Tetrahedron: *Asymmetry* xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Design, iterative synthesis and structure of novel optically active trispiro-dendritic melamines incorporating '*open-chain*' versus '*closed-chain*' serinolic peripheral units

Oana Moldovan [a], Iulia Nagy [a], Pedro Lameiras [b], Cyril Antheaume [c], Carmen Sacalis [a], Mircea Darabantu [a,*]

[a] *Babes-Bolyai University, Department of Chemistry, 11 Arany János St., 400028 Cluj-Napoca, Romania*
[b] *University of Reims Champagne-Ardenne, ICMR, UMR 7312, BP 1039, 51687 Reims, France*
[c] *University of Strasbourg, Faculty of Pharmacy, 74 Rhin St., BP 60024, 67401 Illkirch Cedex, France*

ARTICLE INFO

Article history:
Received 2 March 2015
Accepted 1 May 2015
Available online xxxx

Dedicated to Dr. Emil POP

ABSTRACT

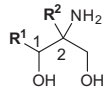
Starting from commercial C-2-substituted 2-aminopropane-1,3-diols (*serinols*, '*open-chain*' peripheral units) and optically active amino-1,3-dioxanes ('*closed-chain*' peripheral units) as cycloacetals of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (*p-nitrophenylserinol*) or its 2-dimethylamino analogue, we herein report a new series of di- and trimeric G-1 trispiro-dendritic melamines, they were synthesised convergently by iterative chemoselective amination of cyanuric chloride. Depending on the number of hydroxymethyl groups in the '*open-chain*' peripheral unit and the type of the rigid amino-anchorage (axial or equatorial) of the '*closed-chain*' counterpart, the classic restricted rotation about the C(*s*-triazine)–N(exocyclic) partial double bonds induced, progressively, specific spatial arrangements in angularly connected G-0 and G-1 dendrons, including axial chirality in G-1 dimeric or G-1 trimeric melamines.

1. Introduction

Serinol is the trivial nomenclature for 2-aminopropane-1,3-diol, seen as the reduced form of *serine*, and the parent term of a series comprising its *C*-substituted commercial analogues (Scheme 1).[1]

The resourceful reactivity of C-2-substituted serinols **A**–**C** with electrophiles has been a challenging task in organic synthesis since the 1940-s.[2] Optically active C-1-substituted (1*R*,2*R*)-(*p-nitro*)*phenylserinols* are well-known key intermediates in the manufacturing of the classical antibiotic *Chloromycetin* (*Chloramphenicol*) as early as 1947.[3,4]

In a 'dendritic context', it was in 1985, when Newkome et al.[5] used TRIS **C** (Scheme 1) in the preparation of the first so-called 'arborol', that the chemistry of dendrimers was born. Later developments of these 'cascade syntheses'[6] recommended TRIS as a very practical building-block for such polymeric architectures, because it could play almost all crucial roles within these innovative structures: a peripheral unit, a tetravalent branch-cell and a core.[5b] *Serinol* itself, as well as its 5-amino-1,3-dioxane derivatives, are of interest for iterative construction of macromolecules in biomedicine[7a–e] and nanomaterials.[7f,g] Except for our previously reported results,[8] no attention, however, has been paid to *methylserinol* **A** and *ethylserinol* **B**.



R^1	R^2	Trivial nomenclature
H	**H**	***Serinol***
C-2-substituted *serinols*		
H	Me	*Methylserinol* (**A**)
H	Et	*Ethylserinol* (**B**)
H	CH_2OH	TRIS, THAM (**C**)
C-1-substituted *Serinols*		
Ph	H	(1*R*,2*R*) or (1*S*,2*S*) "*Threo*"-***ph***enylserinol
***p*-NPh** (p-O_2N-C_6H_4)	H	(1*R*,2*R*) or (1*S*,2*S*) "*Threo*"-***p-nitroph***enylserinol

Scheme 1.

Arising from the pioneering achievements of Simanek et al. in 2000,[9] there has been increasing interest in melamine-based dendrimers. Many approaches to this new class of macromolecules have been reported first, in the domain of iterative convergent[9,10] versus divergent syntheses[9,10a,11] by exploiting the 'classic' (but still versatile) chemoselective amination of cyanuric chloride.

* Corresponding author. Tel.: +40 264 59 38 33; fax: +40 264 59 08 18.
E-mail addresses: darab@chem.ubbcluj.ro, m.darabantu@upcmail.ro (M. Darabantu).

http://dx.doi.org/10.1016/j.tetasy.2015.05.003
0957-4166/

Later on, Simanek et al. described manipulations specifically correlated with the peripheral groups of dendritic melamines.[12] Thus, two major applications of these macromolecules, organic nanomaterials[13] and vehicles for drug delivery systems,[14] were highlighted and recently reviewed.[15]

Targeting bioactive *N*-substituted melamines, the amination of cyanuric chloride with *C*-substituted (optionally *O*,*O*-'masked') serinols has rarely been mentioned since 1979.[16] It was our group which reported on the developments of this new facet of serinolic chemistry,[17] that is, the convergent synthesis of the first serinolic G-2 melamine dendrimer incorporating optically active *p*-nitrophenylserinol[17a,c] or C-2-substituted serinols **A**–**C** as peripheral units.[17f] These macromolecular melamines manifested interesting electrochemical properties[17g] and stereodynamic behaviour.[8,17] They both were due to the well-documented restricted rotation about the C(*s*-triazine)–N(exocyclic) partial double bonds.[18] For example, this intrinsic structural feature can promote the so-called 'dendritic choreography' (Moreno and Simanek in 2008)[18l] and the 'open gates–closed gates frontier mechanism' thereof containing C-2-substituted serinols **A**–**C** (Scheme 1) as peripheral units (our data in 2012).[8] In this context, we recently described the use of mono-[8] or trispiranic motifs[17f] (as peripheral units or linkers, respectively) in the iterative synthesis of some G-2 and G-1 dendritic melamines. According to the literature, very few spirane dendrimers have been reported.[19] Therefore, our aim herein consists of the convergent synthesis of new trispiro-dendritic melamines comprising various (*O*,*O*-protected)serinols as peripheral units whose oriented rotamerism about the C(*s*-triazine)–N(exocyclic) partial double bonds can induce distinct spatial arrangements, including axial chirality phenomena at the dendritic scale.

2. Results and discussion

2.1. Synthesis

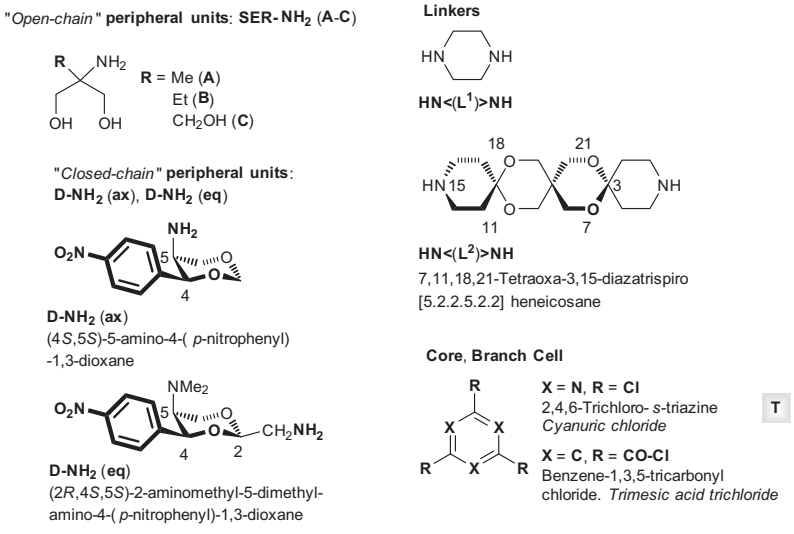
2.1.1. Starting materials and their designed roles

The starting materials were either commercial or prepared with *a priori* designed roles (Scheme 2). **SER-NH$_2$** (**A**–**C**) were assigned as '*open-chain*' peripheral units, while the 'sugar-like' anancomeric amino-1,3-dioxanes[17b,20] **D-NH$_2$** (**ax**) or **D-NH$_2$** (**eq**) were designated as '*closed-chain*' peripheral units. The optically active building-blocks are readily available by ring closure of (1*S*,2*S*)-*p*-nitrophenylserinol (Scheme 1) or its (1*S*,2*S*)-*N*,*N*-dimethyl analogue[21] upon treatment with equimolar amounts of *p*-formaldehyde [→**D-NH$_2$** (**ax**)] or 2,2-dimethoxyethylamine [→**D-NH$_2$** (**eq**)], respectively, following our 'sulfuric' and non-epimerisable (trans)acetalisation methodology.[1,17b,22] By combining these two types of amino-nucleophiles, we previously described the convergent manipulation of two tandems, **SER-NH$_2$** (**A**–**C**)/**D-NH$_2$** (**ax**) and **SER-NH$_2$** (**A**–**C**)/**D-NH$_2$** (**eq**), up to the G-0 melamine dendrons in a preliminary publication.[17e] Herein, a third tandem, **D-NH$_2$** (**ax**)/**D-NH$_2$** (**eq**), is included.

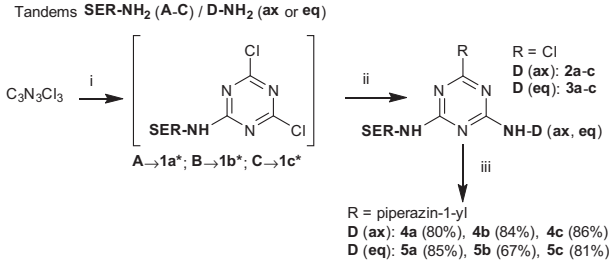
Piperazine (Scheme 2) **HN<(L^1)>NH** is a traditional linker in dendritic melamines' chemistry.[15,17] Instead, we utilised this diamino-nucleophile for mono-*N*-functionalisation, taking into account its transannular effect[13e,f] and Simanek's 'relative reactivity maps',[10b] referring to a large variety of monoamines- and (non)symmetric (di)amines in reaction with cyanuric chloride.[23] In contrast, the trispirotetraacetal diamine linker **HN<(L^2)>NH** (Scheme 2) was not previously known to play such a role. This compound was of special interest due to its easily improvable preparation by double cyclocondensation of pentaerythritol with the commercially available 'monohydrate' of piperidone hydrochloride (95%, our yield,[17f] 56%, lit. yield[24]). With **HN<(L^2)>NH** in hand, we recently demonstrated[17f] both its configurational and conformational chirality using deeper approaches than those of Dodziuk[25] and, later on, of Grosu et al., which focused on spiranic stereochemistry.[26]

2.1.2. Synthesis of G-0 melamine dendrons as building blocks

Scheme 3 shows the first three amination steps (i–iii) affording G-0 melamines **4a**–**c**, **5a**–**c** and **7**. As already reported,[17e] the one-pot synthesis of G-0 chlorodendrons **2a**–**c** and **3a**–**c** consisted of the use of C-2-substituted serinols, **A**–**C**, as the first amino-nucleophiles (i) and amino-1,3-dioxanes **D-NH$_2$** (**ax** or **eq**, (ii) as the second. In series **2**, the inverted addition of reagents caused lower yields, for example, in the case of **2c**, the yields decreased from 84% to 55%. However, targeting series **3**, previous data from us[17b] and from others[27] supported the (non)-selective interaction between equimolar amounts of cyanuric chloride and tertiary amines, that is, the 5-dimethylamino-1,3-dioxane **D-NH$_2$** (**eq**), as side oligomerisations and demethylation occurred, both in low yield. Therefore, primary amination with **SER-NH$_2$** (**A**–**C**), followed by treatment with **D-NH$_2$** (**eq**), was advised. **D-NH$_2$** (**eq**) was also used as the second amino nucleophile in the preparation of the new compound **6**. In particular, we noted that the clean aminations



Scheme 2.



Key

(**i**): 1 equiv. **SER-NH$_2$** (**A-C**), 1 equiv. K_2CO_3, THF / 0 °C → r.t. (24 h)
(**ii**): 1 equiv. **D-NH$_2$** (**ax** or **eq**), 1 equiv. K_2CO_3, THF / *T* (°C), t (h)
(**iii**): 5×0.2 equiv. **2a-c** or **3a-c** added every 2 h to 4.0 equiv. piperazine, 1.0 equiv. K_2CO_3, THF / r.t. (24 h)

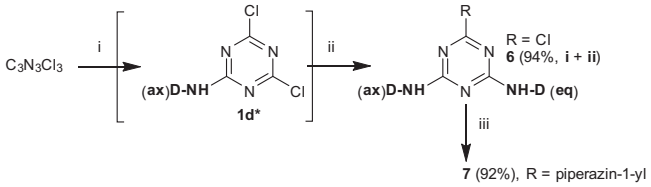
Axial anchorage of **D** (**ax**)

No.	*T* (°C) / t (h)	yield (%) (**i** + **ii**)
2a	65 / 16	80
2b	65 / 22	66
2c	65 / 12	84

Equatorial anchorage of **D** (**eq**)

No.	*T* (°C) / t (h)	yield (%) (**i** + **ii**)
3a	-10 → r.t. / 24; 65 / 14	83
3b	-10 → r.t. / 24; 65 / 16	42
3c	-10 → r.t. / 24; 65 / 12	95

Tandem **D-NH$_2$** (**ax**) / **D-NH$_2$** (**eq**)



Key

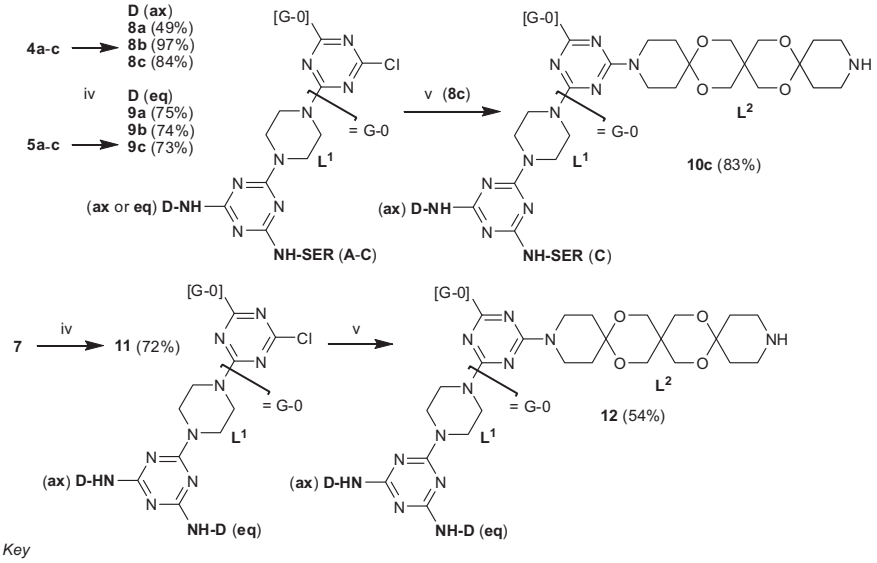
(**i**): 1 equiv. **D-NH$_2$** (**ax**), 1 equiv. K_2CO_3, $CHCl_3$ / -5 °C → r.t. (24 h)
(**ii**): 1 equiv. **D-NH$_2$** (**eq**), 1 equiv. K_2CO_3 / r.t. (48 h) / reflux (8 h)
(**iii**): 5×0.2 equiv. **6** added every 2 h to 4.0 equiv. piperazine, 1.0 equiv. K_2CO_3, THF / r.t. (14 h)
*not isolated (for the full characterisation of these intermediates, see Ref. [17b, 17c])

Scheme 3.

1a–c → **3a–c** and **6** → **7** were caused, most likely, by the sterically crowded and rigid location of the axial C-5 dimethylamino group in **D-NH$_2$** (**eq**).[17b] The chemoselective attachment of the first linker (iii) was performed based on our earlier reported procedures,[8,17c–e] that is, the portionwise addition of G-0 chlorodendrons **2a–c**, **3a–c** and **6** to a four-fold molar amount of piperazine at room temperature. No contamination with dimeric side products was detected by TLC, NMR or MS in the G-0 melamine dendrons.

2.1.3. Synthesis of G-1 chloro- and melamine dendrons: feasibilities and failures

In the next two steps of our convergent strategy (iv and v, Scheme 4), we realised the two-fold connexion of G-0 melamines **4a–c**, **5a–c** and **7** to cyanuric chloride to access G-1 chlorodendrons **8a–c**, **9a–c** and **11** (iv), and then G-1 trispiranic melamines **10c** and **12** (v). Angular dimerisations (iv) occurred in satisfactory to good yields. Except for compound **9b**, all G-1 chlorodendrons required purification by column chromatography on silica gel (when some loss of material due to retention, which was observed), followed by trituration. To ensure chemoselectivity, manipulations started at low temperatures in THF and continued at room temperature. In the case of compounds **8a–c** and **9a–c**, TLC monitoring indicated that the aminations reached completion only if THF was replaced by 1,4-dioxane in the final stage. Overall, in the depicted conditions, we avoided side nucleophilic S_N2-Ar processes, such as C-5-N-demethylation,[17b,27] during transformations **5a–c** → **9a–c** and C(*s*-triazine)-alkoxylations.[28] On the other hand, our protocols also revealed the moderate reactivity of melamines **4a–c**, **5a–c** and **7** with cyanuric chloride. This fact is not quite unexpected, taking into account their rotamerism combined with strong solvation (see later discussion in Section 2.2.2) in hydrogen bond acceptor solvents.[18j] The results of the two subsequent aminations (v), **8c** → **10c** and **11** → **12**, where more forcing conditions (reflux in 1,4-dioxane) had to be applied, supported this analysis. G-1 trispiranic melamines **10c** and **12** were successfully purified by column chromatography on partially deactivated silica gel. The excess of linker **HN**<(**L^2**)>**NH** was easily recovered by a simple



Key

(iv): → **8a-c**, **9a-c**: 0.45 equiv. $C_3N_3Cl_3$, 1.00 equiv. K_2CO_3, THF / -15 °C → r.t. (12 h) / reflux (12 h) then replacement of THF by 1,4-dioxane, reflux (35 h, **8a**, **8c**, **9b**), (30 h, **8b**, **9a**), (40 h, **9c**)
→ **11**: 0.45 equiv. $C_3N_3Cl_3$, 1.00 equiv. K_2CO_3, THF / -12 °C → t.a. (12 h) / reflux (25 h)
(v): → **10c**, **12**: 5×0.2 equiv. **8c** (or **11**) added portionwise every 2 h to 4.0 equiv. **HN**<(**L^2**)>**NH**, 1.0 equiv. K_2CO_3, 1,4-dioxane / reflux (35 h)

Scheme 4.

work-up (up to 80% yield, see Section 4.5). In this context, it should be mentioned that Wessig et al.[29] followed a protection–deprotection strategy in the synthesis of oligomeric spiranes with two terminal 4-piperidones to prevent unwanted double reactions.

At this stage of our work, we report two failures:

(a) The triple amination of cyanuric chloride by G-1 dendron **10c** was unsuccessful. This tentatively yielded a multi-component crude reaction mixture. The formation of the targeted G-2 dendritic melamine could be only deduced by MS (MALDI+) as a constituent of the crude material. Therefore, mono-attachment of linker **HN<(L²)>NH** to G-1 chlorodendrons **8a** and **8b** was not attempted.

(b) We also failed to follow step (v) based on G-1 chlorodendrons **9a–c** (Scheme 4). The envisaged G-1 melamines, having the tandem **SER-NH** (**A–C**)/**D-NH** (**eq**) as peripheral units, appeared unstable during their preparation and/or their isolation.

Therefore, at this point of our work, we had to keep the ensuing interest limited to building-blocks **8a–c**, **11** and **12**, that is, those mandatory for the presence of the **D** (**ax**) *N*-ligand as the peripheral unit.

2.1.4. Synthesis of G-1 dimeric and G-1 trimeric dendrimers

In the final steps of our iterative synthesis, we coupled G-1 chlorodendrons **8a–c** and **11** through the trispiranic linker **HN<(L²)>NH** (linear connexion, vi) and trimerised G-1 melamine **12** with the use of trimesic acid trichloride (angular connexion, vii) (Scheme 5). The depicted aminations were viable, in moderate yields, if the starting G-1 dendrons contained the **D** (**ax**) *N*-ligand as the main **D-NH** (**ax**) peripheral unit. The crude products required purification by column chromatography and trituration, while a loss of material was observed. The same synthetic strategy did not work using G-1 chlorodendrons **9a–c** [*N*-ligands **SER** (**A–C**)/**D** (**eq**)], because the targeted compounds decomposed during preparation and/or column chromatography in the presence of C_1–C_3 alcohols, as these were the only suitable solvents for TLC elution. The tentative trimerisation of **12** in reaction with cyanuric chloride failed, as it also had been the case starting from **10c** (see Section 1.3). Therefore, a *meta*-trivalent aromatic partner more electrophilic than cyanuric chloride, benzene-1,3,5-tricarbonyl chloride, was considered instead. The G-2 dendrimer **15** was obtained smoothly, with a satisfactory optimised yield.

