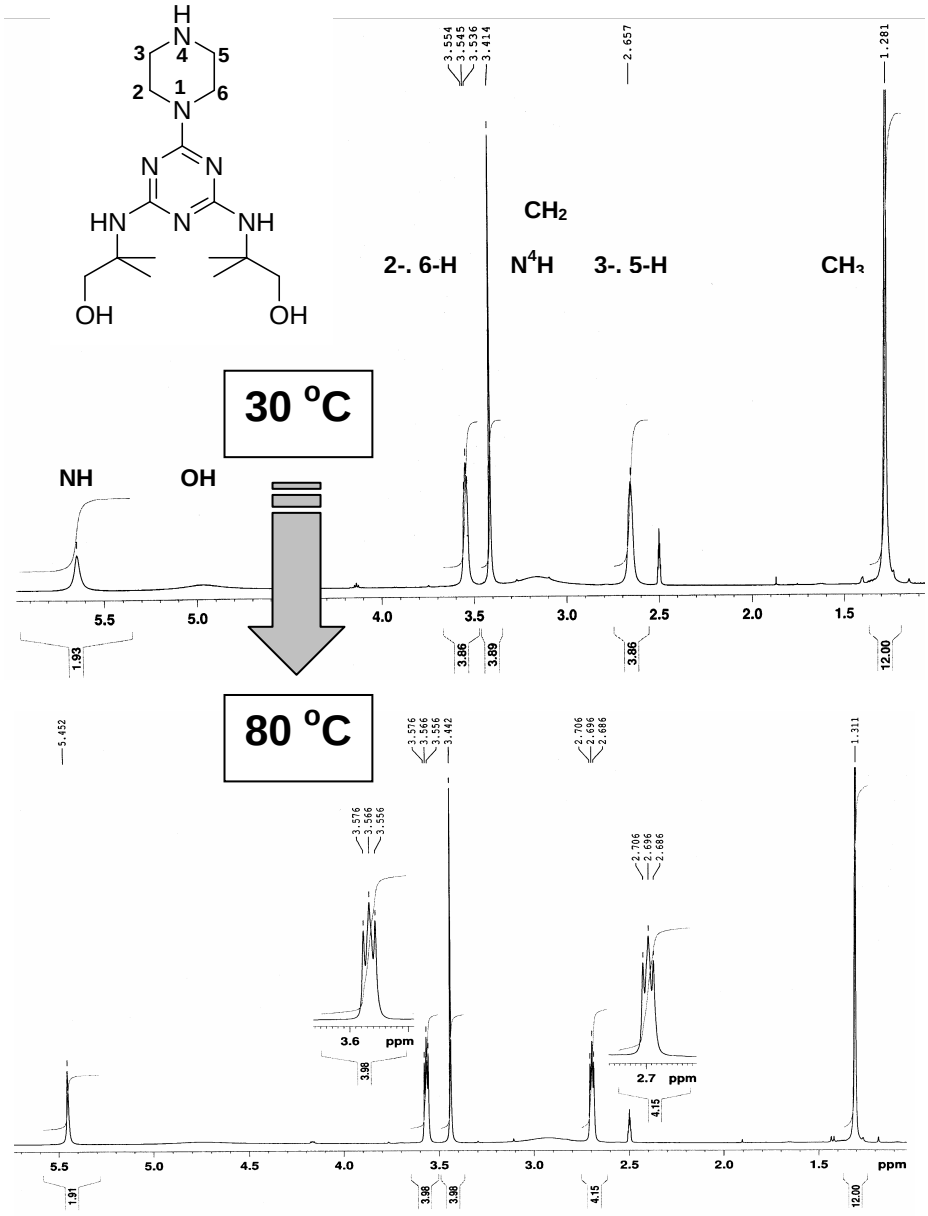


Figure 3. ^{1}H DNMR evolution of compound **2** (DMSO-d_6, 500 MHz)

As in the case of the previously reported by us **1a**, because of the fail in discriminating *directly* by means of NMR the rotamers **1**(*s*-*s*) *vs.* **1**(*a*-*a*), we proceeded to an *indirect* assignment.* Thus, we ascertained rotamer **1**(*a*-*a*) as providing the most downfield environment for the isochronous protons N(')H since i) they were positioned towards the close strong dipole moment created by the remainder *s*-triazine chlorine [1a, 4h] and ii) involved in two identically oriented intramolecular hydrogen bonds with the lone pairs of triazine nitrogens N-1, -3; hence, δN(')H(*a*-*a*) ≈ δN(')H(*a*-*s*) > δN(')H(*s*-*a*) ≈ δN(')(*s*-*s*) (Figure 2).