2.2. Structural approach on rotational asymmetry phenomena about the C(*s*-triazine)–N(exocyclic) partial double bonds in G-1, G-2 dendrons and dendrimers

2.2.1. Brief overview of the problem in the case of melamine G-0 dendrons: the *syn*/*anti* rotamerism

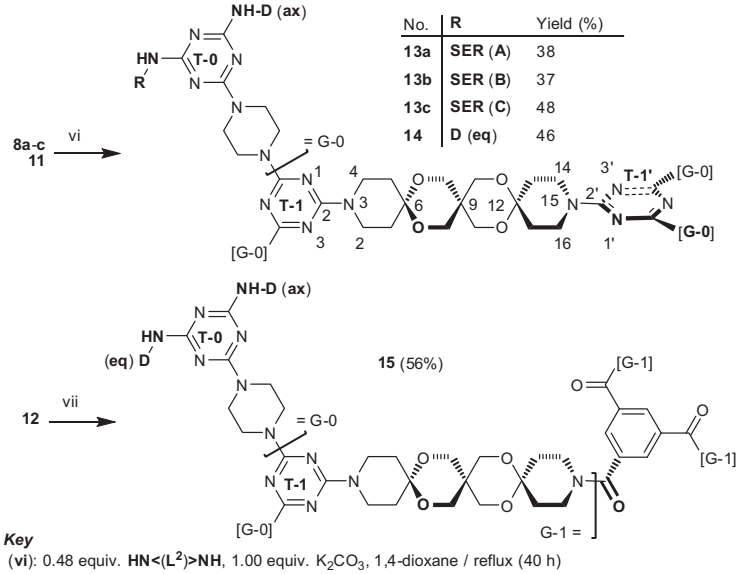
As we demonstrated in a previous preliminary report,[17e] each compound of series **4** and **5** consisted of a four-component mixture of exchangeable rotamers about the C(*s*-triazine)–N(exocyclic) partial double bonds at room temperature. Their number could be easily predicted following a topologically idealised model, which combines the '*a*' (*anti*) and '*s*' (*syn*) location of each *N*-ligand, **SER** or **D** (**ax**, **eq**), with respect to the piperazine ligand (Scheme 6).

The same situation was found for the new melamine **7** (not depicted in Scheme 6) concerning its *N*-ligands **D** (**ax**) versus **D** (**eq**). This is essentially in contrast with other simpler melamines.[18d–k] In our case, rotamerism was identified by NMR as a classically entitled 'slow exchange status between (un)equally populated sites'.[20,30] On the 1D-^{1}H timescale, the supporting number of broad signals **D-N*H*** (**ax**, **eq**) and **SER-N*H*** (indicative protons) did not entirely correlate with the number of the expected environments because of partial overlapping. However, the 2D-^{1}H,^{1}H-COSY charts, for example, of compounds **4c** and **7**, disclosed four distinct cross-peaks as four times the NH-CH $^3J_{H,H}$ couplings. In conclusion, in melamines **4**, **5** and **7**, there were two axes of diastereomerism along the C(-4, -6, *s*-triazine)–N(exocyclic) bonds. Their discrete existence prevented us from establishing the exact *anti*/*syn* nature between the rotameric species revealed above using 2D-^{1}H,^{1}H-NOESY experiments. Upon heating to 80–90 °C, all G-0 melamines became single mediated structures, in a fast freely rotating status about all C(*s*-triazine)–N(exocyclic) connexions.

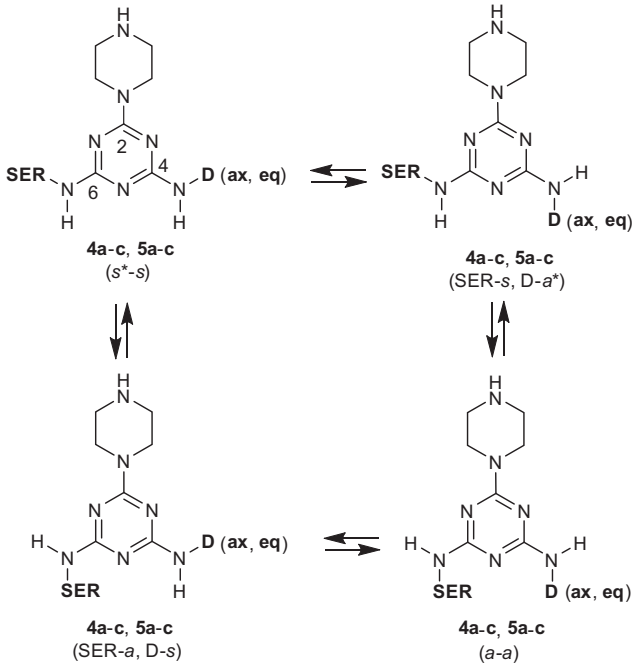
2.2.2. Analysis of G-1 dendrons: The (*in*)/(*out*) global rotamerism inducing homo- and heterotopicity of their G-0 branches

Comparative NMR-based structural analyses of G-1 dendrons **8a–c**, **9a–c**, **10c**, **11** and **12** are shown in Table 1.

Chemical shifts and coupling patterns were similar to those of G-0 precursors.[17e] Temperature gradients of the indicative NH protons revealed major differences between the three types of *N*-ligands. Although this parameter is appropriate for amide



Scheme 5.



Scheme 6.

protons in peptides and proteins,[31] it can also be applied to amino-*s*-triazines, as established by Moreno and Simanek.[18l] Following this extrapolation, if temperature gradient values of 'amide-like' protons in melamines are more negative than −4 ppb/K in strong hydrogen bond acceptor solvents,[18j] such as DMSO-d_6, the NH groups are exposed to the solvent rather than forming intramolecular hydrogen bonds. On the other hand, a temperature gradient value less negative than −4 ppb/K indicates that the NH group preferentially forms intramolecular hydrogen bonds at room temperature. In our cases (Table 1), the following order of temperature gradient values was observed: **D-N*H*** (**eq**)<**D-N*H*** (**ax**)<**SER-N*H***, denoting the progressive diminishing of the exposure to solvent in the C(*s*-triazine)–NH zones. Indeed, the '*closed-chain*' equatorial anchorage **D-N*H***-C(*s*-triazine) was sterically the most permissive to solvation. Conversely, in the '*open-chain*' *N*-ligands, the **SER-N*H*** protons were involved in intramolecular hydrogen bonds with the adjacent hydroxymethyl groups.

As expected, higher hydrodynamic diameters (d_H) were observed in the 2D-^{1}H-DOSY NMR charts of compounds containing the **D** (**eq**) *N*-ligand **9a–c** than in dendrons involving the **D** (**ax**), **8a–c**. Minor changes (**12** vs **11**) or no increase (**10c** vs **8c**) in the d_H values followed attachment of the trispiranic linker.

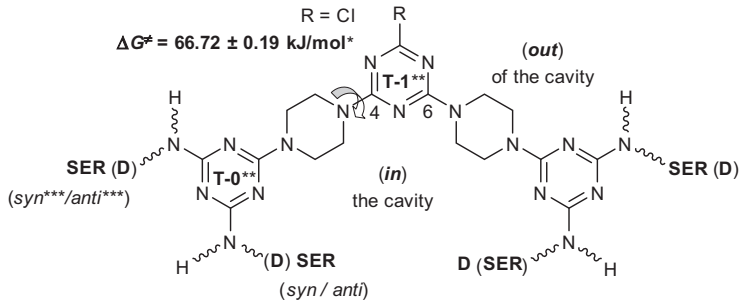
From the point of view of restricted rotational phenomena about the C(*s*-triazine)–N(exocyclic) partial double bonds, we associated the NMR data (Table 1) with the allowance of access towards a library of angularly built rotational species, with a 36-term theoretical diversity. Their discrimination criteria are summarised in Scheme 7.

Thus, the *syn*/*anti local* rotamerism comprising of four species (Scheme 6) was multiplied by an additional one, henceforward entitled *global* rotamerism. We designed the *global* rotational status of G-1 dendrons, hitherto unknown in the *s*-triazine literature, as of type (*in*)/(*out*) (three species) with respect to their angular

Table 1
Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)–N(exocyclic) bonds in G-1 amino-*s*-triazine dendrons **8a–c**, **9a–c**, **10c**, **11** and **12** (on 500 MHz timescale in DMSO-d_6) and their hydrodynamic diameters

No.	T (K)	δ_{NH} (ppm) of the *N*-ligand and multiplicity		Temperature gradients[a]		d_H (nm)[b] [D (μm^2/s)]
Tandem		**D-N*H* (ax)**	**SER-N*H* (A–C)**	**D-N*H* (ax)**	**SER-N*H* (A–C)**	
8a	298	5.92, 5.74 (br s)	5.74, 5.62 (br s)	−4.7, −1.5	−3.1, −0.9	2.18
	353	5.66 (d)[c]	5.57 (s)			[100.2]
8b	298	5.94, 5.79 (br s), 5.70 (br s)	5.65, 5.48 (br s)	−5.5, −2.7, −1.1	−3.8, −0.7	2.17
	353	5.64 (d)	5.44 (s)			[100.4]
8c	298	6.03, 5.97, 5.84 (br s)	5.63, 5.53 (br s)	−5.8, −4.7, −2.4	−2.4, −0.5	2.18
	353	5.71 (br d)	5.50 (s)			[100.1]
10c	298	5.98, 5.90, 5.79 (br s)	5.59, 5.50 (br s)	−5.5, −4.3, −2.6	−2.0, −0.6	2.17
	363	5.62 (d)	5.46 (s)			[100.5]
Tandem		**D-N*H* (eq)**	**SER-N*H* (A–C)**	**D-N*H* (eq)**	**SER-N*H* (A–C)**	
9a	298	6.93, 6.75 (br s)	5.80, 5.68 (br s)	−9.5, −6.2	−3.1, −0.9	2.40
	353	6.41 (bdd app. bt)[d]	5.63 (s)			[90.8]
9b	298	6.96, 6.73, 6.65 (br s)	5.68, 5.53 (br s)	−9.5, −5.3, −3.8	−2.5	2.46
	353	6.44 (br s)	5.54 (s)			[88.7]
9c	298	7.11, 7.00, 6.83, 6.78 (br s)	5.71, 5.54 (br s)	−10.9, −8.9, −5.8, −4.9	−2.0, −1.1	2.55
	353	6.51 (br s)	5.60 (s)			[85.7]
Tandem		**D-N*H* (ax)** **D-N*H* (eq)**		**D-N*H* (ax)** **D-N*H* (eq)**		
11	298	5.96, 5.85 (br s), 5.72 (br d) 6.83, 6.78, 6.73, 6.67 (br s)	—	−5.2, −3.5, −1.5 −8.5, −7.7, −6.9, −6.0	—	2.23 [98.0]
	363	5.62 (br d) 6.28 (br s)	—			
12	298	5.93, 5.88, 5.76, 5.68 (br d) 6.77, 6.65 (br s)	—	−5.5, −4.8, −2.9, −1.7 −8.5, −6.6	—	2.63 [83.0]
	363	5.57 (br d) 6.22 (bt)	—			

[a] Calculated as $(\Delta\delta_{NH}/\Delta T) \times 10^3$ (ppb/K): $\Delta\delta_{NH} = [\delta_{NH}(T) - \delta_{NH}(T_{rt})] < 0$; $\Delta T = (T - T_{rt}) > 0$ (K) where $T = 353$ (or 363) K and T_{rt} is the room temperature, 298 K.
[b] d_H (hydrodynamic diameter) issued from D [diffusion coefficient observed in 2D-^{1}H-DOSY NMR charts in 5 mM DMSO-d_6 (η, dynamic viscosity 2.00×10^{-3} kg m^{-1} s^{-1}) at 298 K] by applying the Stokes–Einstein equation.
[c] (Broad) doublets with a typical $^3J_{H,H}$(ax-NH-5-H-e) = 7.0–9.0 Hz in **D** (**ax**) *N*-ligand of compounds **8a–c** and **10c**.
[d] Broad doublet of doublets as broad triplet with a $^3J_{H,H}$(eq-CH$_2$-NH) = 5.5–6.0 Hz in **D** (**eq**) *N*-ligand of compounds **9a–c** and **12**.



R = Cl (**8a-c**, **9a-c**, **11**); R = **N<(L²)>NH** (**10c**, **12**)

*Ref. [8], [17c]
s-Triazines according to generation, **0 or **1**
***stereochemical descriptors *syn* and *anti* refer to the *N*-ligand orientations against piperazine about the C(*s*-triazine **T-0**)-NH< partial double bonds; additional stereochemical descriptors (**ax**) and (**eq**) were omitted for reasons of simplicity.

Scheme 7.

Table 2
Proposed criteria for assignment of the (*in*)/(*out*) *global* rotamerism in compounds **8a–c**, **9a–c**, **11** and **12**

Criteria		Proposed assignments	
C.I.P. ranking of the *N*-ligands	(i) **D** (**eq**) > **D** (**ax**) > **SER** (**A–C**)[a]; (ii) ***N***-ligand (*out*) > ***N***-ligand (*in*)		
Rotameric arrangements	*Non-alternant*	(***out–out***)	**D** (***out***)-**SER** (*in*)-**SER** (*in*)-**D** (***out***)
			D (**eq**) (***out***)-**D** (**ax**) (*in*)-**D** (**ax**) (*in*)-**D** (**eq**) (***out***)
	Non-alternant	(***in–in***)	**SER** (*out*)-**D** (***in***)-**D** (***in***)-**SER** (*out*)
			D (**ax**) (*out*)-**D** (**eq**) (***in***)-**D** (**eq**) (***in***)-**D** (**ax**) (*out*)
	Alternant	(***out–in*** ≡ ***in–out***)	**D** (***out***)-**SER** (*in*)-**D** (***in***)-**SER** (*out*)
			D (**eq**) (***out***)-**D** (**ax**) (*in*)-**D** (**eq**) (***in***)-**D** (**ax**) (*out*)
^{1}H NMR assignment of the indicative NH protons[b,c]	**D** *N*-ligand	$\delta_{NH\text{-}in}$ (***in–in***) > $\delta_{NH\text{-}in}$ (***in–out***) > $\delta_{NH\text{-}out}$ (***in–out***) > $\delta_{NH\text{-}out}$ (***out–out***)	
	SER *N*-ligand	$\delta_{NH\text{-}in}$ (***in–out***) > $\delta_{NH\text{-}in}$ (***out–out***) > $\delta_{NH\text{-}out}$ (***in–out***) > $\delta_{NH\text{-}out}$ (***in–in***)	

[a] In the decreasing order of structural complexity.
[b] Suggested by the variable vicinity of the most π-deficient rings, *s*-triazine **T-1** and *p*-nitrophenyl, seen as deshielding factors, that is, δ_{NH}-*in* > δ_{NH}-*out*.
[c] The basic assignment as δ_{NH} **D-N*H*** (**eq**) > δ_{NH} **D-N*H*** (**ax**) > δ_{NH} **SER-N*H*** (**A-C**) is given (Table 1).

cavity. In Table 2, some proposed criteria for assignment of this novel stereodynamism are presented.

Concerning G-1 chlorodendrons **8a–c** and **9a–c** (Scheme 7), we previously demonstrated the frozen rotamerism, at room temperature, about the C-4, -6 (*s*-triazine **T-1**)–N(piperazine) partial double bonds with the simpler 'model compound', 2-chloro-4,6-bis(4-oxopiperidin-1-yl)-*s*-triazine.[8,17c†] The 2D-^{1}H,^{1}H-NOESY charts of series **8** (compound **8b**, Fig. 1a), whose compounds **8a–c** had the tandem **SER-NH** (**A–C**)/**D-NH** (**ax**) as peripheral units, were consistent with the presence of just one type of *local* rotamerism, *syn*/*syn*. As shown in Scheme 8, the only three resulting (*in*)/(*out*) *global* rotamers (Table 2) are slowly interchangeable by a single rotation about the (*s*-triazine **T-0**)–N(piperazine) bonds/equilibrium.

In spite of inherent overlapping, the step by step integration of the indicative NH broad singlets of **8b** (Fig. 1) was in agreement with the number of species above. In addition, the ^{13}C NMR spectrum (Fig. 1b) supported not more than four distinct magnetic environments for certain key positions, that is, C-2(6) (*p*-NPh, **D-ax**), C-3(5) (*p*-NPh, **D-ax**), C-4, -6 (**T-0**) and C-4, -6 (**T-1**). These key *C*-nuclei are isochronous in each of the C_2 symmetric *non-alternant* rotamers but anisochronous in the C_1 *alternant* one.

Furthermore, because the (*in*)/(*out*) *global* rotamerism was *local syn*/*syn* diastereoselective, one must observe the two homomorphic[‡] branches [G-0] of compounds **8a–c** becoming homotopic[§] as [G-0^1] or [G-0^2] in the *non-alternant* (***out–out***) or (***in–in***) rotamers, respectively, but diastereotopic, [G-0^1] ≠ [G-0^2], in the *alternant* (***out–in***) one. Moreover, as shown in Scheme 8, the (*in*)/(*out*) rotameric distribution was non-statistical, the decreasing content of the *alternant* stereoisomer (**T-1**)[**G-0^1**][**G-0^2**] being **8c** (80%)>**8b** (70%)>**8a** (60%). Statistics were reasonably established in the case of the G-1 chlorodendron **11**, possessing the tandem **D-NH** (**ax**)/**D-NH** (**eq**) as peripheral units.

The same rotational *syn*/*syn local* diastereoselectivity was found in G-1 trispiranic melamines **10c** and **12**. The content of the (*in*)/(*out*) *global* arrangements was statistical in **12** and less stereoselective in **10c** (60% *alternant*) against **8c** (80% *alternant*).

No rotational diastereoselectivity was observed in series **9**, having the peripheral tandem **SER-NH** (**A–C**)/**D-NH** (**eq**). Thus, the 2D-^{1}H,^{1}H-NOESY charts of compounds **9a–c** exposed no relevant magnetic dipolar interactions of type H (piperazine)/H [**D** (**eq**)] or H (piperazine)/H [**SER** (**A–C**)], that is, we had to presume that the entire 36 species rotational diversity referred to compounds **9a–c** only.

Therefore, we rationalised the discussion above as follows:

(a) The presence of the **D** (**ax**) *N*-ligand was mandatory for the *syn*/*anti local* rotamerism become *syn*/*syn* selective.

(b) Only the tandem of the peripheral units **SER-NH** (**A–C**)/**D-NH** (**ax**) can promote the non-statistical (*in*)/(*out*) *global* rotamerism. The non-statistical rotamerism also depends on the π-deficiency of the *s*-triazine **T-1** branch-cell (see above, higher in **8c** vs **10c**), that is, on the strength of the partial double bond character of the C(*s*-triazine **T-1**)–N(piperazine) bonds.

Our attempt to explain at least the observed *syn*/*syn local* stereopreference in compounds **8a–c** and **10c**, recalled some of our

† For the use of this 'simulation method' in similar cases, see also Ref. 18l.
‡ 'Ligands that are structurally (including configurationally) identical when detached' (Ref. 20a).
§ 'Homomorphic ligands in constitutionally and configurationally equivalent positions' (Ref. 20a).

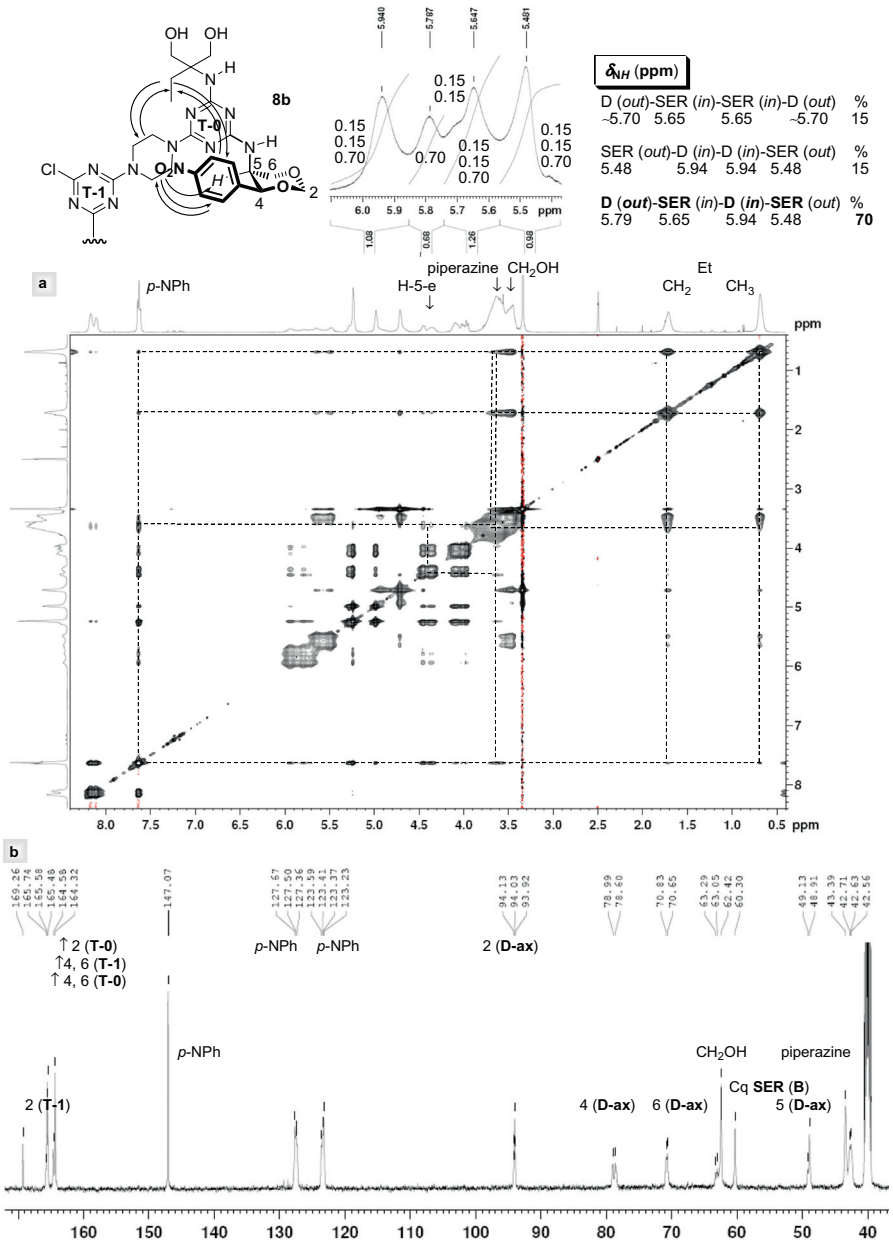


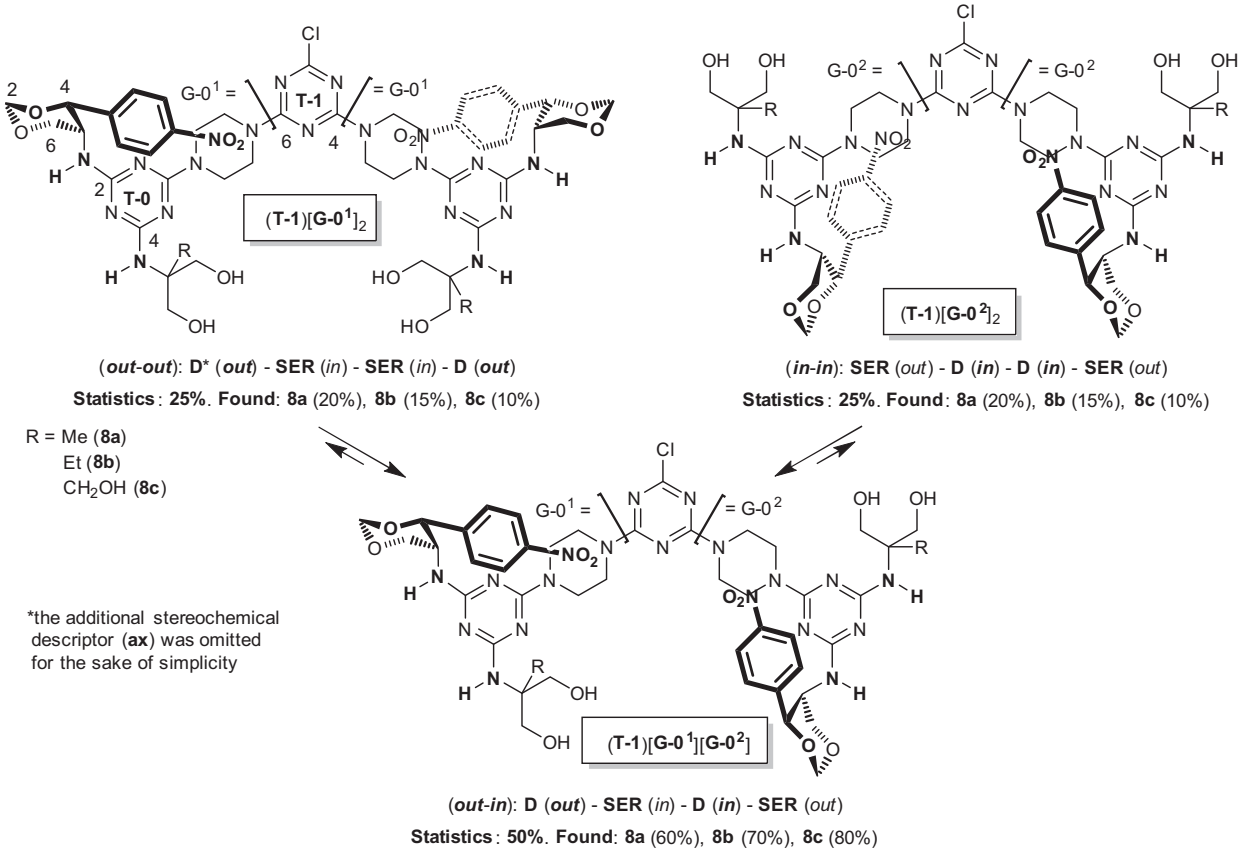
Figure 1. (a) 2D-^{1}H,^{1}H-NOESY Chart of compound **8b** (on 500 MHz timescale in DMSO-d_6 at 298 K) and the relevant magnetic dipolar interactions; (b) ^{13}C NMR spectrum of compound **8b** (on 125 MHz timescale in DMSO-d_6 at 298 K); labelling of the active nuclei as 'C' was omitted for reasons of simplicity.

previous similar findings showing the influence of dipole–dipole interactions on diamino-*s*-triazines containing the **D** (**ax**) *N*-ligand and an additional stronger electron donor *N*-group.[17b] The examples given herein relate to the piperazine nitrogen N-1 in G-0 melamines **4a–c** versus the N-4 in G-1 chlorodendrons **8a–c** (Scheme 9).

Thus, in **8a–c**, a *syn*-orientation of the **D** (**ax**) *N*-ligand should be favoured by the dipole–dipole attraction between the two proximal aromatic rings. The latter are exposed to opposite electronic influences, the π-deficient benzene ring by the presence of a strong electron-attracting *p*-nitro group versus the *s*-triazine by the electron-donating ability of the N-4 'dialkylated' piperazine nitrogen. A similar stabilisation was less plausible in compounds **4a–c** because of the fast acid–base interchange involving the piperazine nitrogen N-4. We previously discussed this detail as occurring in some G-0 serinolic melamines comprising of the piperazine motif.[17e,8] This dynamic behaviour would create a third dipole moment with a repulsive orientation against that of the *p*-nitrophenyl ring. In contrast, for the rotational *syn* option of the **SER** (**A–C**) *N*-ligand, at the present state of our knowledge, just a π-stacking interaction of type –O…H…π (*s*-triazine) could be invoked. This is in line with the results of Insight II 98 calculations by Fuchs et al. in 2002[19a] in the case of G-1 dendritic 2,4,8,10-tetraoxaspiro[5.5]undecanes of some aryl aldehydes. However, the Fuchs example referred to a tris-*O*,*O*-protected 1,3,5-tricarbaldehyde as an aromatic branch-cell richer in π-electrons.

2.2.3. Analysis of trispiranic G-1, G-2 dendrimers: the incidence of the axial (pro)chirality promoted by the (*in*)/(*out*) global rotamerism

The main ^{1}H NMR data for the title dendrimers are shown in Table 3. Except for the normal increase in the d_H values, all ^{1}H parameters, δ_{NH} and temperature gradients, were in the range of those of the G-1 precursors **8a–c**, **11** and **12**. Therefore, we focused

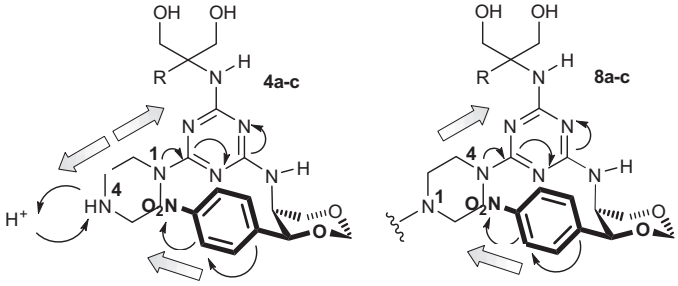


Scheme 8.

our analysis on the prevailing slow-exchange *global* (*in*)/(*out*) rotational stereodynamism in duplicate (compounds **13a–c**, **14**) or in triplicate (**15**), and the *syn*/*syn local* stereoselectivity being rediscovered.

When G-1 chlorodendrons **8a–c** and **11** were linked thorough the trispiranic linker **HN<(L²)>NH**, the newly created partial double bonds, C(2)⁽′⁾[*s*-triazine **T-1**⁽′⁾]–N(3 or 15)(trispirane) (Scheme 5), required the perpendicular arrangement of the planes containing the proximal atoms C(2)/C(4)(trispirane)/N(1)/N(3) (**T-1**) versus C(14)/C(16)(trispirane)/N(1′)/N(3′)/(**T-1**′). Due to the odd number of spiranic carbons in the central linker, a mediated axis connecting the flipping positions (C-2, **T-1**)∼N(3)∼C(6)∼C(9)∼C(12)∼N(15)∼[C-2⁽′⁾,**T-1**⁽′⁾], exists as *pseudo*-allenic.[17f] Subsequent definitions of this axis concern six arrangements as illustrated in Table 4: *achiral* (in **I** and **II**), *proprochiral* (in **III**), *prochiral* (in **IV** and **V**) and *chiral* (in **VI**). Our discrimination takes into account, once again, the homo- and/or heterotopic[¶] relationship between the homomorphic [G-0] branches,[17f] created by the (*in*)/(*out*) *global* rotamerism, [G-0¹] and/or [G-0²]. As one can see, the *axially (pro)chiral* arrangements **IV**, **V** and **VI** are statistically favoured, each one at 25%. Furthermore, the ^{1}H NMR line shape of the indicative NH protons (Fig. 2) was consistent with the expected slow exchange status between the unequally populated sites **I**–**VI**. The same calculations as in the case of the G-1 dendrons (Fig. 1) provided the rotameric occurrences in **13a–c** being different from statistics although they refer to just one terminal site of the dendrimer (Fig. 2).

Therefore, the following assignments are reasonably limited:



Scheme 9.

(a) Since statistical calculations resulted in equal contents of *achiral* **I**, **II** and *proprochiral* **III** dendritic species, 6.25% (Table 4), which were not found experimentally, except in the case of the peripheries of compound **13b** (Fig. 2), we were unable to predict any 'rule' for certain terminal stereoselective couplings **8a–c** → **13a–c**. (b) By combining statistics versus experiment, we could estimate, however, the occurrence of axially *prochiral* (**IV** and **V**) and *axially chiral* **VI** arrangements as shown in Table 4. As an example calculation in the case of compound **13b**, one has the rotameric abundance of the *alternant* arrangement, as *one type* of *one* terminal site, as 87% (Fig. 2). This abundance is disseminated, statistically, in **IV** (25%) (containing *one alternant* terminal site), **V** (25%) (containing *one alternant* terminal site) and **VI** (25%) (containing *two alternant* terminal sites) in a **IV/V/VI** = 1:1:1 ratio. This follows an experimental abundance of 29:29:29%.

(c) The same approach was applied in the case of compound **14** (Fig. 2, not included in Table 4) by defining its homomorphic branches [G-0] as [G-0¹] = [**D** (**eq**) (*out*)][**D** (**ax**) (*in*)](**T-0**)(**L¹**)-different from [G-0²] = [**D** (**eq**) (*in*)][**D** (**ax**) (*out*)](**T-0**)(**L¹**)-in a

[¶] 'Two homomorphic ligands are heterotopic if replacement of each in turn by a new ligand, not already present at the sites of attachment of the ligands, gives rise to distinct products' (Ref. 20a).

Table 3
Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)–N(exocyclic) bonds in G-1 dimeric **13a–c**, **14** and G-2 trimeric **15** dendrimers (on 500 MHz timescale in DMSO-d_6) and their hydrodynamic diameters

No.	T (K)	δ_{NH} (ppm) of the *N*-ligand and multiplicity		Temperature gradients		d (nm) [D (μm^2/s)]
Tandem		**D-N*H* (ax)**	**SER-N*H* (A–C)**	**D-N*H* (ax)**	**SER-N*H* (A–C)**	
13a	298	5.86, 5.70 (br s)	5.70, 5.60 (br s)	−4.9, −2.5	−3.4, −1.8	2.89
	363	5.54 (d)	5.48 (s)			[75.5]
13b	298	5.87, 5.71 (br s)	5.71, 5.59, 5.47 (br s)	−4.8, −2.3	−4.9, −3.1, −1.2	3.06
	363	5.56 (d)	5.39 (s)			[71.4]
13c	298	5.99, 5.91, 5.79 (br s)	5.59, 5.50 (br s)	−5.6, −4.5, −2.6	−2.0, −0.6	3.08
	363	5.62 (d)	5.46 (s)			[70.9]
Tandem		**D-N*H* (ax)** **D-N*H* (eq)**		**D-N*H* (ax)** **D-N*H* (eq)**		
14	298	5.92, 5.89, 5.76, 5.69 (br s) 6.76, 6.65 (br s)	–	−5.2, −4.8, −2.8, −1.7 −8.3, −6.6	–	3.12 [70.0]
	363	5.58 (br d) 6.22 (br s)	–			
15	298	5.93, 5.90, 5.77, 5.69 (br s) 6.75, 6.64 (br s)	–	−5.7, −5.1, −3.1, −1.8 −8.5, −6.8	–	4.20 [52.0]
	363	5.57 (br d) 6.20 (bt)	–			

spirodendritic environment. Calculations gave very similar results as in the case of precursors **11** and **12** of **14**, that is, a statistical rate of the (*in*)/(*out*) *global* rotamerism.

On the quantitative ^{13}C NMR time scale, spectra of compounds **13a–c** and **14** fully confirmed the desired structures. In continuation of our previous findings with respect to the relevance of *s*-triazine *C*-nuclei integrations disclosing skeleton asymmetries at the dendritic level,[8] the present analysis confirmed and completed the ^{1}H NMR assignments. As shown in Figure 3, compounds **13a** and **14** exhibited more than five of the expected types of *s*-triazine carbons. Overall, the asymmetry of dendrimers **13a–c** and **14** was best revealed as *C*-anisochrony in *s*-triazines **T-1** branch-cells, where between two and four δ_C values were displayed by the carbon nuclei in positions 4 against 6. It follows that the steric non-equivalence between dendritic branches, [G-0^1] ≠ [G-0^2], was immediate.

Finally, the most relevant features concerning dendrimer **15** are illustrated in Figure 4. On the ^{1}H NMR timescale (Fig. 4a), one cannot distinguish any significant difference between **15** and its precursors **11** and **12** (Table 1) or its dimeric analogue **14** (Table 2). The peripheral tandem **D-NH** (**eq**)/**D-NH** (**ax**) revealed the same statistical (*in*)/(*out*) orientation with respect to the angular cavities.

The quantitative ^{13}C NMR spectrum was much more informative (Fig. 4).

(a) First of all, in the core-region, each of the three different types of 1,3,5-tricarbonylbenzene *C*-nuclei showed a unique resonance as CH (123.4 ppm), C_q (148.9) and >C=O (168.0). Therefore, a *propeller* arrangement[18j] of the three dendritic branches [G-1^1], [G-1^2] and [G-1^3] around the proximity of the core was deduced. However, this C_3 symmetric organisation concerned only the central part of the macromolecule.

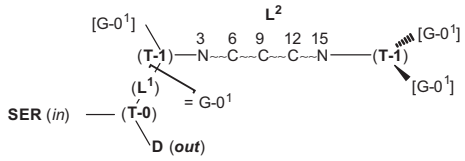
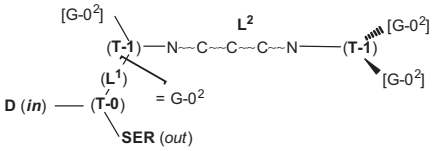
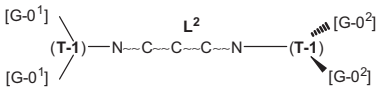
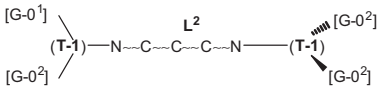
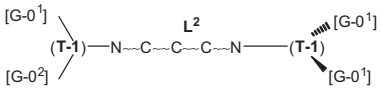
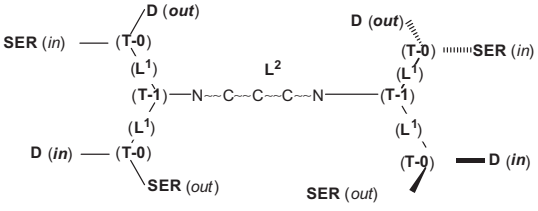
(b) Furthermore, we followed the same postulated rules with respect to δ_C values as those already listed in Figure 3. Thus, certain unequal integrations of the *s*-triazine **T-1** carbons (Fig. 4b) indicated two unexpected situations of anisochrony. The integrals of each of the anisochronous carbons C-4 and C-6 in *s*-triazines **T-1**[G-1^{1,2}] ($\delta_{C\text{-}4} \neq \delta_{C\text{-}6}$) were double compared with the integral of the anisochronous carbons C-4 and C-6 ($\delta_{C\text{-}4} \neq \delta_{C\text{-}6}$) in *s*-triazines **T-1**[G-1^3]. Next, the integral of the isochronous carbons C-2 in *s*-triazines **T-1**[G-1^{1,2}] was also double versus the integral referring to the anisochronous C-2 carbon in *s*-triazine **T-1**[G-1^3], that is, $\delta_{C\text{-}2,\ \mathbf{T\text{-}1}}$[G-1^1] = $\delta_{C\text{-}2,\ \mathbf{T\text{-}1}}$[G-1^2] ≠ $\delta_{C\text{-}2,\ \mathbf{T\text{-}1}}$[G-1^3]. All peripheral C-4 carbons in branch-cells **T-0**[G-1$^{1-3}$] were isochronous, as were C-6 in the same *s*-triazines. Our attempts to explain these differences started, again, from the statistical manner in which this dendrimer was built. Thus, the three branches [G-1] were homomorphic before trimerisation because the *syn*/*syn local* and *alternant* (*in*)/(*out*) *global* orientations were simultaneously adopted by the peripheral units. After trimerisation, a sterical (non)-equivalence as [G-1^1] = [G-1^2] ≠ [G-1^3] appeared. Indeed, as depicted in Figure 4, following trimerisation, branches [G-1^1] and [G-1^2] had the same orientation of the *alternant* [G-0] peripheries, **D** (**eq**) 'front'/**D** (**ax**) '*rear*'. Meanwhile, this order was inverted in branch [G-1^3] as **D** (**ax**) 'front'/**D** (**eq**) '*rear*'. To conclude, one has the statistical combination of three elements, [G-1^1], [G-1^2] and [G-1^3], against just two oriented options, 'front'/'rear'.

(c) Axial chirality was present, in triplicate, because, in each branch [G-1$^{1-3}$], the *pseudo*-allenic axis mediating positions —C(=O, amide)∼N(3)∼C(6)∼C(9)∼C(12)∼N(15)∼(C-2, **T-1**) bears two different ligands at each terminal position. In branch [G-1^3], one has {[G-1^1][G-1^2]*m*-C_6H_3} ≠ (=O, amide) against peripheral [G-0^1] ≠ [G-0^2]; in branch [G-1^2], one has {[G-1^1][G-1^3]*m*-C_6H_3} ≠ (=O, amide) against peripheral [G-0^1] ≠ [G-0^2]; in branch [G-1^1], one has {[G-1^2][G-1^3]*m*-C_6H_3} ≠ (=O, amide) against peripheral [G-0^1] ≠ [G-0^2].