This assignment was different in comparison with **1a** (Table 1) where molecular mechanics predicted rotamer **1a**(*s*-*s*) as being the most stable [1b], and so δN(')H(*s*-*s*) ≈ δN(')H(*s*-*a*) > δN(')H(*a*-*s*) ≈ δN(')(*a*-*a*).

There are some additional reasons motivating the above opposite rotameric distribution of **1** vs. **1a** (Table 1):

i) in DMSO-d_6, a hydrogen bond acceptor solvent [6g], *s*-triazine **1a** was by far more solvated than **1**, imposing rotamer **1a**(*s*-*s*), although the most sterically hindered, to be dominant since it best exposed the four hydroxyl groups to solvent cages. Consequently, protons OH in **1a** were, globally, more deshielded than in **1**. That is, for the tetrahydroxy derivative **1a** the rotameric occurrence was imposed by solvation effects [1b].

ii) solvation was less important for the dihydroxy derivative **1**, able to adopt a different spatial arrangement dictated mainly by steric factors: as a result, rotamer **1**(*a*-*a*), the less congested, was dominant. Protons N(')H in **1** were throughout located downfield in comparison with **1a** (Table 1) to disclose the stronger deshileding influence of the chlorine atom in **1** vs. **1a**.

If chlorine was replaced by a strong R_2N type donor substituent, as in melamine **2**, its ^{1}H NMR spectrum (Figure 3) was consistent, at room temperature, with a unique mediated structure, hence a free rotating molecule. However, some minor modifications were observed upon heating the NMR sample, consisting of an A_2X_2 type clarification in the vicinal coupling pattern of piperazine methylenes C-3, -5. Since the chair-chair flipping of piperazine ring was better observed at 80 ^{o}C, we were suspicious that, in normal conditions, some residual rotamerism had initially involved the C-2(*s*-triazine)-N-1(piperazine) bond.

On 300 MHz time scale, more elaborated structures (compounds **3**-**5**) displayed richness of conformational rotamerism giving rise to spectral complexity with respect to signal number, degeneracy, and broad lines, similar to melamine **2**, seen as a *model compound* [1b, 7a] for the whole series.

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*The *indirect* assignment of the rotamerism in *N*-substituted 2-chloro-4,6-diamino-*s*-triazines appeared to us to be in current use approach, for example by comparison with 2-chloro-6-ethyl-4-isopropyl-*s*-triazine (Atrazine®) [7].

CONCLUSION

Starting from 2-methyl-2-propanol, we successfully developed a convergent five steps iterative synthesis directed to a G-2 melamine dendron possessing the title amino alcohol as peripheral groups. Rotational diastereomerism about C(*s*-triazine)-N(exocyclic) partial double bonds was typically revealed for the first two model precursors of the G-2 dendron.

EXPERIMENTAL SECTION

General. Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. A Brucker® DMX500 instrument was used for ^{1}H DNMR Experiments. All NMR spectra were measured in anhydrous commercially available DMSO-d_6. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^{n}J_{H,H}$ values) are given throughout in Hz. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin-Elmer® Paragon FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) were recorded on a Brucker® Esquire Instrument.

*Preparation of compound **1***

To anhydrous K_2CO_3 (2.76 g, 20.00 mmol) suspended in dry THF (75 ml), cyanuric chloride (1.80 g, 9.76 mmol) was added with vigorous stirring. The resulted suspension was cooled at -10 ^{o}C when 2-amino-2-methylpropanol (1.78 g, 20.00 mmol) as dry THF (25 ml) solution was injected portionwise (5 mL/portion each hour). The reaction mixture was let to reach room temperature and kept as such for additional 20 hrs. At this stage, TLC monitoring (eluent toluene/isopropanol 2:1) indicated the formation of **1** contaminated with the corresponding intermediate, the *N*-substituted-2,4-dichloro-*s*-triazine. The reaction mixture was heated to 45 ^{o}C for additional 13 hrs. until TLC monitoring revealed completion of the amination, then cooled at room temperature. Minerals were filtered off and well washed with dry THF. The organic filtrate was evaporated under reduced pressure to dryness and the resulted white powder was crystallised from min. boiling ethanol affording 1.97 g **1** (70% yield with respect to cyanuric chloride).