3. Conclusion

Starting from optically active amino-1,3-dioxanes of (1*S*,2*S*)-*p*-nitrophenylserinol (or its dimethylamino analogue), designed as '*closed-chain*' peripheral units **D-NH$_2$** in tandem with commercial C-2-substituted serinols as '*open-chain*' peripheral units **SER-NH$_2$**, we have described the iterative synthesis and structure of a new family of G-1 dimeric and G-1 trimeric spirodendritic melamines. In our convergent strategy, we omitted protection–deprotection steps. The entire chemistry was feasible only if the anancomeric amino-1,3-dioxane building-block had the amino group in an axial C-5 position **D-NH$_2$** (**ax**), in partnership with **SER-NH$_2$** or an anancomeric amino-1,3-dioxane possessing an aminomethyl group located in the equatorial C-2 position, **D-NH$_2$** (**eq**). The first use of a trispirotetraacetal diamine linker was reported, together with its versatile aptitude to be chemoselectively attached to elaborated, *N*,*N*′-unsymmetrically substituted chlorodiamino-*s*-triazines as G-1 chlorodendrons. Some (un)surmountable synthetic problems originated from the restricted rotational phenomena in amino-*s*-triazines about their C(*s*-triazine)–N(exocyclic) partial

Table 4
Possible co-orientations of global rotamers (*in*)/(*out*) (*alternant* vs *non-alternant*) in dimeric G-1 dendrimers **13a–c**

Nature of the *pseudo*-allenic axis mediating positions (C-2-**T-1**)~N(3)~C(6~9~12)~N(15)~[C-2$^{(')}$-**T-1**$^{(')}$]	Possible co-orientations of rotamers and their statistical versus experiment calculated abundances
I. ***Achiral*** in [**G-0**^{1}]$_2$(**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{1}]$_2$[a] Branches [**G-0**^{1}]: homotopic	Non-alternant versus non-alternant identical: (***out–out***) versus (***out–out***) 
II. ***Achiral*** in [**G-0**^{2}]$_2$(**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{2}]$_2$ Branches [**G-0**^{2}]: homotopic	Statistics: 6.25%; found: — Non-alternant versus non-alternant identical: (***in–in***) versus (***in–in***) 
III. ***Proprochiral*** in [**G-0**^{1}]$_2$(**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{2}]$_2$ Branches [**G-0**^{1}]: homotopic Branches [**G-0**^{2}]: homotopic	Statistics: 6.25%; found: — Non-alternant versus non-alternant different: (***out–out***) versus (***in–in***) 
IV. ***Prochiral*** in [**G-0**^{1}][**G-0**^{2}](**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{2}]$_2$ Geminal [**G-0**^{2}]$_2$ branches: enantiotopic	Statistics: 12.5%; found: — Alternant versus non-alternant: (***out–in***) versus (***in–in***) 
V. ***Prochiral*** in [**G-0**^{1}][**G-0**^{2}](**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{1}]$_2$ Geminal branches [**G-0**^{1}]$_2$: enantiotopic	Statistics: 25% Found: 13a (20%), **13b** (29%), **13c** (20%) Alternant versus non-alternant: (***out–in***) versus (***out–out***) 
VI. ***Chiral*** in [**G-0**^{1}][**G-0**^{2}](**T-1**)-(**L**^{2})-(**T-1**)[**G-0**^{1}][**G-0**^{2}] Branches [**G-0**^{1}]: enantiotopic Branches [**G-0**^{2}]: enantiotopic	Statistics: 25% Found: **13a** (20%), 13b (29%), **13c** (20%) Alternant versus alternant: (***out–in***) versus (***out–in***)  Statistics: 25% Found: **13a** (20%), **13b** (29%), **13c** (20%)

[a] Additional labelling as (**ax**), **A**–**C**, (') and (") were omitted for reasons of simplicity as well as —NH— and >N— bridges.

double bonds, combined with solvation effects. This classic feature was gradually rediscovered in our chemistry. Angular dimerisation of G-0 melamines yielded G-1 chlorodendrons as libraries with an expected 36 rotational term topological diversity. Nevertheless, the tandems of peripheral *N*-ligands **SER**/**D**(**ax**) and **D** (**ax**)/**D** (**eq**) demonstrated their existence as only three *global* (*in*)/(*out*) non-

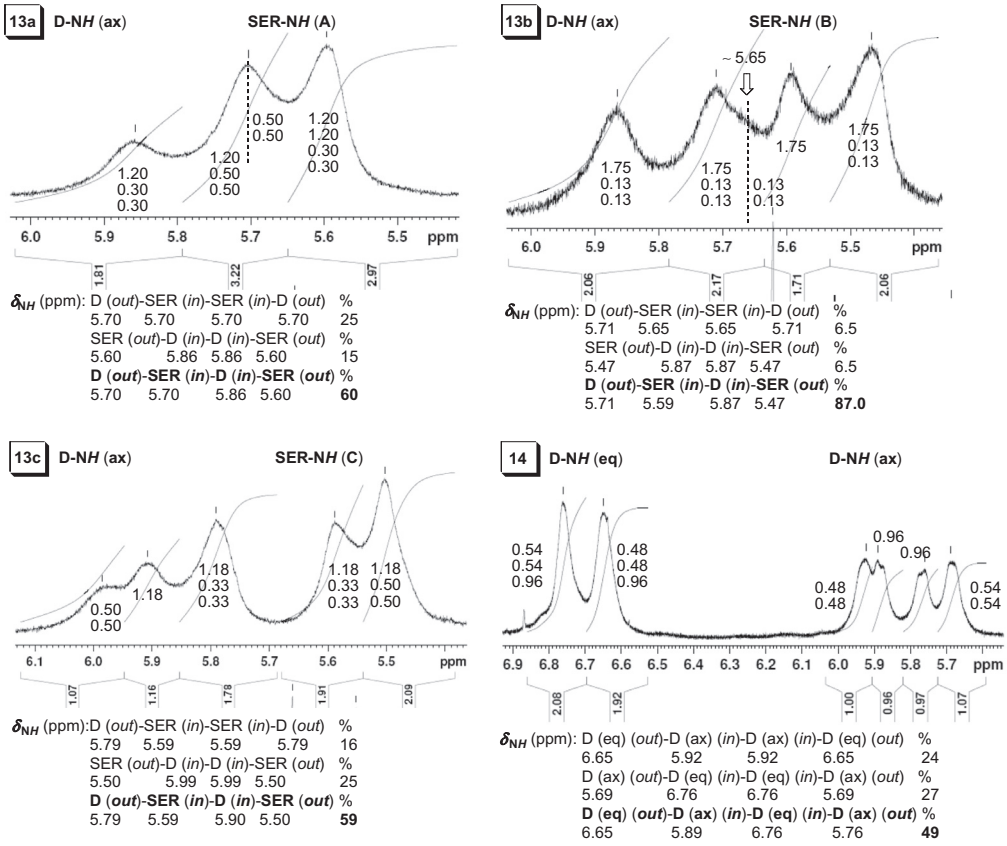


Figure 2. Rotameric (*in*)/(*out*) abundance in dendrimers **13a–c** and **14** with respect to *one terminal site* (details from ^{1}H NMR of the indicative protons NH zone on 500 MHz timescale in DMSO-d_6 at 298 K).

statistical arrangements with respect to the angular cavity, because the *local* G-0 rotamerism became *syn–syn* diastereoselective. First discrimination of G-1 rotameric dendrons in terms of homo- and heterotopicity of their [G-0] branches was discussed. Finally, linear connexion of G-1 chlorodendrons through a trispirotetraacetalic diamine linker gave G-1 dimers exhibiting axial (pro)chirality promoted by the heterotopic nature of the [G-0] branches. Angular trimerisation of a G-1 spirodendritic melamine allowed the detection of axial chirality in triplicate, based on the same concepts as above, in the resulting G-2 dendrimer.

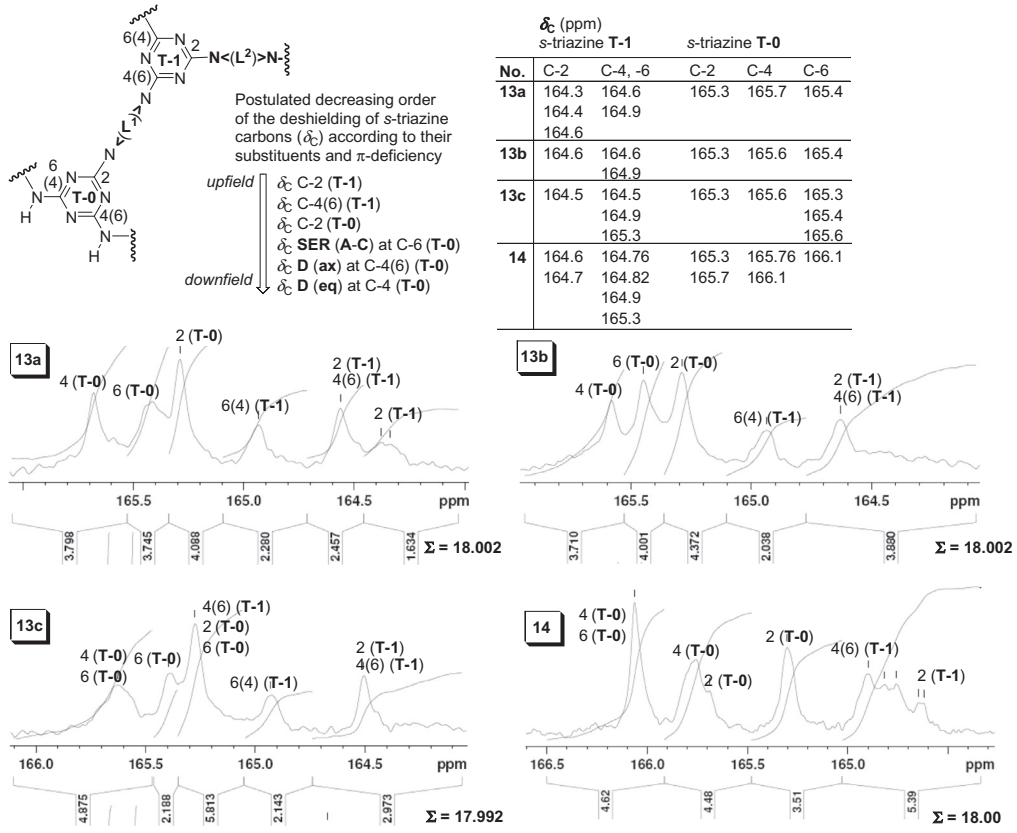
4. Experimental

4.1. General

Melting points were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Bruker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. VT ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY, 2D-^{1}H-DOSY NMR, Quantitative and ^{13}C-DEPT experiments were recorded on Bruker® AV 400 or 500 instruments operating at 400 or 500 MHz for ^{1}H and at 100 or 125 MHz for ^{13}C nuclei. All chemical shifts (δ values) are given in parts per million (ppm); all homocoupling patterns ($^{n}J_{H,H}$ values) are given in Hertz. For determining ^{13}C NMR quantitative integration, all 1D-^{13}C spectra were acquired using the inverse gated proton decoupling pulse sequence: zgig. All 2D-^{1}H-DOSY spectra were performed using the ledbpgp2s pulse sequence: 2D sequence for diffusion measurement using stimulated echo and longitudinal eddy current delay (LED). The diffusion times (Δ) were from 150 to 250 ms and the gradient pulse lengths (δ) were from 1.5 to 2 ms. The size of the raw data sets were 32×8192. The gradient intensity values were equally spaced from 2% to 95%. For getting 2D-^{1}H,^{1}H-NOESY Experiments, the mixing times were from 550 to 900 ms. In the NMR descriptions, some specific abbreviations were used: 'br d' (broad doublet), 'br t' (broad triplet), 'bdd' (broad doublet of doublets), 'brm' (broad multiplet), Pip (Piperazine linker), *p*-NPh (*p*-nitrophenyl), Tsp (trispirane linker), T-0, -1 (*s*-triazine, branch cell), SER A–C, D-ax, D-eq (peripheral *N*-ligand, Scheme 2). TLC was performed by using aluminium sheets with silica gel 60 F254 (Merck®); column chromatography was conducted on Silica gel Si 60 (40–63 mm, Merck®). IR spectra were recorded on a JASCO® FT-IR 6100 Spectrometer. Only relevant absorption maxima are listed, throughout, in cm^{-1}: s (strong), m (medium) and w (weak). Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra were carried out as follows: ESI spectra on a Bruker® Esquire Instrument with ions trapping in electrospray mode; MALDI spectra on Micromass TOF-SpecE MALDI® Instrument equipped with a time of flight analyser and a nitrogen pulsed laser (337 nm). Specific rotations $[\alpha]_D^{20}$ were measured on a POLAMAT® Karl-Zeiss Jena instrument All reagents and solvents were of commercial quality and used as such with no supplementary purification. The starting (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol had a 99% enantiomeric purity. Synthesis and data of compounds **2**–**5a**–**c** are reported elsewhere.[17e]

4.2. 2-Chloro-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino-*s*-triazine 6

To anhydrous K_2CO_3 (0.80 g, 5.80 mmol) suspended in anhydrous $CHCl_3$ (100 mL), freshly prepared (4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxane **D-NH$_2$** (**ax**) (1.30 g, 5.80 mmol) was



δC (ppm)

	s-triazine T-1		s-triazine T-0		
No.	C-2	C-4, -6	C-2	C-4	C-6
13a	164.3 164.4 164.6	164.6 164.9	165.3	165.7	165.4
13b	164.6	164.6 164.9	165.3	165.6	165.4
13c	164.5	164.5 164.9 165.3	165.3	165.6	165.3 165.4 165.6
14	164.6 164.7	164.76 164.82 164.9 165.3	165.3 165.7	165.76 166.1	166.1

Figure 3. Details from the quantitative ^{13}C NMR spectra of dendrimers **13a–c** and **14** in the *s*-triazines region (on 125 MHz time scale in DMSO-d_6 at 298 K); labelling of the active nuclei as 'C' as well as their discrimination with additional symbols (') and (") was omitted for reasons of simplicity.

added with vigorous stirring. The resulting suspension was cooled at −5 °C when cyanuric chloride (1.07 g, 5.80 mmol) was added. The reaction mixture was then allowed to gently reach room temperature and was kept as such for an additional 24 h. After this period, TLC monitoring indicated the intermediate 2,4-dichloro-6-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine **1d** as a single spot (ligroin/acetone 1.5:1 v/v, R_f = 0.90). Freshly prepared (2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxane **D-NH$_2$** (**eq**) (1.60 g, 5.80 mmol) and anhydrous K_2CO_3 (0.80 g, 5.80 mmol) were added and the reaction mixture was stirred at room temperature for 48 h then heated at reflux (60 °C) for additional 8 h (TLC monitoring, ligroin/acetone 1.5:1 v/v). When **D-NH$_2$** (**eq**) and **1d** were detected in small traces only, the reaction mixture was cooled at room temperature. Minerals were filtered off and washed with anhydrous $CHCl_3$. The organic filtrate was evaporated under reduced pressure to dryness to provide 3.80 g of crude product. This was purified by trituration from Et_2O/THF 3:1 (v/v) mixture at −20 °C to give 3.36 g pure **6** (94% yield with respect to cyanuric chloride). Yellowish powder, mp 110–112 °C. Found: C, 50.74; H, 5.05; N, 17.88; $C_{26}H_{29}ClN_8O_8$ (616.18) requires: C, 50.61; H, 4.74; N, 18.16; R_f (60% ligroin/acetone) 0.83; IR ν_{max} (KBr) 3318 (m), 2936 (m), 2858 (m), 2858 (m), 2791 (m), 1575 (s), 1519 (s), 1408 (w), 1346 (s), 1153 (m), 1173 (s), 1083 (s), 1030 (s), 966 (m), 846 (m), 805 (m), 748 (m), 709 (m) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 2.23 (6H, s, NMe_2), 2.89 (1H, s, H-5-e, D-eq), 3.46 (2H, br s, CH_2NH), 3.99 (1H, br s, H-6-a, D-eq), 4.04 (1H, br s, H-6-a, D-ax), 4.11 (1H, br s, H-6-e, D-ax), 4.45 (2H, br s, H-5-e, D-ax; H-6-e, D-eq), 4.93 (1H, s, H-2-a, D-eq), 4.99 (1H, d, $^2J_{H,H}$ = 5.8 Hz, H-2-a, D-ax), 5.18 (1H, s, H-4-a, D-eq), 5.22 (1H, d, $^2J_{H,H}$ = 5.8 Hz, H-2-e, D-ax), 5.26 (1H, s, H-4-a, D-ax), 6.87, 7.05 (1H, br s, D-ax-N*H*), 7.31, 7.53, (1H, br s, D-eq-N*H*), 7.63 (2H d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 7.65 (2H, d, $^3J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 8.11 (2H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 8.15 (2H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 43.8 (NMe_2), 44.16, 44.21, 44.3 (CH_2NH), 49.3, 49.5, 49.6 (C-5, D-ax), 58.5 (C-5, D-eq), 64.4, 64.5, 64.6 (C-6, D-eq), 70.0, 70.1, 70.4, 70.5 (C-6, D-ax), 78.2, 78.3, 78.5 (C-4, D-ax), 79.95, 79.98, 80.07, 80.11, 80.3 (C-4, D-eq), 93.88, 93.94 (C-2, D-ax), 98.9, 99.05, 99.13, 99.2 (C-2, D-eq), 123.18, 123.23, 123.3 (C-2, -6, *p*-NPh), 127.0, 127.6, 127.7, 127.8 (C-3, -5, *p*-NPh), 146.70, 146.74, 146.76, 146.82, 147.1, 148.7, 148.8 (C-1, -4, *p*-NPh), 165.4, 165.5, 165.6, 165.68, 165.74, 165.85, 165.9, 166.0 (C-4, -6, *s*-triazine), 168.2, 168.4, 168.6, 169.0 (C-2, *s*-triazine) ppm; MS (ESI+) *m*/*z* (rel. abund.%) 617.13 (M+H) (100); $[\alpha]_D^{20}$ = +160.1 (0.5% DMSO).

4.3. 1-{4-{[(2*R*,4*S*,5*S*)-5-(Dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino-6-[(4*S*,5*S*)-4-(4nitrophenyl)-1,3-dioxan-5-yl]amino-*s*-triazin-2-yl}-piperazine 7

In a solution obtained by dissolving anhydrous piperazine (1.23 g, 14.26 mmol) in anhydrous THF (125 mL), anhydrous K_2CO_3 (0.49 g, 3.57 mmol) was suspended at room temperature with vigorous stirring. To this suspension, chlorodiamino-*s*-triazine **6** (2.20 g, 3.57 mmol) was added portionwise (5 equal portions, 0.44 g **6**/portion, every 2 h). After each addition and within 2 h, TLC monitoring indicated the completion of reaction as follows: total consumption of **6** (ligroin/acetone = 1.5:1 v/v, visualisation in UV 254 nm) and formation of **7** (EtOH/aq NH_3 25% = 9:1 v/v, R_f = 0.78, double visualisation, UV 254 nm then I_2 bath). Finally, the reaction mixture was stirred at room temperature for additional 24 h. Minerals were filtered off and well-washed with anhydrous THF. The combined THF solution was evaporated under reduced pressure to yield 2.32 g crude material which was purified by

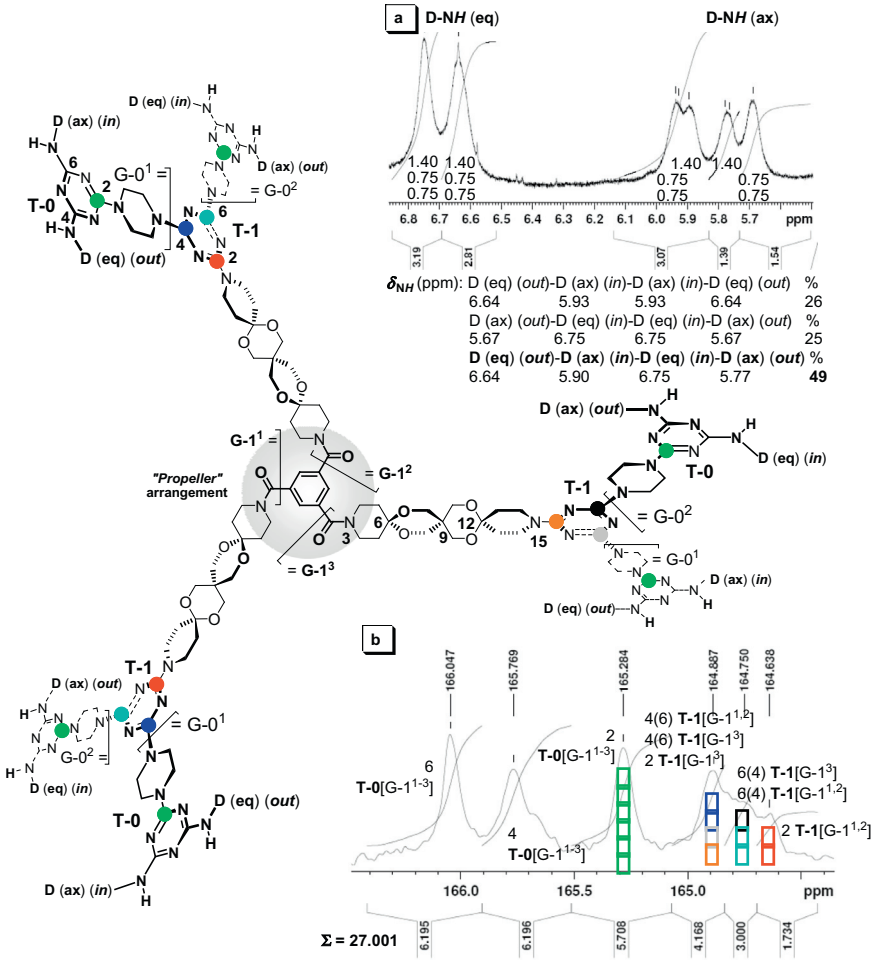


Figure 4. Deduced main structure of dendrimer **15**. (a) Detail from the ^{1}H NMR spectrum in the **D-N*H*** indicative protons region (on 500 MHz timescale in DMSO-d_6 at 298 K); (b) detail from Quantitative ^{13}C NMR spectrum in the *s*-triazines region (on 125 MHz time scale in DMSO-d_6 at 298 K).

trituration from a Et_2O/THF 3:1 (v/v) mixture at −20 °C to give 2.19 g pure **7** (92% yield with respect to **6**). Orange-yellowish powder, mp 155–157 °C (Et_2O/THF = 3:1). Found: C, 54.29; H, 6.06; N, 20.88; $C_{30}H_{38}N_{10}O_8$ (666.29) requires: C, 54.05; H, 5.75; N, 21.01; R_f (90% EtOH/aq NH_3 25% v/v) 0.78; IR ν_{max} (KBr) 2936 (m), 2852 (m), 2791 (m), 1578 (s), 1545 (s), 1522 (s), 1444 (m), 1346 (s), 1173 (m), 1095 (m), 1028 (m), 1016 (m), 849 (w), 807 (m), 709 (m) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 2.23 (6H, s, NMe_2), 2.62–2.64 (4H, m, H-3, -5, Pip), 2.86 (1H, dd app. t, $^{3}J_{H,H}$ = 2.8 Hz, H-5-e, D-eq), 3.45 (2H, dd app. t, $^{3}J_{H,H}$ = 3.5 Hz, C*H*$_2$NH), 3.50 (4H, t, $^{3}J_{H,H}$ = 5.0 Hz, H-2, -6, Pip; 1H, H-4, Pip), 3.96 (1H, dd, $^{2}J_{H,H}$ = 12.5 Hz, $^{3}J_{H,H}$ = 3.0 Hz, H-6-a, D-eq), 4.02 (1H, d, $^{2}J_{H,H}$ = 10.9 Hz, H-6-a, D-ax), 4.10 (1H d, $^{2}J_{H,H}$ = 10.9 Hz, H-6-e, D-ax), 4.45 (1H d, $^{2}J_{H,H}$ = 12.5 Hz, H-6-e, D-eq), 4.46 (1H, d, $^{3}J_{H,H}$ = 8.0 Hz, H-5-e, D-ax), 4.92 (1H, dd app. t, $^{3}J_{H,H}$ = 4.8 Hz, H-2-a, D-eq), 4.99 (1H, d, $^{2}J_{H,H}$ = 5.8 Hz, H-2-a, D-ax), 5.16 (1H, d, $^{3}J_{H,H}$ = 3.5 Hz, H-4-a, D-eq), 5.22 (1H, d, $^{2}J_{H,H}$ = 5.8, H-2-e, D-ax), 5.23 (1H, s, H-4-a, D-ax), 5.49 (1H, d, $^{3}J_{H,H}$ = 8.0 Hz, D-ax-N*H*), 6.12 (1H, br s, D-eq-N*H*), 7.62 (2H, d, $^{3}J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 7.63 (2H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.09 (2H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 8.14 (2H, d, $^{3}J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 43.8 (NMe_2), 44.2, 44.3 (C-2, -6, Pip; CH_2NH), 46.0 (C-3, -5, Pip), 48.6, 48.79, 48.84 (C-5, D-ax), 58.5 (C-5, D-eq), 64.4 (C-6, D-eq), 70.7, 70.8 (C-6, D-ax), 78.9 (C-4, D-ax), 80.1 (C-4, D-eq), 94.0 (C-2, D-ax), 99.8 (C-2, D-eq), 123.19, 123.23, 123.4 (C-2, -6, *p*-NPh), 127.0, 127.4, 127.49, 127.51, 127.55, 127.57 (C-3, -5, *p*-NPh), 146.7, 146.98, 147.00, 147.04, 147.2, 149.0 (C-1, -4, *p*-NPh), 164.63, 164.67, 164.71 (C-2, *s*-triazine), 165.70, 166.1 (C-4, -6, *s*-triazine) ppm. MS (ESI+) *m/z* (rel. abund.%) 667.27 (M+H) (100); $[\alpha]_D^{20}$ = +112.0 (0.5% DMSO).

4.4. Typical procedure for the synthesis of compounds 8a–c, 9a–c and 11. Preparation of compound 8c

Anhydrous K_2CO_3 (0.38 g, 2.76 mmol) was suspended, at room temperature and with vigorous stirring, in a solution obtained by dissolving compound **4c** (1.40 g, 2.76 mmol) in anhydrous THF (120 mL). The resulting suspension was cooled at −15 °C when cyanuric chloride (0.23 g, 1.26 mmol) was added. The reaction mixture was allowed to reach room temperature and was kept as such for additional 12 h with stirring. THF was replaced by 1,4-dioxane and the reaction mixture was refluxed for additional 35 h when TLC monitoring (Toluene/EtOH = 2:1 v/v) confirmed the formation of **8c**. Minerals were filtered off and well-washed with anhydrous 1,4-dioxane. The combined 1,4-dioxane solution was evaporated under reduced pressure to yield 1.54 g crude material which was purified by flash column chromatography (eluent Toluene/EtOH = 2:1 v/v). The isolated **8c** (1.50 g) was then triturated from a Et_2O/THF 4:1 (v/v) mixture at −20 °C to give the pure product (1.18 g **8c**, 84% yield with respect to cyanuric chloride).

4.4.1. 2-Chloro-4,6-bis{4-{6-{[1,3-dihydroxy-2-(methyl)prop-2-yl]-amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 8a

Yield 49% (0.59 g, 0.54 mmol) **8a** starting from 1.20 g (2.45 mmol) **4a** and 0.21 g (1.11 mmol) cyanuric chloride. Yellowish powder, mp 226–229 °C (flash column chromatography, eluent Toluene/^{i}PrOH = 3:1 v/v). Found: C, 49.51; H, 5.51; N, 23.99; $C_{45}H_{58}ClN_{19}O_{12}$ (1091.42) requires C, 49.47; H, 5.35; N, 24.36; R_f (75% Toluene/^{i}PrOH) 0.60; IR ν_{max} (KBr) 3394 (m), 2862 (m), 1560 (s), 1494 (s), 1439 (s), 1346 (m), 1273 (m), 1173 (m), 1106 (w), 1083 (w), 1028 (m), 978 (m), 997 (m), 852 (w), 810 (m), 745 (w), 712 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 1.23 (6H, s, Me), 3.48 (4H, d, $^{2}J_{H,H}$ = 10.6 Hz, CH_2OH), 3.58 (4H, d, $^{2}J_{H,H}$ = 10.6 Hz, CH_2OH), 3.64 (8H, t, $^{3}J_{H,H}$ = 4.5 Hz, H-3, -5, Pip), 3.71 (8H, d, $^{3}J_{H,H}$ = 4.5 Hz, H-2, -6, Pip), 4.03 (2H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-a, D-ax), 4.13 (2H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-e, D-ax), 4.44 (2H, d, $^{3}J_{H,H}$ = 8.0 Hz, H-5-e, D-ax), 4.57 (4H, br s, OH), 5.01 (2H, d, $^{2}J_{H,H}$ = 6.3 Hz, H-2-a, D-ax), 5.24 (2H, d, $^{2}J_{H,H}$ = 6.3 Hz, H-2-e, D-ax), 5.25 (2H, s, H-4-a, D-ax), 5.57 (2H, s, SER-N*H*), 5.66 (2H, d, $^{3}J_{H,H}$ = 8.0 Hz, D-ax-N*H*), 7.64 (4H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-2, -6, *p*-NPh), 8.12 (4 H d, $^{3}J_{H,H}$ = 8.8 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 19.2 (Me), 42.7, 42.6 (C-3, -5, Pip), 43.4 (C-2, -6, Pip), 48.9, 49.2 (C-5, D-ax), 57.9, 58.0, 58.4 (C-2, SER A), 64.5, 64.8 (CH$_2$OH), 70.6, 70.7 (C-6, D-ax), 78.5, 78.6, 78.9 (C-4, D-ax), 94.0 (C-2, D-ax), 123.3, 123.5 (C-2, -6, *p*-NPh), 127.4, 127.6 (C-3, -5, *p*-NPh), 141.07, 141.14 (C-1, -4, *p*-NPh), 164.2 (C-2, T-0), 164.3, 164.5 (C-4, -6, T-1), 165.4, 165.7 (C-4, -6, T-0), 169.3 (C-2, T-1) ppm; MS (ESI+) *m*/*z* (rel. abund.%) 1130.4 (M+K) (0.45), 1126.5 (M+Cl) (1.9), 1114.4 (M+Na) (1.2), 1092.5 (M+H) (1.8), 1090.6 (M−H) (0.55); $[\alpha]_D^{20}$ = +72.3 (0.5% DMSO).

4.4.2. 2-Chloro-4,6-bis{4-{{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 8b

Yield 97% (1.37 g, 1.23 mmol) **8b** starting from 1.40 g (2.78 mmol) **4b** and 0.23 g (1.26 mmol) cyanuric chloride. Yellowish powder, mp 227–229 °C (flash column chromatography, eluent Toluene/EtOH = 4:1 v/v). Found: C, 50.51; H, 5.55; N, 23; $C_{47}H_{62}ClN_{19}O_{12}$ (1119.45) requires: C, 50.38, H, 5.58, N, 23.75; R_f (80% Toluene/EtOH) 0.85; IR ν_{max} (KBr) 3406 (m), 2862 (m), 2362 (w), 1564 (s), 1493 (s), 1441 (s), 1346 (s), 1272 (m), 1231 (m), 1174 (m), 1106 (m), 1085 (m), 1029 (m), 999 (m), 978 (m), 873 (w), 852 (w), 810 (m), 743 (w), 710 (w), 583 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 0.74 (6H, t, $^{3}J_{H,H}$ = 7.3 Hz, Me), 1.72 (2H, ddd, $^{2}J_{H,H}$ = 12.5 Hz, $^{3}J_{H,H}$ = 7.2 Hz, CH_2CH$_3$), 1.78 (2H, ddd, $^{2}J_{H,H}$ = 12.5 Hz, $^{3}J_{H,H}$ = 7.2 Hz, CH_2CH$_3$), 3.51 (4H, d, $^{2}J_{H,H}$ = 10.3 Hz, CH_2OH), 3.57 (4H, d, $^{2}J_{H,H}$ = 10.3 Hz, CH_2OH) 3.63 (8H, s, H-3, -5, Pip), 3.71 (8H, s, H-2, -6, Pip), 4.03 (2H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-a, D-ax), 4.13 (2H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-e, D-ax), 4.43 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-5-e, D-ax), 4.58 (4H, br s, OH), 5.01 (2H, d, $^{2}J_{H,H}$ = 6.0 Hz, H-2-a, D-ax), 5.24 (2H, d, $^{2}J_{H,H}$ = 6.0 Hz, H-2-e, D-ax), 5.25 (2H, s, H-4-a, D-ax), 5.44 (2H, s, SER-N*H*), 5.64 (2H, d, $^{3}J_{H,H}$ = 8.8 Hz, D-ax-N*H*), 7.63 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.11 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 8.1 (Me), 23.45, 23.53 (CH_2CH$_3$), 42.56, 42.63, 42.7 (C-3, -5, Pip), 43.4 (C-2, -6, Pip), 48.9, 49.1 (C-5, D-ax), 60.3 (C-2, SER B), 62.4, 63.0, 63.3 (CH$_2$OH), 70.7, 70.8 (C-6, D-ax), 78.6, 79.0 (C-4, D-ax), 93.9, 94.0, 94.1 (C-2, D-ax), 123.2, 123.37, 123.41, 123.6 (C-2, -6, *p*-NPh), 127.4, 127.5, 127.7 (C-3, -5, *p*-NPh), 147.1 (C-1, -4, *p*-NPh), 163.3 (C-2, T-0), 164.6 (C-4, -6, T-1), 165.5, 165.6, 165.7 (C-4, -6, T-0), 169.3 (C-2, T-1) ppm; HRMS (ESI+) *m*/*z* (rel. abund. × 10^{6}%) calcd for $C_{47}H_{63}ClN_{19}O_{12}$ 1120.4592; found 1120.4583 (M+H) (100); $[\alpha]_D^{20}$ = +89.5 (0.5% DMSO).

4.4.3. 2-Chloro-4,6-bis{4-{6-{[1,3-dihydroxy-2-(hydroxymethyl)-prop-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 8c

Yellowish powder, mp 278–280 °C (flash column chromatography, eluent Toluene/EtOH = 2:1 v/v). Found C, 48.38; H, 5.15; N, 24.01; $C_{45}H_{58}ClN_{19}O_{14}$ (1123.41) requires C, 48.06; H, 5.20; N, 23.67; R_f (67% Toluene/EtOH) 0.85; IR ν_{max} (KBr) 3392 (m), 2864 (m), 1565 (s), 1492 (s), 1441 (s), 1347 (s), 1274 (m), 1231 (m), 1174 (m), 1104 (m), 1026 (m), 978 (m), 874 (w), 852 (w), 809 (m), 743 (w), 711 (w), 584 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 3.64 (20H, s, CH_2OH; H-3, -5, Pip), 3.72 (8H, s, H-2, -6, Pip), 4.04 (2H, d, $^{2}J_{H,H}$ = 11.5 Hz, H-6-a, D-ax), 4.13 (2H, d, $^{2}J_{H,H}$ = 11.5 Hz, H-6-e, D-ax), 4.43 (2H, br s, H-5-e, D-ax), 4.54 (6H, br s, OH), 5.01 (2H, d, $^{2}J_{H,H}$ = 6.3 Hz, H-2-a, D-ax), 5.24 (2H, d, $^{2}J_{H,H}$ = 6.3 Hz, H-2-e, D-ax), 5.25 (2H, s, H-4-a, D-ax), 5.50 (2H, s, SER-N*H*), 5.71 (2H, bd, $^{3}J_{H,H}$ = 9.0 Hz, D-ax-N*H*), 7.64 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.13 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 42.6 (C-3, -5, Pip), 43.4 (C-2, -6, Pip), 48.9 (C-5, D-ax), 61.2 (C-2, SER C), 61.4 (CH$_2$OH), 70.6, 70.7, 70.8, 70.9 (C-6, D-ax), 78.36, 78.41, 78.5, 78.9, 79.0 (C-4, D-ax), 93.9, 94.0, 94.1 (C-2, D-ax), 123.3, 123.6 (C-2, -6, *p*-NPh), 127.3, 127.6 (C-3, -5, *p*-NPh), 147.0, 147.1, 147.2 (C-1, -4, *p*-NPh), 164.3, 164.5, 165.4 (C-2, -4, -6, T-0) 165.20, 165.23, 165.3, 165.6, 165.7 (C-4, -6, T-1), 169.3 (C-2, T-1) ppm; HRMS (ESI+) *m*/*z* (rel. abund.%) 1124.4210 (M+H) (100); $[\alpha]_D^{20}$ = +98.8 (0.5% DMSO).

4.4.4. 2-Chloro-4,6-bis{4-{{[1,3-dihydroxy-2-(methyl)prop-2-yl]-amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 9a

Yield 75% (0.90 g, 0.75 mmol) **9a** starting from 1.20 g (2.19 mmol) **5a** and 0.18 g (0.99 mmol) cyanuric chloride. Orange-yellow powder, mp 220–223 °C (flash column chromatography, eluent EtOH/acetone = 1:1 v/v). Found C, 51.11; H, 6.35; N, 24.22; $C_{51}H_{72}ClN_{21}O_{12}$ (1205.54) requires C, 50.76; H, 6.01; N, 24.38; R_f (50% EtOH/acetone) 0.68; IR ν_{max} (KBr) 3373 (m), 2932 (m), 2868 (m), 1567 (s), 1494 (s), 1440 (s), 1347 (m), 1276 (m), 1225 (m), 1152 (w), 1109 (w), 1048 (m), 999 (m), 974 (m), 873 (w), 852 (w), 810 (m). 709 (w), 575 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 1.29 (6H, s, Me), 2.24 (12H, s, NMe$_2$), 2.86 (2H, dd app. t, $^{3}J_{H,H}$ = 3.0 Hz, H-5-e, D-eq), 3.52 (2H, ddd, $^{2}J_{H,H}$ = 10.0 Hz, $^{3}J_{H,H}$ = 5.0 Hz, CH_2NH), 3.53 (2H, ddd, $^{2}J_{H,H}$ = 10.0 Hz, $^{3}J_{H,H}$ = 6,0 Hz, CH_2NH), 3.54 (4H, d, $^{2}J_{H,H}$ = 10.5 Hz, CH_2OH), 3.62 (4H, d, $^{2}J_{H,H}$ = 10.5 Hz, CH_2OH), 3.74 (16H, s, Pip), 3.97 (2H, dd, $^{2}J_{H,H}$ = 12.5 Hz, $^{3}J_{H,H}$ = 2.5 Hz, H-6-a, D-eq), 4.46 (2H, d, $^{2}J_{H,H}$ = 12.5 Hz, H-6-e, D-eq), 4.68 (4H, br s, OH), 5.01 (2H, dd app. t, $^{3}J_{H,H}$ = 4.5 Hz, H-2-a, D-eq), 5.19 (2H, d, $^{3}J_{H,H}$ = 3.0 Hz, H-4-a, D-eq), 5.63 (2H, s, SER-N*H*), 6.41 (2H, bdd app. bt, $^{3}J_{H,H}$ = 5.8 Hz, D-eq-N*H*), 7.65 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.17 (4H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 19.3 (Me), 42.7, 42.8, 42.9, 43.4 (C-3, -5, Pip), 43.8 (NMe$_2$), 44.3, 44.5 (C-2, -6, Pip), 58.0 (C-2, SER A), 58.1, 58.5, 58.6 (C-5, D-eq), 64.6, 64.8 (CH$_2$OH), 65.4 (C-6, D-eq), 80.2, 80.4 (C-4, D-eq), 99.7, 100.06, 100.14 (C-2, D-eq), 123.2, 123.3 (C-2, -6, *p*-NPh), 127.1 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 148.9 (C-4, *p*-NPh), 164.3, 164.8, 166.0 (C-2, -4, -6, T-0; C-4, -6, T-1), 169.3 (C-2, T-1) ppm; HRMS (ESI+) *m*/*z* (rel. abund.%) 1206.5433 (M+H) (100); $[\alpha]_D^{20}$ = +184.5 (0.5% DMSO).