2-Chloro-4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazine (1). White crystalline powder, mp 171.4-172.3 °C (EtOH). Anal. calcd. for $C_{11}H_{20}ClN_5O_2$ (289.13): C, 45.60; H, 6.96; N, 24.17. Found: C, 45.77; H, 6.69; N, 23.98. R_f (66% toluene/isopropanol)=0.80. IR (KBr): ν=3370 (s), 3271 (m), 2980 (w), 2839 (w), 1598 (s), 1532 (s), 1474 (m), 1301 (w), 1270 (m), 1196 (m), 1056 (m), 1037 (m), 996 (w), 903 (w), 803 (m), 770 (w), 704 (w), 667 (w), 531 (w), 510 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.32 (s, 12H, CH_3), 3.50 (d, $^3J_{H,H}$=5.5 Hz, 4H, 1-, 1'-H), 4.82, 4.96 (t and bt respectively, $^3J_{H,H}$=5.6 Hz, 2H, O-, O'-H), 6.61, 6.94, 7.01, 7.13 (4×s, 2H, N-, N'-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=23.4, 23.5 (4C, CH_3), 54.4, 54.5, 54.6 (2C, C-2, -2'), 66.8, 67.1 (2C, C-1, -1'), 164.0, 164.5, 164.8 (2C, C-4, -6, *s*-triazine), 166.8 (1C, C-2, *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane): m/z (%)=290 (100) [M^++1], 346 (15), 328 (5), 312 (10), 256 (50), 240 (<5), 224 (10), 184 (5), 113 (<5), 85 (<5), 73 (10).

*Preparation of compound **2***

To anhydrous K_2CO_3 (0.96 g, 6.90 mmol) suspended in dry THF (50 ml), anhydrous piperazine (2.37 g, 27.51 mmol) was added with vigorous stirring. To this suspension, at room temperature, 2-chloro-4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazine **1** (2.00 g, 6.90 mmol) as dry THF (20 mL) solution was added portionwise. Thus, after each 4 ml of this solution, added within 90 min., TLC monitoring (eluent toluene/isopropanol 2:1) established that all starting material **1** was consumed. The use of an alternative TLC eluent (chloroform/ethanol 1:1) indicated the formation of the desired **2**, as largely major, together with the corresponding 1,4-disubstituted piperazine derivative **II** in traces. Minerals were filtered off and thoroughly washed with dry THF. The organic filtrate was evaporated under reduced pressure to dryness. The solid residue was separated by column chromatography on silica gel as follows: the side product **II** was separated as the first fraction (0.10 g, 5% conversion of **1**, eluent chloroform/ethanol 1:1) then **2** (2.01 g, 86% conversion of **1**, eluent ethanol containing 2.5% ammonia).

1-{4,6-Bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl} piperazine (2). White crystalline powder, mp 156.5-157.4 °C (flash column chromatography, ethanol/2.5% ammonia). Anal. calcd. for $C_{15}H_{29}N_7O_2$ (339.24): C, 53.08; H, 8.61; N, 28.89. Found: C, 52.88; H, 8.69; N, 29.05. R_f (ethanol/ 2.5% ammonia)=0.85. IR (KBr): ν=3275 (s), 2968 (s), 2926 (s), 2858 (m), 1597 (s), 1554 (s), 1504 (s), 1441 (s), 1363 (s), 1275 (s), 1242 (m), 1200 (m), 1125 (w), 1050 (m), 811 (m), 614 (w) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 30 °C): δ=1.28 (s, 12H, CH_3), 2.66 (bs, 4H, 3-, 5-H-ax., -eq., piperazine), 3.15 (bs, 1H, NH, piperazine), 3.41 (s, 4H, 1-, 1'-H), 3.55 (t, $^3J_{H,H}$=4.5 Hz, 2H, 2-, 6-H-ax., -eq., piperazine), 5.00 (bs, 2H, O-, O'-H), 5.64 (bs, 2H, N-, N'-H) ppm; ^1H NMR (500 MHz, DMSO-d_6, 80 °C): δ=1.31 (s, 12H, CH_3),