4.4.5. 2-Chloro-4,6-bis{4-{{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 9b

Yield 74% (0.59 g, 0.48 mmol) **9b** starting from 0.80 g (1.43 mmol) **5b** and 0.12 g (0.65 mmol) cyanuric chloride. Orange-

yellow powder, mp 170–173 °C (flash column chromatography, eluent EtOH/Toluene/aq NH_3 25% = 1:2.5:0.1). Found C, 51.39; H, 6.55; N, 24.06; $C_{53}H_{76}ClN_{21}O_{12}$ (1233.57) requires C, 51.55; H, 6.20; N, 23.82; R_f (10% EtOH/69% Toluene/aq NH_3 25%) 0.55; IR ν_{max} (KBr) 3388 (m), 2959 (m), 2925 (m), 2862 (m), 1567 (s), 1492 (s), 1438 (s), 1346 (s), 1256 (s), 1232 (s), 1150 (m), 1106 (m), 999 (m), 972 (m), 852 (w), 808 (m), 708 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 0.80 (6H, t, $^3J_{H,H}$ = 7.5 Hz, Me), 1.82 (4H, q, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3), 2.24 (12H, s, NMe_2), 2.87 (2H, dd app. t, $^3J_{H,H}$ = 2.9 Hz, H-5-e, D-eq), 3.51 (2H, dd, $^3J_{H,H}$ = 4.5 Hz, CH_2NH), 3.56 (4H, d, $^2J_{H,H}$ = 10.8 Hz, CH_2OH), 3.63 (4H, d, $^2J_{H,H}$ = 10.8 Hz, CH_2OH), 3.74 (16H, s, Pip), 3.97 (2H, dd, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 2.8 Hz, H-6-a, D-eq), 4.47 (2H, d, $^2J_{H,H}$ = 12.4 Hz, H-6-e, D-eq), 4.67 (4H, br s, OH), 5.01 (2H, dd app. t, $^3J_{H,H}$ = 4.5 Hz, H-2-a, D-eq), 5.19 (2H, d, $^3J_{H,H}$ = 2.9 Hz, H-4-a, D-eq), 5.54 (2H, s, SER-N*H*), 6.44 (2H, br s, D-eq-N*H*), 7.65 (4H, d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.17 (4H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 8.3 (Me), 23.5, 23.6 (CH_2CH_3), 42.6, 43.4 (C-3, -5, Pip), 43.8 (NMe_2), 44.6 (C-2, -6, Pip), 58.6 (C-5, D-eq), 60.4 (C-2, SER B), 62.6, 64.5 (C-6, D-eq), 80.2, 80.4 (C-4, D-eq), 99.8, 100.1 (C-2, D-eq), 123.3 (C-2, -6, *p*-NPh), 127.0 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 148.9 (C-4, *p*-NPh), 164.3 (C-2, T-0), 164.8 (C-4, -6, T-1), 165.9, 166.0 (C-4, -6, T-0), 169.2 (C-2, T-1) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^6%) 1268.6 (M+Cl) (1.35), 1234.6 (M+H) (1.65); $[\alpha]_D^{20}$ = +163.3 (0.5% DMSO).

4.4.6. 2-Chloro-4,6-bis{4-{{[1,3-dihydroxy-2-(hydroxymethyl)-prop-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 9c

Yield 73% (1.85 g, 1.49 mmol) **9c** starting from 2.50 g (4.44 mmol **5c**) and 0.37 g (2.02 mmol) cyanuric chloride. Orange-yellowish powder, mp 270–272 °C (flash column chromatography, eluent acetone/EtOH = 1:1 v/v). Found C, 49.55; H, 6.15; N, 24.11; $C_{51}H_{72}ClN_{21}O_{14}$ (1237.53) requires C, 49.45; H, 5.86; N, 23.75; R_f (50% acetone/EtOH) 0.40; IR ν_{max} (KBr) 3382 (m), 2932 (m), 2866 (m), 2788 (m), 1563 (s), 1494 (s), 1436 (s), 1348 (s), 1273 (m), 1230 (m), 1152 (m), 1109 (m), 1049 (m), 998 (m), 977 (m), 873 (w), 852 (w), 809 (m), 753 (w), 710 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 353 K) δ_H 2.42 (12H, s, NMe_2), 2.87 (2H, dd app. t, $^3J_{H,H}$ = 2.9 Hz, H-5-e, D-eq), 3.51 (2H, d, $^3J_{H,H}$ = 5.5 Hz, CH_2NH), 3.52 (2H, d, $^3J_{H,H}$ = 5.5 Hz, CH_2NH), 3.69 (12H, s, CH_2OH), 3.74 (16H, s, Pip), 3.98 (2H, dd, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 3.0 Hz, H-6-a, D-eq), 4.47 (2H, d, $^2J_{H,H}$ = 12.5 Hz, H-6-e, D-eq), 4.64 (6H, br s, OH), 5.02 (2H, d, $^3J_{H,H}$ = 4.5 Hz, H-2-a, D-eq), 5.20 (2H, d, $^3J_{H,H}$ = 2.9 Hz, H-4-a, D-eq), 5.60 (2H, s, SER-N*H*), 6.51 (2H, br s, D-eq-N*H*), 7.65 (4H, d, $^3J_{H,H}$ = 8.8 Hz, H-2, -6, *p*-NPh), 8.17 (4H, d, $^3J_{H,H}$ = 8.8 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 42.6, 42.8, 43.1, 43.4 (C-3, -5, Pip), 43.9 (NMe_2), 44.3, 44.7 (C-2, -6, Pip), 58.6 (C-5, D-eq), 61.3 (CH_2OH), 61.5 (C-2, SER C), 61.7 (CH_2OH), 64.5 (C-6, D-eq), 80.2, 80.4 (C-4, D-eq), 99.7, 99.8 (C-2, D-eq), 123.3 (C-2, -6, *p*-NPh), 127.0, 127.1 (C-3, -5, *p*-NPh), 146.7 (C-1, *p*-NPh), 149.0 (C-4, *p*-NPh), 164.3 (C-2, T-0), 164.7, 165.9 (C-4, -6, T-1), 165.5, 165.8 (C-4, -6, T-0), 169.28, 169.32 (C-2, T-1) ppm; HRMS (ESI+) *m*/*z* (rel. abund.%) 1238.5338 (M+H) (100); $[\alpha]_D^{20}$ = +183.3 (0.5% DMSO).

4.4.7. 2-Chloro-4,6-bis{4-{4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazine 11

Yield 72% (1.20 g, 0.83 mmol) **11** starting from 1.70 g (2.55 mmol) **7** and 0.21 g (1.16 mmol) cyanuric chloride. Yellow powder, mp 212–215 °C (flash column chromatography, eluent EtOH/Toluene/Et_2O = 1:3:1.5 v/v/v). Found: C, 52.47; H, 5.42; N, 22.63; $C_{63}H_{74}ClN_{23}O_{16}$ (1443.54) requires C, 52.37; H, 5.16; N 22.30; R_f (10% EtOH/55% Toluene/Et_2O) 0.65; IR ν_{max} (KBr) 3430 (m), 2857 (m), 2779 (w), 1567 (s), 1550 (s), 1517 (s), 1491 (s), 1441 (s), 1346 (s), 1271 (m), 1232 (m), 1173 (m), 1096 (m), 1028 (m), 999 (m), 980 (m), 871 (w), 851 (m), 810 (m), 741 (w), 710 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 2.24 (12H, s, NMe_2), 2.86 (2H, dd app. t, $^3J_{H,H}$ = 3.2 Hz, H-5-e, D-eq), 3.46 (4H, ddd, $^3J_{H,H}$ = 5.5 Hz, CH_2NH), 3.66 (8H, t, $^3J_{H,H}$ = 5.5 Hz, H-3, -5, Pip), 3.69 (8H, t, $^3J_{H,H}$ = 5.5 Hz, H-2, -6, Pip), 3.97 (2H, dd, $^2J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 2.5 Hz, H-6-a, D-eq), 4.04 (2H, d, $^2J_{H,H}$ = 10.8 Hz, H-6-a, D-ax), 4.11 (2H, d, $^2J_{H,H}$ = 10.8 Hz, H-6-e, D-ax), 4.46 (2H, d, $^2J_{H,H}$ = 12.8 Hz, H-6-e, D-eq), 4.49 (2H, d, $^3J_{H,H}$ = 8.0 Hz, H-5-e, D-ax), 4.94 (2H, dd app. t, $^3J_{H,H}$ = 5.0 Hz, H-2-a, D-eq), 5.01 (2H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-a, D-ax), 5.17 (2H, d, $^3J_{H,H}$ = 3.2 Hz, H-4-a, D-eq), 5.23 (2H, s, H-4-a, D-ax), 5.24 (2H, d, $^2J_{H,H}$ = 6.0, H-2-e, D-ax), 5.62 (2H, bd, $^3J_{H,H}$ = 8.0 Hz, D-ax-N*H*), 6.28 (2H, bdd app. bt, $^3J_{H,H}$ = 5.5 Hz, D-eq-N*H*), 7.63 (4H, d, $^3J_{H,H}$ = 7.0 Hz, H-2, -6, *p*-NPh), 7.64 (4H, d, $^3J_{H,H}$ = 8.0 Hz, H-2, -6, *p*-NPh), 8.10 (4H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 8.15 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 43.4 (C-3, -5, Pip), 43.8 (NMe_2), 44.2 (C-2, -6, Pip), 44.4 (CH_2NH), 48.7, 48.86, 48.89, 48.90 (C-5, D-ax), 58.5 (C-5, D-eq), 64.5 (C-6, D-eq), 70.7, 70.8 (C-6, D-ax), 78.5, 78.6, 78.9 (C-4, D-ax), 80.1, 80.3 (C-4, D-eq), 94.0 (C-2, D-ax), 99.5, 99.6, 99.68, 99.71, 99.84, (C-2, D-eq), 123.2, 123.3, 123.4 (C-2, -6, *p*-NPh), 127.0, 127.34, 127.5, 127.6 (C-3, -5, *p*-NPh), 146.7, 147.05, 147.13 (C-1, *p*-NPh), 148.9 (C-4, *p*-NPh), 164.3, 164.6, 164.7, 164.8 (C-2, T-0; C-4, -6, T-1), 165.8, 166.1 (C-4, -6, T-0), 169.2 (C-2, T-1) ppm; MS (ESI+) *m*/*z* (rel.abund. × 10^4%) 1444.6 (M+H) (5.25), 1430.6 (2.15); $[\alpha]_D^{20}$ = +128.5 (0.5% DMSO).

4.5. Typical procedure for the synthesis of compounds 10c and 12. Preparation of compound 10c

In a solution obtained by dissolving the trispirotetraacetalic diamine linker **HN**<(**L**^{2})>**NH** (1.06 g, 3.57 mmol) in anhydrous 1,4-dioxane (100 mL), anhydrous K_2CO_3 (0.12 g, 0.89 mmol) was added. The resulting suspension was heated at reflux with vigorous stirring. At this temperature, compound **8c** (1.00 g, 0.89 mmol) was added in five equal portions (0.20 g/portion) every 2 h. Within 2 h, the starting **8c** was consumed (TLC monitoring, eluent toluene/EtOH = 2:1 v/v). The formation of the desired product **10c** was monitored by TLC (EtOH/aq NH_3 25% = 3:1 v/v, visualisation UV-254 nm, then I_2-bath). After cooling at room temperature, the reaction mixture was evaporated under reduced pressure to dryness. At room temperature, the solid residue was taken with cooled water (10 mL) under vigorous stirring for 1 h, filtered off and washed with cooled water to neutrality, to yield 1.27 g of crude material. This was purified by flash column chromatography (eluent EtOH/aq NH_3 25% = 3:1 v/v) to afford 1.02 g of compound **10c** (83% yield with respect to **8c**). *Linker recovery*: the aqueous filtrate (see above) containing the excess of linker **HN**<(**L**^{2})>**NH** (0.80 g, 2.68 mmol) was saturated with NaCl and then extracted with chloroform (3 × 50 mL). After separation, the organic layer was dried over anhydrous Na_2SO_4. After filtering off and washing minerals with dry chloroform, the organic solution was evaporated under reduced pressure to dryness. The resulted solid was crystalised at −20 °C from ligroin to provide 0.64 g (80% yield) of recovered linker **HN**<(**L**^{2})>**NH**.

4.5.1. 3-{4,6-Bis{4-{{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin-2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro[5.2.2.5.2.2]heneicosane 10c

Yellowish powder, mp 238–240 °C (flash column chromatography, eluent EtOH/aq NH_3 25% = 3:1 v/v). Found C, 51.71; H, 6.15; N,

20.91; $C_{60}H_{83}N_{21}O_{18}$ 1386.6303 requires C, 51.98; H, 6.03; N, 21.22; R_f (75% EtOH/aq NH_3 25%) 0.56; IR ν_{max} (KBr) 3338 (s), 2964 (m), 2867 (m), 1546 (s), 1489 (s), 1438 (s), 1347 (m), 1252 (m), 1174 (s), 1098 (s), 893 (w), 808 (w), 743 (w), 711 (w), 618 (m) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.74 (4H, t, $^3J_{H,H}$ = 5.5 Hz, H-1, -5, Tsp), 1.79 (4H, t, $^3J_{H,H}$ = 5.0 Hz, H-13, -17, Tsp), 2.73 (2H, dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 5.0 Hz, H-14, -16, Tsp), 2.74 (2H, dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 5.0 Hz, H-14, -16, Tsp), 3.60 (4H, t, $^3J_{H,H}$ = 5.5 Hz, H-2, -4, Tsp), 3.65 (13H, s, CH_2OH, H-15, Tsp), 3.68 (16H, t, $^3J_{H,H}$ = 4.8 Hz, Pip), 3.72 (4H, s, H-8, -20, Tsp), 3.74 (4H, s, H-10, -19, Tsp), 4.04 (2H, d, $^2J_{H,H}$ = 10.8 Hz, H-6-a, D-ax), 4.13 (2H, d, $^2J_{H,H}$ = 10.8 Hz, H-6-e, D-ax), 4.44 (2H, bd, $^3J_{H,H}$ = 8.5 Hz, H-5-e, D-ax), 4.51 (6H, br s, OH), 5.02 (2H, d, $^2J_{H,H}$ = 5.8 Hz, H-2-a, D-ax), 5.24 (2H, d, $^2J_{H,H}$ = 5.8 Hz, H-2-e, D-ax), 5.25 (2H, s, H-4-a, D-ax), 5.46 (2H, s, SER-N*H*), 5.62 (2H, d, $^3J_{H,H}$ = 8.5 Hz, D-ax-N*H*), 7.64 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 8.12 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 32.4, 32.6 (C-9, Tsp), 33.2 (C-13, -17, Tsp), 40.0 (C-1, -5, Tsp), 42.8 (C-14, -16, Tsp), 43.0 (C-2, -4, Tsp, Pip), 48.9 (C-5, D-ax), 61.2, 61.4 (C-2, SER C, CH_2OH), 62.5 (C-10, -19, Tsp), 62.8 (C-8, -20, Tsp), 70.6, 70.8 (C-6, D-ax), 78.5, 78.9 (C-4, D-ax), 94.0, (C-2, D-ax), 97.0 (C-12, Tsp), 97.3 (C-6, Tsp), 123.3, 123.6 (C-2, -6, *p*-NPh), 127.3, 127.6 (C-3, -5, *p*-NPh), 147.0 (C-1, *p*-NPh), 147.2 (C-4, *p*-NPh), 164.6 (C-2, T-1), 164.74, 164.79 (C-4, -6, T-1), 164.82 (C-2, T-0), 164.9, 165.3, 165.7 (C-4, -6, T-0) ppm; HRMS (ESI+) *m*/*z* (rel. abund. × 10^4%) 1386.6255 (M+H) (40); $[\alpha]_D^{20}$ = +75.1 (0.5% DMSO).

4.5.2. 3-{4,6-Bis{4-{4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino-*s*-triazin-2-yl}-piperazin-1-yl}-*s*triazin-2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro[5.2.2.5.2.2]heneicosane 12

Yield 54% (0.38 g, 0.22 mmol) **12** starting from 0.55 g (0.38 mmol) **11** and 0.45 g (1.52 mmol) **HN<(L²)>NH**. Orange yellowish powder, mp 210–213 °C (flash column chromatography EtOH/CH_2Cl_2/aq NH_3 25% = 1:2.5:0.1 v/v/v). Found C, 55.03; H, 6.11; N, 20.25; $C_{79}H_{99}N_{25}O_{20}$ (1706.78) requires C, 54.89; H, 5.85; N, 20.52; R_f (10% EtOH/69% CH_2Cl_2/aq NH_3 25%) 0.45; IR ν_{max} (KBr) 3420 (w), 2930 (m), 2860 (m), 2785 (w), 1542 (s), 1525 (s), 1438 (s), 1347 (s), 1256 (m), 1174 (s), 1096 (s), 1000 (s), 851 (m), 810 (m), 740 (w), 710 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.76 (4H, t, $^3J_{H,H}$ = 5.0 Hz, H-1, -5, Tsp), 1.77 (4H, t, $^3J_{H,H}$ = 5.0 Hz, H-13, -17, Tsp), 2.24 (12H, s, NMe_2), 2.74 (2H, t, $^3J_{H,H}$ = 5.0 Hz, H-14, -16, Tsp), 2.86 (2H, dd app. t, $^3J_{H,H}$ = 2.5 Hz, H-5-e, D-eq), 3.46 (4H, ddd, $^3J_{H,H}$ = 5.0 Hz, CH_2NH), 3.63 (8H, t, $^3J_{H,H}$ = 5.3 Hz, H-3, -5, Pip), 3.64 (8H, t, $^3J_{H,H}$ = 5.3 Hz, H-2, -6, Pip; 1H, H-15, Tsp), 3.70 (2H,t, $^3J_{H,H}$ = 5.3 Hz, H-2, -4, Tsp), 3.71 (2H, t, $^3J_{H,H}$ = 5.3 Hz, H-2, -4, Tsp), 3.72 (4H, s, H-8, -20, Tsp), 3.73 (4H, s, H-10, -19, Tsp), 3.97 (2H, dd, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 3.0 Hz, H-6-a, D-eq), 4.04 (2H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-a, D-ax), 4.11 (2H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-e, D-ax), 4.45 (2H, d, $^2J_{H,H}$ = 12.5 Hz, H-6-e, D-eq), 4.49 (2H, d, $^3J_{H,H}$ = 9.0 Hz, H-5-e, D-ax), 4.94 (2H, dd app. t, $^3J_{H,H}$ = 5.3 Hz, H-2-a, D-eq), 5.01 (2H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-a, D-ax), 5.17 (2H, d, $^3J_{H,H}$ = 3.5 Hz, H-4-a, D-eq), 5.23 (2H, s, H-4-a, D-ax), 5.24 (2H, d, $^2J_{H,H}$ = 6.0, H-2-e, D-ax), 5.57 (2H, bd, $^3J_{H,H}$ = 9.0 Hz, D-ax-N*H*), 6.22 (2H, bt, $^3J_{H,H}$ = 6.0 Hz, D-eq-N*H*), 7.63 (4H, d, $^3J_{H,H}$ = 8.0 Hz, H-2, -6, *p*-NPh), 7.64 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 8.10 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh), 8.15 (4H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 32.4, 32.6, 33.0 (C-9, -13, -17, Tsp), 42.7, 42.8, 43.0 (C-1, -5, Tsp; C-3, -5, Pip), 43.8 (NMe_2), 44.4 (C-2, -6, Pip; C-2, -4, -14, -16, Tsp; CH_2NH), 48.6, 48.8 (C-5, D-ax), 58.47, 58.52 (C-5, D-eq), 62.5, 62.6, 62.7, 62.8 (C-8, -10, -19, -20, Tsp), 64.4, 64.5 (C-6, D-eq), 70.64, 70.66, 70.69, 70.8 (C-6, D-ax), 78.52, 78.55, 78.59, 78.9 (C-4, D-ax), 80.1, 80.3 (C-4, D-eq), 94.0 (C-2, D-ax), 96.9 (C-12, Tsp), 97.2 (C-6, Tsp), 99.5, 99.67, 99.70, 99.8, 99.9 (C-2, D-eq), 123.2, 123.3, 123.4 (C-2, -6, *p*-NPh), 127.0, 127.3, 127.4, 127.5, 127.6 (C-3, -5, *p*-NPh), 146.7, 147.02, 147.04, 147.1 (C-1, *p*-NPh), 148.9 (C-4, *p*-NPh), 164.3, 164.6, 164.8 (C-2, T-0; C-4, -6, T-1), 165.8, 166.1 (C-4, -6, T-0), 169.2 (C-2, T-1) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^4%) 1720.0 (M+2H+Na) (0.02), 1707.0 (M+2H) (1.1), 1430.6 (1.8); $[\alpha]_D^{20}$ = +147.0 (0.5% DMSO).

4.6. Typical procedure for the synthesis of compounds 13a–c and 14. Preparation of compound ^{13}C

In a solution obtained by dissolving compound **8c** (0.35 g, 0.31 mmol) and trispirotetraacetalic diamine linker **HN<(L²)>NH** (0.04 g, 0.15 mmol) in anhydrous 1,4-dioxane (15 mL), anhydrous K_2CO_3 (0.04 g, 0.31 mmol) was added and the resulting suspension was refluxed, with vigorous stirring, until TLC monitoring (EtOH/$CHCl_3$/Toluene = 1:2:0.5 v/v) indicated the presence of the starting materials in small traces only (about 40 h). After cooling at room temperature, the reaction mixture was evaporated under reduced pressure to dryness. The resulting solid was taken with water (5 mL). After stirring at room temperature for 1 h, the suspension was filtered off and washed with water to yield 0.36 g of crude material, which was purified by flash column chromatography (eluent EtOH/$CHCl_3$/toluene = 1:2:0.5 v/v/v). The isolated ^{13}C 0.16 g was triturated from a Et_2O/THF 4:1 (v/v) mixture at −20 °C to give 0.14 g of pure ^{13}C (48% yield with respect to linker **HN<(L²)>NH**).

4.6.1. 3,15-Bis{4,6-bis{4-{6-{[1,3-dihydroxy-2-(methyl)prop-2-yl]-amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro[5.2.2.5.2.2]heneicosane 13a

Yield 38% (0.14 g, 0.06 mmol) **13a** starting from 0.35 g (0.38 mmol) **8a** and 0.05 g (0.15 mmol) **HN<(L²)>NH**. Yellowish powder, mp 225–227 °C (flash column chromatography, eluent EtOH/$CHCl_3$/Toluene = 1:2:1 v/v/v). Found C, 51.98; H, 6.01; N, 23.15; $C_{105}H_{140}N_{40}O_{28}$ (2409.08) requires C, 52.32; H, 5.85; N, 23.24; R_f (10% EtOH/50% $CHCl_3$/Toluene) 0.70; IR ν_{max} (KBr) 3394 (m), 2931 (m), 2852 (m), 1545 (s), 1494 (s), 1436 (s), 1346 (s), 1265 (m), 1173 (m), 1081 (m), 1028 (m), 997 (m), 896 (w), 807 (m), 737 (w), 709 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.22 (12H, s, Me), 1.81 (8H, t, $^3J_{H,H}$ = 5.3 Hz, H-1, -5, -13, -17, Tsp), 3.48 (8H, dd, $^2J_{H,H}$ = 10.5 Hz, $^3J_{H,H}$ = 5.0 Hz, CH_2OH), 3.58 (8H, m, CH_2OH), 3.60 (16H, t, $^3J_{H,H}$ = 4.7 Hz, H-2, -6, Pip), 3.68 (16H, t, ^3J = 4.7 Hz, H-3, -5, Pip), 3.72 (8H, t, $^3J_{H,H}$ = 5.3 Hz, H-2, -4, -14, -16, Tsp), 3.76, 3.78 (8H, s, H-8, -10, -19, -20, Tsp), 4.04 (4H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-a, D-ax), 4.13 (4H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-e, D-ax), 4.44 (4H, d, $^3J_{H,H}$ = 9.3 Hz, H-5-e, D-ax), 4.56 (8H, dd as t, $^3J_{H,H}$ = 5.0 Hz, OH), 5.02 (4H, d, $^2J_{H,H}$ = 6.5 Hz, H-2-a, D-ax), 5.24 (4H, d, $^2J_{H,H}$ = 4.5 Hz, H-2-e, D-ax), 5.25 (4H, s, H-4-a, D-ax), 5.48 (4H, s, SER-N*H*), 5.54 (4H, d, $^3J_{H,H}$ = 9.3 Hz, D-ax-N*H*), 7.64 (8H, d, $^3J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 8.12 (8H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; Quantitative ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 19.2 (4C, Me), 32.5 (5C, C-1, -5, -9, -13, -17, Tsp), 43.0 (20C: 16C, Pip; 4C, C-2, -4, -14, -16, Tsp), 48.9 (4C, C-5, D-ax), 57.9 (4C, C-2, SER A), 62.8 (4C, C-8, -10, -19, -20, Tsp), 64.5 (8C, CH_2OH), 70.7, 70.8 (4C, C-6, D-ax), 78.6, 79.0 (4C, C-4, D-ax), 94.0 (4C, C-2, D-ax), 97.3 (2C, C-6, -9, Tsp), 123.3, 123.50, 123.53, 123.6 (8C, C-2, -6, *p*-NPh), 127.4, 127.6 (8C, C-3, -5, *p*-NPh), 147.08, 147.14 (8C, C-1, -4, *p*-NPh), 164.3, 164.4, 164.6 (2C, C-2, T-1), 164.6, 164.9 (4C, C-4, -6, T-1), 165.3 (4C, C-2, T-0), 165.4, 165.7 (8C, C-4, -6, T-0) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^4%) 2448.8 (M+K) (1.4), 2432.8 (M+Na) (2.4), 2410.9 (M+H) (1.7); $[\alpha]_D^{20}$ = +76.3 (0.5% DMSO).

4.6.2. 3,15-Bis{4,6-bis{4-{6-{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro[5.2.2.5.2.2]heneicosane 13b

Yield 37% (0.09 g, 0.03 mmol) **13b** starting from 0.25 g (0.22 mmol) **8b** and 0.03 g (0.11 mmol) **HN**<(**L**^{2})>**NH**. Yellowish powder, mp 221–224 °C (flash column chromatography, eluent EtOH/CH_2Cl_2/Toluene = 1:3:2 v/v/v). Found C, 52.88; H, 6.21; N 22.95; $C_{109}H_{148}N_{40}O_{28}$ (2465.14) requires C, 53.08; H, 6.05; N, 22.71; R_f (10% EtOH/50% CH_2Cl_2/Toluene) 0.55; IR ν_{max} (KBr) 3406 (m), 2970 (m), 2936 (m), 2860 (m), 1545 (s), 1491 (s), 1438 (s), 1345 (s), 1262 (s), 1174 (s), 1084 (s), 1028 (s), 1000 (m), 896 (w), 810 (m), 741 (w), 712 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 0.75 (12H, t, $^{3}J_{H,H}$ = 7.2 Hz, Me), 1.75 (8H, dd app. q, $^{3}J_{H,H}$ = 7.2 Hz, C*H*$_2$CH$_3$), 1.80 (8H, dd app. q, $^{3}J_{H,H}$ = 5.6 Hz, H-1, -5, -13, -17, Tsp), 3.52 (8H, d, ^{2}J = 11.8 Hz, C*H*$_2$OH), 3.58 (8H, d, $^{2}J_{H,H}$ = 11.8 Hz, C*H*$_2$OH), 3.60 (8H, t, $^{3}J_{H,H}$ = 5.2 Hz, H-2, -6, Pip), 3.68 (8H, t, ^{3}J = 5.2 Hz, H-3, -5, Pip), 3.72 (8H, t, $^{3}J_{H,H}$ = 5.6 Hz, H-2, -4, -14, -16, Tsp), 3.77 (8H, s, H-8, -10, -19, -20, Tsp), 4.04 (4H, d, $^{2}J_{H,H}$ = 10.8 Hz, H-6-a, D-ax), 4.13 (4H, d, $^{2}J_{H,H}$ = 10.8 Hz, H-6-e, D-ax), 4.44 (4H, d, $^{3}J_{H,H}$ = 10.0 Hz, H-5-e, D-ax), 4.55 (8H, br s, OH), 5.02 (4H, d, $^{2}J_{H,H}$ = 5.5 Hz, H-2-a, D-ax), 5.24 (4H, d, $^{2}J_{H,H}$ = 5.5 Hz, H-2-e, D-ax), 5.25 (4H, s, H-4-a, D-ax), 5.39 (4H, s, SER-N*H*), 5.56 (4H, d, $^{3}J_{H,H}$ = 10.0 Hz, D-ax-N*H*), 7.64 (8H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-2, -6, *p*-NPh), 8.11 (8H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-3, -5, *p*-NPh) ppm; Quantitative ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 8.1 (4C, Me), 23.4 (4C, *C*H$_2$CH$_3$), 32.3, 32.68, 32.70 (5C, C-1, -5, -9, -13, -17, Tsp), 43.0 (20C: 16C, Pip; 4C, C-2, -4, -14, -16, Tsp), 48.9, 49.2 (4C, C-5, D-ax), 60.3 (4C, C-2, SER B), 62.4 (8C, CH$_2$OH), 62.9 (4C, C-8, -10, -19, -20, Tsp), 70.6, 70.7, 70.81, 70.84 (4 C, C-6, D-ax), 78.5, 78.6, 78.97, 79.00 (4 C, C-4, D-ax), 94.0 (4 C, C-2, D-ax), 97.3 (2C, C-6, -9, Tsp), 123.2, 123.4, 123.6 (8C, C-2, -6, *p*-NPh), 127.3, 127.5, 127.6 (8C, C-3, -5, *p*-NPh), 147.1 (8C, C-1, -4, *p*-NPh), 164.6 (2C, C-2, T-1), 164.6, 164.9 (4C, C-4, -6, T-1), 165.3 (4C, C-2, T-0), 165.4, 165.6 (8C, C-4, -6, T-0) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^{4}%) 2504.8 (M+K) (0.7), 2488.8 (M+Na) (2.9); isotope pattern for $C_{109}H_{148}N_{40}O_{28}Na$: monoisotopic Mwt 2488.128441; average Mwt 2489.664; $[\alpha]_D^{20}$ = +79.4 (0.5% DMSO).

4.6.3. 3,15-Bis{4,6-bis{4-{6-{[1,3-dihydroxy-2-(hydroxymethyl)-prop-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro[5.2.2.5.2.2]heneicosane ^{13}C

Yellowish powder, mp 265–267 °C (flash column chromatography, eluent EtOH/$CHCl_3$/Toluene = 1:2:0.5 v/v/v). Found C, 51.28; H, 6.01; N, 22.88; $C_{105}H_{140}N_{40}O_{32}$ (2473.06) requires C, 50.97; H, 5.70; R_f (10% EtOH/57% $CHCl_3$/Toluene) 0.75; IR ν_{max} (KBr) 3390 (m), 2931 (m), 2856 (m), 1553 (s), 1491 (s), 1436 (s), 1346 (s), 1268 (s), 1100 (m), 1026 (s), 851 (w), 809 (m), 744 (w), 710 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.81 (8H, dd app. t, $^{3}J_{H,H}$ = 5.6 Hz, H-1, -5, -13, -17, Tsp), 3.60 (8H, t, $^{3}J_{H,H}$ = 5.1 Hz, H-2, -6, Pip), 3.69 (8H, t, ^{3}J = 5.1 Hz, H-3, -5, Pip), 3.70 (24H, s, C*H*$_2$OH), 3.72 (8H, t, $^{3}J_{H,H}$ = 5.6 Hz, H-2, -4, -14, -16, Tsp), 3.78 (8H, s, H-8, -10, -19, -20, Tsp), 4.04 (4H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-a, D-ax), 4.13 (4H, d, $^{2}J_{H,H}$ = 11.3 Hz, H-6-e, D-ax), 4.44 (4H, d, $^{3}J_{H,H}$ = 9.0 Hz, H-5-e, D-ax), 4.51 (12H, br s, OH), 5.02 (4H, d, $^{2}J_{H,H}$ = 5.3 Hz, H-2-a, D-ax), 5.24 (4H, d, $^{2}J_{H,H}$ = 5.3 Hz, H-2-e, D-ax), 5.25 (4H, s, H-4-a, D-ax), 5.46 (4H, s, SER-N*H*), 5.62 (4H, d, $^{3}J_{H,H}$ = 9.0 Hz, D-ax-N*H*), 7.65 (8H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-2, -6, *p*-NPh), 8.13 (8H, d, $^{3}J_{H,H}$ = 8.8 Hz, H-3, -5, *p*-NPh) ppm; Quantitative ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 32.7 (5C, C-1, -5, -9, -13, -17, Tsp), 43.0 (20C: 16C, Pip; 4C, C-2, -4, -14, -16, Tsp), 48.9 (4C, C-5, D-ax), 61.1 (4C, C-2, SER C), 61.4 (12C, CH$_2$OH), 62.8 (4C, C-8, -10, -19, -20, Tsp), 70.6, 70.8 (4C, C-6, D-ax), 78.5, 78.6, 78.9, 79.1 (4C, C-4, D-ax), 94.0 (4C, C-2, D-ax), 97.3 (2C, C-6, -9, Tsp), 123.3, 123.6 (8C, C-2, -6, *p*-NPh), 127.3, 127.6 (8C, C-3, -5, *p*-NPh), 147.1 (8C, C-1, -4, *p*-NPh), 164.5 (2C, C-2, T-1), 164.5, 164.9, 165.3 (4C, C-4, -6, T-1), 165.3 (4C, C-2, T-0), 165.3, 165.4, 165.6 (8C, C-4, -6, T-0) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^{4}%) 2512.8 (M+K) (0.2), 2496.8 (M+Na) (4.2); $[\alpha]_D^{20}$ = +81.7 (0.5% DMSO).

4.6.4. 3,15-Bis{4,6-bis{4-{6-{{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro-[5.2.2.5.2.2]heneicosane 14

Yield 46% (0.15 g, 0.05 mmol) **14** starting from 0.33 g (0.23 mmol) **11** and 0.03 g (0.11 mmol) **HN**<(**L**^{2})>**NH**. Yellowish powder, mp 253–255 °C (flash column chromatography, eluent EtOH/$CHCl_3$/Toluene = 1:2:2 v/v/v). Found C, 54.69; H, 5.87; N, 21.81; $C_{141}H_{172}N_{48}O_{36}$ (3113.31) requires C, 52.36; H, 5.57; N, 21.58; R_f (20% EtOH/40% $CHCl_3$/Toluene) 0.60; IR ν_{max} (KBr) 3422 (m), 2929 (m), 2857 (m), 1545 (s), 1438 (s), 1347 (s), 1265 (s), 1174 (m), 1094 (m), 1028 (m), 1013 (m), 852 (m), 810 (m), 741 (w), 710 (w) cm^{-1}; ^{1}H NMR, 2D-^{1}H,^{1}H-COSY, 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.78 (8H, s, H-1, -5, -13, -17, Tsp), 2.24 (24H, s, NMe$_2$), 2.87 (4H, s, H-5-e, D-eq), 3.47 (8H, dd app. t, $^{3}J_{H,H}$ = 5.5 Hz, C*H*$_2$NH), 3.63 (16H, br s, H-2, -6, Pip), 3.65 (16H, br s, H-3, -5, Pip), 3.68 (8H, s, H-2, -4, -14, -16, Tsp), 3.77 (8H, s, H-8, -10, -19, -20, Tsp), 3.97 (4H, dd, $^{2}J_{H,H}$ = 12.4 Hz, $^{3}J_{H,H}$ = 2.3 Hz, H-6-a, D-eq), 4.04 (4H, d, $^{2}J_{H,H}$ = 11.0 Hz, H-6-a, D-ax), 4.11 (4H, d, $^{2}J_{H,H}$ = 11.0 Hz, H-6-e, D-ax), 4.46 (4H, d, $^{2}J_{H,H}$ = 12.4 Hz, H-6-e, D-eq), 4.50 (4H, d, $^{3}J_{H,H}$ = 8.0 Hz, H-5-e, D-ax), 4.94 (4H, dd app. t, $^{3}J_{H,H}$ = 4.8 Hz, H-2-a, D-eq), 5.00 (4H, d, $^{2}J_{H,H}$ = 5.8 Hz, H-2-a, D-ax), 5.17 (4H, d, $^{3}J_{H,H}$ = 3.5 Hz, H-4-a, D-eq), 5.23 (4H, s, H-4-a, D-ax), 5.24 (4H, d, $^{2}J_{H,H}$ = 5.8 Hz, H-2-e, D-ax), 5.58 (4H, bd, $^{3}J_{H,H}$ = 8.0 Hz, D-ax-N*H*), 6.22 (4H, br s, D-eq-N*H*), 7.63 (8H, d, $^{3}J_{H,H}$ = 8.0 Hz, H-2, -6, *p*-NPh), 7.64 (8H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.09 (8H, d, $^{3}J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 8.15 (8H, d, $^{3}J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; Quantitative ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 32.4, 32.7 (1C, C-9, Tsp), 42.8, 43.0 (12C: 4C, C-1, -5, -13, -17, Tsp; 8C, C-2, -6, Pip), 43.8 (8C, NMe$_2$), 44.4, 44.5 (16C: 8C, C-3, -5, Pip; 14C, C-2, -4, -14, -16, Tsp; 4C, CH$_2$NH), 48.64, 48.67, 48.74, 48.83, 48.85, 48.88, 48.92 (4C, C-5, D-ax), 58.49, 58.55 (4C, C-5, D-eq), 62.72, 62.78, 62.81 (4C, C-8, -10, -19, -20, Tsp), 64.4, 64.5 (4C, C-6, D-eq), 70.7, 70.8 (4C, C-6, D-ax), 78.52, 78.54, 78.59, 78.61, 78.62, 78.65 (4C, C-4, D-ax), 80.1, 80.3, (4C, C-4, D-eq), 94.0 (4C, C-2, D-ax), 97.3 (2C, C-6, -12, Tsp), 99.5, 99.67, 99.72, 99.8, 99.9 (4C, C-2, D-eq), 123.2, 123.5 (16C, C-2, -6, *p*-NPh), 127.0, 127.4, 127.5, 127.6 (16C, C-3, -5, *p*-NPh), 146.7, 147.03, 147.06, 147.2, 148.9 (16C, C-1, -4, *p*-NPh), 164.6, 164.7, (2C, C-2, T-1), 164.76, 164.82, 164.9, 165.3 (4C, C-4, -6, T-1), 165.3, 165.7 (4C, C-2, T-0), 165.76, 166.1 (8C, C-4, -6, T-0) ppm; MS (ESI+) *m*/*z* (rel. abund. × 10^{5}%) 3114.3129 (M+H) (0.9); $[\alpha]_D^{20}$ = +121.5 (0.5% DMSO).

4.6.5. 1,3,5-Tris{{15-{4,6-bis{4-{4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan]-2-yl}methylamino-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin-2-yl}-7,11,18,21-tetraoxa-3,15-diazatrispiro-[5.2.2.5.2.2]heneicosan-3-yl}-carbonyl}benzene 15

Compound **12** (0.26 g, 0.15 mmol) was suspended in anhydrous THF (50 mL) after which anhydrous K_2CO_3 (0.02 g, 0.15 mmol) was added with vigorous stirring. The resulting suspension was cooled at −15 °C at which point benzene-1,3,5-tricarbonyl chloride (0.01 g, 0.05 mmol) as clear anhydrous THF (1 mL) solution was injected rapidly. The reaction mixture was allowed to gently reach room temperature and was kept as such for an additional 12 h with