2.70 (t, $^3J_{H,H}$=5.0 Hz, 4H, 3-, 5-H-ax., -eq., piperazine), 2.90 (bs, 1H, NH, piperazine), 3.44 (s, 4H, 1-, 1'-H), 3.57 (t, $^3J_{H,H}$=5.0 Hz, 2H, 2-, 6-H-ax., -eq., piperazine), 4.75 (bs, 2H, O-, O'-H), 5.45 (bs, 2H, N-, N'-H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C): δ=24.4 (4C, CH_3), 44.4 (2C, C-3, -5, piperazine), 46.0 (2C, C-2, -6, piperazine), 54.1 (2C, C-2, -2'), 69.0 (2C, C-1, -1'), 164.4 (1C, C-2, *s*-triazine), 165.6 (2C, C-4, -6, *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane): m/z (%)=396 (15) [M^++1+*i*-BuH], 340 (100) [M^+ +1], 324 (<5), 308 (10), 268 (15), 236 (<5), 196 (<5), 169 (<5), 146 (<5), 113 (10), 97 (5), 85 (15), 73 (30), 61 (<10).

Alternative preparation of compound ***II***

To anhydrous K_2CO_3 (0.56 g, 4.05 mmol) suspended in dry THF (50 ml), anhydrous piperazine (0.17 g, 1.97 mmol) and 2-chloro-4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazine **1** (1.16 g, 4.00 mmol) were added with vigorous stirring. The reaction mixture was heated at reflux for 12 hrs. After this period, TLC monitoring (eluent toluene/isopropanol 2:1) showed the formation of **II** as major component of a mixture containing also the starting **1** and the intermediate **2**. THF was replaced by 1,4-dioxane and refluxing was continued for additional 12 hrs. After this period TLC monitoring revealed the presence of **1** and **2** in small traces only. Minerals were filtered off and thoroughly washed with dry THF. The organic filtrate was evaporated under reduced pressure to dryness. Flash column chromatography (eluent chloroform/ ethanol 1:1) afforded pure **II** (0.89 g, 76% yield with respect to piperazine).

1,4-Bis{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl} piperazine (II). White crystalline powder, mp 230-235 °C (flash column chromatography, eluent chloroform/ethanol 1:1). Anal. calcd. for $C_{26}H_{48}N_{12}O_4$ (592.39): C, 52.68; H, 8.16; N, 28.36. Found: C, 53.02; H, 7.79; N, 28.44. R_f (50% chloroform/ethanol)=0.80. IR (KBr): ν=3502 (s), 3419 (s), 3346 (s), 3168 (s), 2964 (s), 2931 (s), 1563 (s), 1494 (s), 1440 (s), 1360 (s), 1281 (s), 1254 (s), 1199 (m), 1167 (s), 1060 (s), 1048 (s), 1017 (m), 994 (m), 898 (w), 833 (m), 809 (s), 743 (w), 595 (w), 563 (w) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.319, 1.322 (s, 24H, CH_3), 3.47 (bs, 8H, piperazine), 3.69 [bs, 8H, 2×(1-, 1'-H)], 5.03 [bs, 4H, 2×(O-, O'-H)], 5.81 [bs, 4H, 2×(N-, N'-H)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6 25 °C): δ=20.8, 20.9 (8C, CH_3), 42.0 (4C, piperazine), 53.7 [4C, 2×(C-2, -2')], 68.4 [4C, 2×(C-1, -1')], 164.0 (2C, C-2, -2', *s*-triazine), 165.0 (4C, C-4, -4', -6, -6', *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane): m/z (%)=649 (5) [M^++*i*-BuH], 593 [M^+] (100), 562 (10).

To anhydrous K_2CO_3 (0.44 g, 3.18 mmol) suspended in dry THF (50 ml), cyanuric chloride (0.29 g, 1.57 mmol) was added with vigorous stirring and the resulted suspension was cooled at -10 ^oC. At this temperature, 1-{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl}piperazine (**2**) (1.08 g, 3.18 mmol) as dry THF (25 mL) solution was injected very slowly. The reaction mixture was let to warm up to room temperature overnight when TLC monitoring (eluent toluene/isopropanol 2:1) revealed the presence of **3** and the unreacted **2** as well. THF was replaced by 1,4-dioxane and the reaction mixture was heated at 90 ^oC for additional 8 hrs. After this period, TLC monitoring confirmed the formation of **3** as largely major in the reaction mixture. At 90 ^oC minerals were filtered off and thoroughly washed with anhydrous and hot THF. The organic filtrate was evaporated under reduced pressure to dryness and the resulted crude product was triturated from EtOH/Et_2O affording pure **3** (1.12 g, 90% yield with respect to cyanuric chloride).