stirring. The formation of the desired product **15** was monitored by TLC (eluent EtOH/$CHCl_3$/Toluene = 1:3:1.5 v/v/v). The reaction mixture was heated at 40 °C for an additional 72 h when TLC monitoring confirmed the formation of **15**. After cooling at room temperature, the reaction mixture was evaporated under reduced pressure to dryness. The resulting solid was taken with water (4 mL) with stirring at room temperature for 1 h, then the suspension was filtered off and washed with water to yield 0.25 g of crude material. This was purified by flash column chromatography (eluent EtOH/$CHCl_3$/toluene = 1:3:1.5 v/v/v) to afford 0.11 g of compound **15** (56% yield with respect to benzene 1,3,5-tricarbonyl chloride). Orange-yellowish powder, mp 232-234 °C (flash column chromatography, eluent EtOH/$CHCl_3$/Toluene = 1:3:1.5 v/v/v). Found C, 54.98; H, 5.71; N, 20.19; $C_{243}H_{297}N_{75}O_{63}$ (5273.23) requires C, 55.31; H, 5.67; N, 19.91; R_f (10% EtOH/55% $CHCl_3$/Toluene) 0.65; IR ν_{max} (KBr) 2964 (m), 2931 (m), 2858 (m), 1542 (s), 1441 (s), 1346 (s), 1262 (s), 1173 (m), 1095 (s), 1030 (m), 1000 (m), 851 (w), 810 (m), 743 (w), 709 (w) cm^{-1}; ^1H NMR, 2D-^1H,^1H-COSY, 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 363 K) δ_H 1.78 (12H, br s, H-13, -17, Tsp), 1.87 (12H, br s, H-1, -5, Tsp), 2.23 (36H, s, NMe_2), 2.86 (6H, dd app. t, $^3J_{H,H}$ = 3.0 Hz, H-5-e, D-eq), 3.47 (12H, dd app. t, $^3J_{H,H}$ = 4.5 Hz, CH_2NH), 3.62 (24H, br s, H-2, -6, Pip), 3.64 (24H, br s, H-3, -5, Pip), 3.70 (24H, br s, H-2, -4, -14, -16, Tsp), 3.756-3,763 (24H, br s, H-8, -10, -19, -20, Tsp), 3.96 (6H, dd, $^2J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 2.3 Hz, H-6-a, D-eq), 4.03 (6H, d, $^2J_{H,H}$ = 10.5 Hz, H-6-a, D-ax), 4.11 (6H, d, $^2J_{H,H}$ = 10.5 Hz, H-6-e, D-ax), 4.45 (6H, d, $^2J_{H,H}$ = 12.2 Hz, H-6-e, D-eq), 4.49 (6H, d, $^3J_{H,H}$ = 8.5 Hz, H-5-e, D-ax), 4.94 (6H, dd app. t, $^3J_{H,H}$ = 4.5 Hz, H-2-a, D-eq), 5.00 (6H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-a, D-ax), 5.16 (6H, d, $^3J_{H,H}$ = 3.5 Hz, H-4-a, D-eq), 5.22 (6H, s, H-4-a, D-ax), 5.23 (6H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-e, D-ax), 5.57 (6H, bd, $^3J_{H,H}$ = 8.5 Hz, D-ax-N*H*), 6.20 (6H, bt, $^3J_{H,H}$ = 6.3 Hz, D-eq-N*H*), 7.47 (3H, s, H-2, -4, -6, benzene) 7.62 (12H, d, $^3J_{H,H}$ = 8.0 Hz, H-2, -6, *p*-NPh), 7.63 (12H, d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 8.08 (12H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh), 8.14 (12H, d, $^3J_{H,H}$ = 9.0 Hz, H-3, -5, *p*-NPh) ppm; Quantitative ^{13}C NMR, DEPT (125 MHz, DMSO-d_6, 298 K) δ_C 32.3, 32.4 (3C, C-9, Tsp), 42.8, 42.96, 43.03 (24C: 12C, C-1, -5, -13, -17, Tsp; 12C, C-2, -6, Pip), 43.8 (12C, NMe_2), 44.4 (30C: 12C, C-3, -5, Pip; 12C, C-2, -4, -14, -16, Tsp; 6C, CH_2NH), 48.8 (6C, C-5, D-ax), 58.49, 58.54 (6C, C-5, D-eq), 62.76, 62.84, 62.9 (12C, C-8, -10, -19, -20, Tsp), 64.4, 64.5 (6C, C-6, D-eq), 70.7, 70.8 (6C, C-6, D-ax), 78.5, 78.6, 78.9 (6C, C-4, D-ax), 80.1, 80.30, 80.34 (6C, C-4, D-eq), 94.0 (6C, C-2, D-ax), 97.0, 97.3 (6C, C-6, -12, Tsp), 99.5, 99.72, 99.75, 99.9 (6C, C-2, D-eq), 123.2, 123.3, 123.4 (27C: 24C, C-2, -6, *p*-NPh; 3C, C-2, -4, -6, benzene), 127.0, 127.4, 127.50, 127.53 (24C, C-3, -5, *p*-NPh), 146.6, 147.0, 147.1, 148.9 (27C: 24C, C-1, -4, *p*-NPh; 3C, C-1, -3, -5, benzene), 164.6 (2C, C-2, T-1 [G-$1^{1,2}$], 164.8 (1C, C-6(4), T-1 [G-1^3]), 164.8 (2C, C-6(4), T-1 [G-$1^{1,2}$]), 164.9 (1C, C-2, T-1 [G-1^3]), 164.9 (1C, C-4(6), T-1 [G-1^3]), 164 9 (2C, C-4(6), T-1 [G-$1^{1,2}$]), 165.3 (6C, C-2, T-0 [G-1^{1-3}]), 165.8 (6C, C-4, T-0, [G-1^{1-3}]), 166.0 (6C, C-6, T-0 [G-1^{1-3}]), 168.3 (3C, >C=O) ppm; MS (MALDI, DHB) *m*/*z* (rel. abund. × 10^4%) 5123.530 (M-3 × NO_2) (2.6); MS (ESI+) *m*/*z* (rel. abund.%) 5277.0361 [M+H], $[\alpha]_D^{20}$ = +147.0 (0.5% DMSO).

Acknowledgments

The financial support from a Grant provided by the Research Council Romania (project PN-II-ID-PCE-2011-3-0128) is gratefully acknowledged. O.M. thanks University *Babes-Bolyai* for the financial support awarded as *Young Researcher* (GTC 34053/2013-2014). We wish to thank Prof. Jurgen Liebscher (Humboldt University) for reading the Manuscript and suggesting improvements.

References

1. For reviews referring to (maked)serinols as molecules, biomolecules, building-blocks, supramolecules see (a) Darabantu, M. *Curr. Org. Synth.* **2010**, *7*, 235–275; (b) Darabantu, M. *Curr. Org. Synth.* **2010**, *7*, 120–152.
2. (a) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515–1519; (b) Tilford, H. C.; Van Campen, M. G., Jr.; Shelton, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 2902–2906; (c) Pierce, J. S.; Wotiz, J. *J. Am. Chem. Soc.* **1951**, *73*, 2594; (d) Pierce, J. S.; Lunsford, C. D.; Raiford, R. W., Jr.; Rush, J. L.; Riley, D. W. *J. Am. Chem. Soc.* **1951**, *73*, 2595–2596; (e) Pierce, J. S.; Lunsford, C. D. *J. Am. Chem. Soc.* **1951**, *73*, 2596–2598; (f) Bergmann, E. D. *Chem. Rev.* **1953**, *53*, 309–353.
3. (a) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Josylyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417; (b) Smadel, J. E.; Jackson, E. B. *Science* **1947**, *106*, 418–419; (c) Rebstock, M. C.; Crooks, H. M.; Controulis, J.; Bartz, R. Q. *J. Am. Chem. Soc.* **1949**, *71*, 2458–2462; (d) Controulis, J.; Rebstock, M. C.; Crooks, H. M. *J. Am. Chem. Soc.* **1949**, *71*, 2463–2468; (e) Long, M. L.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2469–2472; (f) Long, M. L.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2473–2475.
4. Darabantu, M.; Mager, S.; Plé, G.; Puscas, C. *Heterocycles* **1995**, *41*, 2327–2356. and the literature cited therein.
5. (a) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003–2004; (b) Newkome, G. R.; Schreiner, C. *Chem. Rev.* **2010**, *110*, 6338–6442.
6. Vögtle, F.; Richard, G.; Werner, N. *Dendrimer Chemistry (Concepts, Syntheses, Properties, Applications)*; WILEY-VCH: Weinheim, 2009. pp 7–22, 25–44.
7. (a) Ballico, M.; Drioli, S.; Bonora, G. M. *Eur. J. Org. Chem.* **2005**, 2064–2073; (b) Gillies, E. R.; Fréchet, J. M. J. *Bioconjugate Chem.* **2005**, *16*, 361–368; (c) Wharton, T.; Wilson, L. J. *Tetrahedron Lett.* **2002**, *43*, 561–564; (d) Wharton, T.; Wilson, L. J. *Bioorg. Med. Chem.* **2002**, *10*, 3545–3554; (e) Sørbye, K.; Carlssen, P. H. J. *Synth. Commun.* **1997**, *27*, 2813–2816; (f) Wang, A. Y.; Li, J. J.; Chen, H.; Peng, X. *J. Am. Chem. Soc.* **2002**, *124*, 2293–2298; (g) Leopoittevin, B.; Matmour, R.; Francis, R.; Taton, D.; Gnanou, Y. *Macromolecules* **2005**, *38*, 3120–3128.
8. Popa, F.; Lameiras, P.; Moldovan, O.; Tomoaia-Cotisel, M.; Hénon, E.; Martinez, A.; Sacalis, C.; Mocanu, A.; Ramondenc, Y.; Darabantu, M. *Tetrahedron* **2012**, *68*, 8945–8967.
9. Zhang, W.; Simanek, E. E. *Org. Lett.* **2000**, *2*, 843–845.
10. (a) Steffensen, M. B.; Simanek, E. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5178–5180; (b) Moreno, X. K.; Simanek, E. E. *Tetrahedron Lett.* **2008**, *49*, 1152–1154.
11. (a) Hollink, E.; Simanek, E. E. *Org. Lett.* **2006**, *8*, 2293–2295; (b) Lim, J.; Mintzer, M. A.; Perez, L. M.; Simanek, E. E. *Org. Lett.* **2010**, *12*, 1148–1151.
12. (a) Umali, A. P.; Simanek, E. E. *Org. Lett.* **2003**, *5*, 1245–1247; (b) Zhang, W.; Tichy, S. E.; Perez, L. M.; Maria, C. G.; Lindahl, P. A.; Simanek, E. E. *J. Am. Chem. Soc.* **2003**, *125*, 5086–5094; (c) Umali, A. P.; Crampton, L. H.; Simanek, E. E. *J. Org. Chem.* **2007**, *72*, 9866–9874; (d) Patra, S.; Kozura, B.; Huang, A. Y.-T.; Enciso, A. E.; Sun, X.; Hsieh, J.-T.; Kao, C.-L.; Chen, H.-T.; Simanek, E. E. *Org. Lett.* **2013**, *15*, 3808–3811.
13. For example (a) Zhang, W.; Gonzalez, S. O.; Simanek, E. E. *Macromolecules* **2002**, *35*, 9015–9021; (b) Acosta, E. J.; Deng, Y.; White, G. N.; Dixon, J. B.; McInnes, K. J.; Senseman, S. A.; Frantzen, A. S.; Simanek, E. E. *Chem. Mater.* **2003**, *15*, 2903–2909; (c) Acosta, E. J.; Gonzalez, S. O.; Simanek, E. E. *J. Polym. Sci., Part A* **2005**, *43*, 168–177; (d) Yoo, S.; Lunn, D. J.; Gonzalez, S.; Ristich, J. A.; Simanek, E. E.; Shantz, D. *Chem. Mater.* **2006**, *18*, 2935–2942; (e) Lai, L. L.; Wang, L. Y.; Lee, C. H.; Lin, C. Y.; Cheng, K. L. *Org. Lett.* **2006**, *8*, 1541–1544; (f) Lai, L. L.; Lee, C. H.; Wang, L. Y.; Cheng, K. L.; Hsu, H. F. *J. Org. Chem.* **2008**, *73*, 485–490; (g) Yooa, S.; Yeua, S.; Sherman, R. L.; Simanek, E. E.; Shantza, D. F.; Ford, D. M. *J. Membr. Sci.* **2009**, *334*, 16–22; (h) Lalwani, S.; Venditto, V. J.; Chouai, A.; Rivera, E. G.; Shaunak, S.; Simanek, E. E. *Macromolecules* **2009**, *42*, 3152–3161.
14. For example (a) Bell, S. A.; McLean, M. E.; Oh, S.-K.; Tichy, S. E.; Zhang, W.; Corn, R. M.; Crooks, R. M.; Simanek, E. E. *Bioconjugate Chem.* **2003**, *14*, 488–493; (b) Neerman, M. F.; Zhang, W.; Parrish, A. R.; Simanek, E. E. *Int. J. Pharm.* **2004**, *281*, 129–132; (c) Chen, H. T.; Neerman, M. F.; Parrish, A. R.; Simanek, E. E. *J. Am. Chem. Soc.* **2004**, *126*, 10044–10048; (d) Lim, J.; Simanek, E. E. *Mol. Pharm.* **2005**, *2*, 273–277; (e) Venditto, V. J.; Allred, K.; Allred, C. D.; Simanek, E. E. *Chem. Commun.* **2009**, 5541–5542; (f) Merkel, M. O.; Mintzer, M. A.; Sitterberg, J.; Bakowsky, U.; Simanek, E. E.; Kissel, T. *Bioconjugate Chem.* **2009**, *20*, 1799–1806; (g) Lim, J.; Venditto, V. J.; Simanek, E. E. *Bioorg. Med. Chem.* **2010**, *18*, 5749–5753.
15. (a) Astruc, D.; Boisselier, E.; Ornelas, C. *Chem. Rev.* **2010**, *110*, 1857–1959; (b) Steffensen, M. B.; Hollink, E.; Kuschel, F.; Bauer, M.; Simanek, E. E. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 3411–3433; (c) Crampton, H. L.; Simanek, E. E. *Polym. Int.* **2007**, *56*, 489–496; (d) Simanek, E. E.; Abdou, H.; Lalwani, S.; Lim, J.; Mintzer, M.; Venditto, V. J.; Vittur, B. *Proc. R. Soc. A., Ser. A* **2010**, *466*, 1445–1468; (e) Lim, J.; Simanek, E. E. *Adv. Drug Del. Rev.* **2012**, *64*, 826–835; (f) Simanek, E. E.; Enciso, A. E.; Pavan, G. M. *Expert Opin. Drug Disc.* **2013**, *8*, 1057–1069.
16. (a) Kraiz, B. O.; Remizov, A. L. Zh. *Org. Khim.* **1979**, *15*, 1282–1289; (b) Baxi, G.; Pandya, A.; Pakikh, A. R. *J. Inst. Chem. (India)* **1996**, *68*, 44–45.
17. (a) Darabantu, M.; Pintea, M.; Fazekas, M.; Lameiras, P.; Berghian, C.; Delhom, I.; Silaghi-Dumitrescu, I.; Plé, N.; Turck, A. *Lett. Org. Chem.* **2006**, *3*, 905–910; (b) Fazekas, M.; Pintea, M.; Lameiras, P.; Lesur, A.; Berghian, C.; Silaghi-Dumitrescu, I.; Plé, N.; Darabantu, M. *Eur. J. Org. Chem.* **2008**, *14*, 2473–2494; (c) Pintea, M.; Fazekas, M.; Lameiras, P.; Cadis, I.; Berghian, C.; Silaghi-Dumitrescu, I.; Popa, F.; Bele, C.; Plé, N.; Darabantu, M. *Tetrahedron* **2008**, *64*, 8851–8870; (d) Popa, F.; Lameiras, P.; Hénon, E.; Moldovan, O.; Martinez, A.; Bâtiu, C.; Ramondenc, Y.; Darabantu, M. *Can. J. Chem.* **2011**, *89*, 1207–1221; (e)

Moldovan, O.; Lameiras, P.; Hénon, E.; Popa, F.; Martinez, A.; Harakat, D.; Sacalis, C.; Ramondenc, Y.; Darabantu, M. *Centr. Eur. J. Chem.* **2012**, *10*, 1119–1136; (f) Moldovan, O.; Lameiras, P.; Nagy, I.; Opruta, T.; Popa, F.; Antheaume, C.; Ramondenc, Y.; Darabantu, M. *Tetrahedron* **2013**, *69*, 2199–2213; (g) Lates, V.; Gligor, D.; Darabantu, M.; Muresan, L. M. *J. Appl. Electrochem.* **2007**, *37*, 631–636.

18. (a) Drakenberg, T.; Forsen, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1404–1405; (b) Mirvish, S. S.; Gannett, P.; Babcook, D. M.; Williamson, D.; Chen, S. C.; Weisenburger, D. D. *J. Agric. Food Chem.* **1991**, *39*, 1205–1210; (c) Willner, I.; Rosengaus, J.; Eichen, Y. *J. Phys. Org. Chem.* **1993**, *6*, 29–43; (d) Katritzky, A. R.; Ghiviriga, I.; Oniciu, D.; Barkock, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 785–792; (e) Katritzky, A. R.; Ghiviriga, I.; Steel, P. G.; Oniciu, D. C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 443–447; (f) Amm, M.; Platzer, N.; Guilhem, J.; Bouchet, J. P.; Volland, J. P. *Magn. Reson. Chem.* **1998**, *36*, 587–596; (g) Brewer, S. A.; Burnell, H. T.; Holpen, I.; Jones, G. B.; Willis, R. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1231–1234; (h) Birkett, H. E.; Harris, R. K.; Hodgkinson, P.; Carr, K.; Charlton, M. H.; Cherryman, J. C.; Chippendale, A. M.; Glover, R. P. *Magn. Reson. Chem.* **2000**, *38*, 504–511; (i) Amm, M.; Platzer, N.; Bouchet, J. P.; Volland, J. P. *Magn. Reson. Chem.* **2001**, *39*, 77–84; (j) Ghiviriga, I.; Oniciu, D. C. *Chem. Commun.* **2002**, 2718–2719; (k) Birkett, H. E.; Cherryman, J. C.; Chippendale, A. M.; Evans, J. S. O.; Harris, R. K.; James, M.; King, I. J.; McPherson, G. *Magn. Reson. Chem.* **2003**, *41*, 324–336; (l) Moreno, X. K.; Simanek, E. E. *Macromolecules* **2008**, *41*, 4108–4114.
19. (a) Lemcoff, N. G.; Fuchs, B. *Org Lett.* **2002**, *4*, 731–734; (b) Newkome, G. R.; Yoo, K. S.; Moorefield, C. N. *Chem. Commun.* **2002**, 2164–2165.
20. (a) Eliel, E. L.; Wilen, H. S. *Stereochemistry of the Organic Compounds*; John Wiley & Sons: New York, 1994. pp 21, 696(697), 1008, 1020, 1025, 1033, 1093, 1120, 1191, 1200; (b) Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293–371.
21. Sokolov, L. B.; Nichugovskaya, K. M.; Karpenko, M. P. *Pharm. Chem. J.* **1978**, *12*, 593–594 (Translated from *Khim.-Farm. Zh.* **1978**, *12*, 45–47).
22. (a) Darabantu, M.; Plé, G.; Mager, S.; Puscas, C.; Cotora, E. *Tetrahedron* **1997**, *53*, 1909–1922; (b) Darabantu, M.; Maiereanu, C.; Plé, G.; Berghian, C.; Condamine, E.; Ramondenc, Y. *Heterocycl. Commun.* **2001**, *7*, 593–598.
23. (a) Steffensen, M. B.; Simanek, E. E. *Org. Lett.* **2003**, *5*, 2359–2361; (b) Chouai, A.; Simanek, E. E. *J. Org. Chem.* **2007**, *73*, 2357–2366; (c) Crampton, H.; Hollink, E.; Perez, L. M.; Simanek, E. E. *New J. Chem.* **2007**, *31*, 1283–1290; (d) Chouai, A.; Venditto, V. J.; Simanek, E. E. *Org. Synth.* **2009**, *86*, 151–160; (e) Chouai, A.; Venditto, V. J.; Simanek, E. E. *Org. Synth.* **2009**, *86*, 141–150.
24. Gala, K. J.; Terrell, R. C. U.S. Patent 4,863,918 (BOC Inc., USA); c.f. *Chem. Abstr.* **1990**, *112*, P235325; http://www.patentbuddy.com/Patent/4863918.
25. (a) Dodziuk, H. *J. Chem. Soc., Perkin Trans. 2* **1986**, 249–251; (b) Dodziuk, H.; Sitkowski, J.; Stefanian, I.; Mursakulov, I. G.; Guseinov, M. M.; Kurbanova, V. A. *Struct. Chem.* **1992**, *3*, 269–276; (c) Dodziuk, H.; Mirowicz, M. *Tetrahedron: Asymmetry* **1990**, *1*, 171–186.
26. (a) Grosu, I.; Mager, S.; Plé, G.; Horn, M. *J. Chem. Soc., Chem. Commun.* **1995**, 167–168; (b) Grosu, S.; Mager, I.; Plé, G. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1351–1357; (c) Cismas, C.; Terec, A.; Mager, S.; Grosu, I. *Curr. Org. Chem.* **2005**, 91287–91314.
27. (a) Galesworthy, R. C.; Show, R. M.; Smith, B. C. *J. Chem. Soc.* **1962**, 1507–1508; (b) Show, R. M.; Ward, P. *J. Chem. Soc.* **1965**, 5446–5451; (c) Stepanov, B. I.; Migachev, G. I.; Ilina, E. F. *Zh. Obshch. Khim.* **1967**, *37*, 2140; (d) Show, R. M.; Ward, P. *J. Chem. Soc.* **1968**, *12*, 1431–1435; (e) Migachev, G. I.; Ilina, E. F.; Stepanov, B. I. *Zh. Obsch. Khim.* **1968**, *38*, 1370–1371; (f) Show, R. M.; Ward, P. *J. Chem. Soc.* **1969**, *6*, 596–599; (g) Boncic-Caricic, G.; Tadic, Z. D.; Muskatirovic, M. D. *J. Serb. Chem. Soc.* **1994**, *59*, 929–933; (h) Reddy, N. D.; Elias, A. J.; Vij, A. *J. Chem. Res. (S)* **1998**, 504–505; (i) Kolesinska, B.; Kaminski, Z. J. *Tetrahedron* **2009**, *65*, 3573–3576.
28. (a) Menicagli, R.; Malanga, C.; Peluso, P. *Synth. Commun.* **1994**, *24*, 2153–2158; (b) Samaritani, S.; Peluso, P.; Malanga, C.; Menicagli, R. *Eur. J. Org. Chem.* **2002**, *9*, 1551–1555; (c) Cuthberson, W. W.; Moffatt, J. S. *J. Chem. Soc.* **1948**, 561–564.
29. Wessig, P.; Möllnitz, K.; Eiserbeck, C. *Chem. Eur. J.* **2007**, *13*, 4859–4872.
30. Friebolin, H. *Basic One- and Two Dimensional NMR Spectroscopy*; VCH Verlagsgesellschaft: Weinheim, New York, 1991. pp 93, 263–291.
31. Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512–523.