2-Chloro-4,6-bis{4-{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-tri-azin-2-yl}piperazin-1-yl}-*s*-triazine (3). White crystalline powder, mp 220-222 ^oC (EtOH/Et_2O). Anal. calcd. for $C_{33}H_{56}ClN_{17}O_4$ (789.44): C, 50.15; H, 7.14; N, 30.13. Found: C, 50.35; H, 6.88; N, 30.31. R_f (66% toluene/ isopropanol)=0.75. IR (KBr): ν=3398 (m), 2967 (m), 2924 (m), 2865 (m), 1566 (s), 1494 (s), 1440 (s), 1361 (s), 1274 (s), 1229 (s), 1169 (m), 1057 (m), 998 (s), 977 (s), 811 (m), 740 (w), 502 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 ^oC): δ=1.34 (bs, 24H, CH_3), 3.47 (bs, 8H, 3-, 3'-, 5-, 5'-H-ax., -eq., piperazine), 3.74 [bs, 16H, 2×(1-, 1'-H), 2-, 2'-, 6-, 6'-H-ax., -eq., piperazine), 5.02 [bs, 4H, 2×(O-, O'-H)], 5.85 [bs, 4H, 2×(N-, N'-H)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 ^oC): δ=23.9 (8C, CH_3), 42.3, 42.9 (8C, piperazine), 53.7 [4C, 2×(C-2, -2')], 68.4 [4C, 2×(C-1, -1')], 163.8, 164.0, 164.7, 165.1 (8C, C-2', -2", C-4, -4', -4", C-6, -6', -6", *s*-triazine), 168.7 (1C, C-2, *s*-triazine) ppm. MS (ESI+, acetone/ DMSO diluted with ACN): m/z (x10^5)=790 [M^+ +1] (3.6), 639.5 (0.5), 595.4 (0.6), 551.4 (0.5), 507.4 (0.4), 463.3 (0.2), 413.3 (0.2), 340.2 (<0.1), 276.6 (<0.2), 240.2 (<0.2).

*Preparation of compound **4***

To anhydrous K_2CO_3 (0.16 g, 1.16 mmol) suspended in dry THF (100 ml), anhydrous piperazine (0.39 g, 4.53 mmol) was added and the suspension was heated at 50 ^oC with vigorous stirring. At this temperature, 2-chloro-4,6-bis{4-{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl}pipera-zin-1-yl}-*s*-triazine (**3**) (0.88 g, 1.11 mmol) as dry THF (35 mL) solution was added portionwise, 7 mL/portion each 90 min. Within this period, TLC monitoring (eluent toluene/isopropanol 3:1) established the complete consumption of the starting **3**. The use of an alternative TLC eluent (chloroform/ ethanol 1:1) indicated the formation of the desired **4**, as largely major, together

with the corresponding 1,4-disubstituted piperazine derivative in very small traces. At 50 ^{o}C, minerals were filtered off and thoroughly washed with hot and dry THF. The organic filtrate was evaporated under reduced pressure to dryness to provide the crude product which was purified by column chromatography (eluent chloroform/ethanol 3:1) yielding pure **4** (0.65 g, 70% yield with respect to **3**). Optional purification of **4** can be carried out by trituration from EtOH/Et_2O (60% yield with respect to **3**).

1-{4,6-Bis{4-{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl}piperazin-1-yl}-*s*-triazin-2-yl}piperazine (4). White crystalline powder, mp 225-230 ^{o}C (flash column chromatography, eluent chloroform/ethanol 3:1). Anal. calcd. for $C_{37}H_{65}N_{19}O_4$ (839.55): C, 52.90; H, 7.80; N, 31.68. Found: C, 53.11; H, 8.09; N, 31.59. R_f (75%chloroform/ethanol)=0.30. IR (KBr): ν=3385 (m), 3330 (m), 2968 (m), 2924 (m), 1543 (s), 1484 (s), 1438 (s), 1359 (m), 1271 (m), 1198 (m), 1054 (w), 999 (m), 809 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 ^{o}C): δ=1.33 (s, 24H, CH_3), 2.84 (bs, 4H, 3-, 5-H-ax., -eq., piperazine), 3.46 (s, 5H, 2-, 6-H-ax., -eq., NH, piperazine), 3.72-3.74 [bd, 24H, 2'-, 2"-, 3'-, 3"-, 5'-, 5"-, 6'-, 6"-H-ax., -eq., piperazine, 2×(1-, 1'-H)], 5.00 [bs, 4H, 2×(O-, O'-H)], 5.80 [bs, 4H, 2×(N-, N'-H)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 ^{o}C): δ= 24.4 (8C, CH_3), 41.4, 43.1, 43.4, 44.9 (12C, piperazine), 54.2 [4C, 2×(C-2, -2')], 68.9 [4C, 2×(C-1, -1')], 164.5, 165.1, 165.2 (9C, C-2, -2', -2", -4, -4', -4", -6, -6', -6", *s*-triazine) ppm. MS (ESI+ MeOH): m/z (x10^6)=862.4 (0.8) [M+Na^+], 840.5 (4.8) [M^++1], 809.5 (0.2), 768.4 (0.4), 696.3 (0.5), 624.2 (0.5), 552.2 (0.6), 413.2 (0.3), 276.5 (1.0).

*Preparation of compound **5***

To anhydrous K_2CO_3 (0.2034 g, 1.472 mmol) suspended in dry THF (90 ml),1-{4,6-bis{4-{4,6-bis[(1-hydroxy-2-methylprop-2-yl)amino]-*s*-triazin-2-yl}piperazin-1-yl}-*s*-triazin-2-yl}piperazine (**4**) (1.236 g, 1.472 mmol) was added with vigorous stirring and cooled at -20 ^{o}C. At this temperature, cyanuric chloride (0.132 g, 0.716 mmol) as dry THF (10 mL) solution was rapidly injected. The reaction mixture was let gently to reach room temperature and was kept as such for additional 12 hrs. After this period, TLC monitoring (eluent chloroform/ethanol 4:1) still indicated the presence of the starting **4**, therefore the reaction mixture was heated to reflux for additional 16 hours then filtered off. Minerals were thoroughly washed with boiling dry THF. The organic filtrate was evaporated under reduced pressure to dryness. The resulting crude product was twice recrystallised from boiling ethanol to afford pure **5** (0.90 g, 70 % with respect to cyanuric chloride).

2-Chloro-4,6-bis{4-{4,6-bis{4-{4,6-bis[(1-hydroxy-2-methyl-prop-2-yl)-amino]-*s*-triazin-2-yl}piperazin-1-yl}-*s*-triazin-2-yl}piperazin-1-yl}-*s*-triazine (5). White crystalline powder, mp 260-270 °C (dec.) (EtOH). Anal. calcd. for $C_{77}H_{128}ClN_{41}O_8$ (1790.06): C, 51.62; H, 7.20; N, 32.05. Found: C51.98; H: 6.81; N: 32.39. R_f (80% chloroform/ethanol)=0.75. IR (KBr): ν=3402 (m), 2970 (m), 2927 (m), 2863 (m), 1547 (s), 1484 (s), 1437 (s), 1361 (m), 1265 (m), 1232 (m), 1199 (w), 1177 (w), 1056 (w), 998 (m), 809 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.33 (bs, 48H, CH_3), 3.48 (bs, 24H, piperazine), 3.77 (bs, 24H, piperazine, 16H, CH_2OH), 5.04 (bs, 8H, CH_2O*H*), 5.84 (bs, 8H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=23.9 (16C, CH_3), 42.6 (24C, piperazine), 53.7 (8C, Cq., C-2), 68.4 (8C, CH_2, C-1), 163.9, 164.7, 165.0 [20C, C-N(exocyclic), *s*-triazine], 168.8 (1C, C-Cl, *s*-triazine) ppm. MS (ESI+, acetone-DMSO diluted with ACN): m/z ($\times 10^4$)=1829.2 (0.5) ($M+K^+$), 1814.2 (1.1) ($M+Na^+$), 1791.3 (2.1) ($M+H^+$), 1206.2 (0.1), 987.7 (0.4), 840.8 (0.1).

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