

Depsipeptide Dendrimers

Jürgen Kress, Alexander Rosner, and Andreas Hirsch*[a]

Abstract: The convergent synthesis of a new class of chiral dendrimers is described. Owing to their structural resemblance to depsipeptides they are called depsipeptide dendrimers. The ex-chiral pool synthesis starts from (*R,R*)-, (*S,S*)-, and *meso*-tartaric acid as branching units and dipeptides or tripeptides consisting of glycine, (*L*)-alanine, and (*L*)-leucine as chiral-spacer building blocks. The key intermediates for the convergent assembly of such depsipeptide

dendrimers are the peptide-tartaric acid conjugates **13a,b**, **19a,b**, **25**, and **27**, which contain either an unprotected C terminus of the peptide chain (**13a,b**, **25**) or two unprotected hydroxy groups within the tartaric acid termini. Dendrimers up to the third-generation, by using

Keywords: amino acids • chiral pool • chirality • combinatorial chemistry • dendrimers

different combinations of stereoisomeric building blocks, were synthesized and completely characterized. Since this construction principle of chiral depsipeptide dendrimers allows for a wide variation of the length, the primary structure of the peptide spacer, and the configuration of both the amino acid and the tartaric acid moieties, access to new combinatorial libraries is conceptually provided.

Introduction

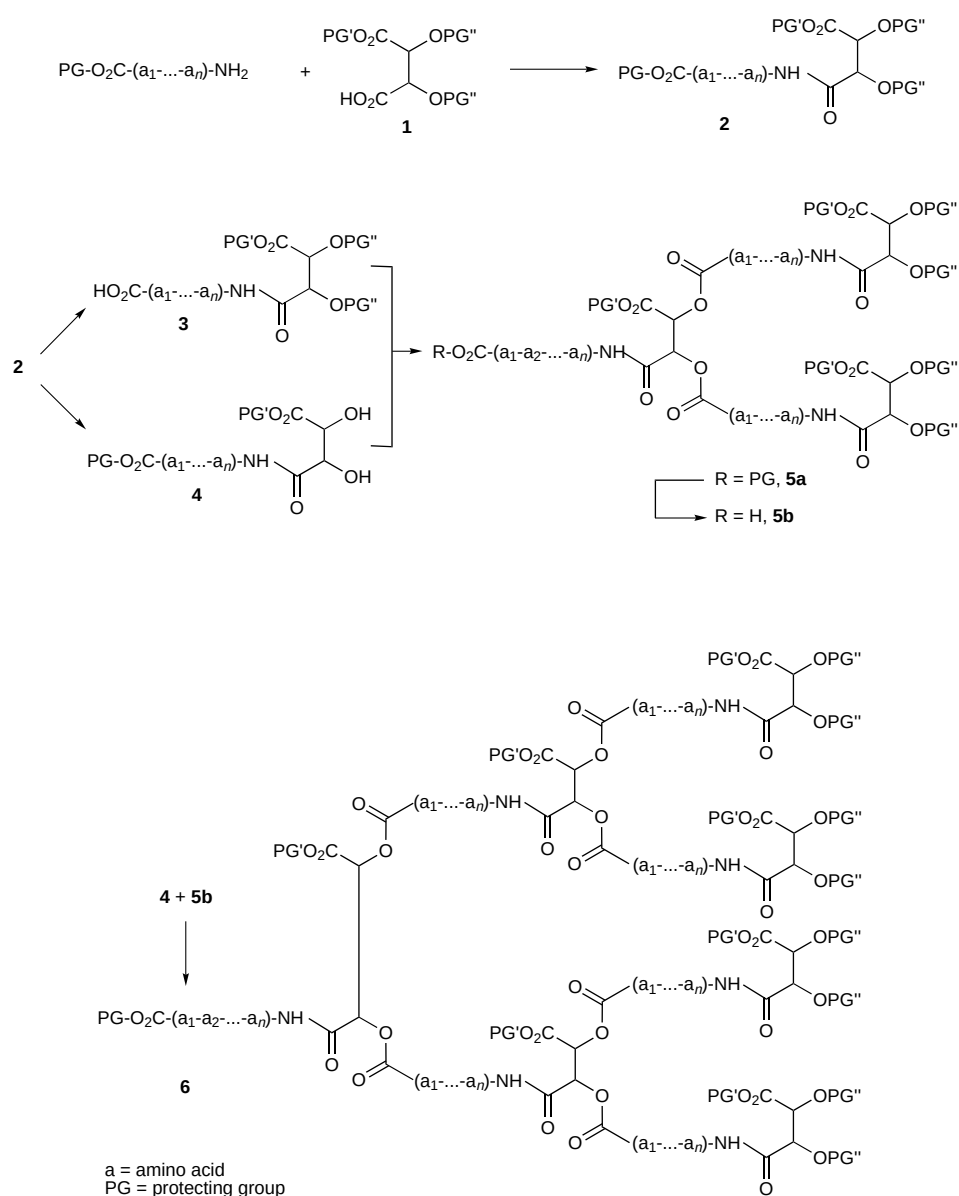
Since Vögtle's first report in 1978^[1] dendrimers have become a vast growing field in chemistry and material science. The subject has been extensively reviewed.^[2] More recently chiral dendrimers became an attractive synthetic goal.^[3] Their chiroptical properties with respect to folding phenomena, their ability to stereoselectively bind guest molecules, and their potential as catalysts for stereoselective syntheses have been investigated. The chirality of the dendritic structures reported so far stems from i) four different branches attached to a tetrasubstituted carbon atom,^[4] ii) a chiral core,^[5] iii) chiral branching units,^[5–8] iv) chiral end groups,^[5, 9–12] and v) a chiral core and chiral branching units.^[13, 14] We now introduce a new concept of chiral dendrimers that are named depsipeptide dendrimers owing to their structural resemblance to depsipeptides. The expression depsipeptides was introduced by Schemjakin^[15] to describe a class of natural products that consist of α -hydroxy and α -amino acids which are connected by ester and amide linkages, respectively. The most prominent example is probably valinomycin, which makes mitochondria membranes permeable for K^+ .^[16] The chiral dendrimers presented here contain both chiral branching units and chiral spacer units, represented by tartaric acid and peptide building blocks, respectively.

Results and Discussion

Our general concept of the synthesis and the structure of depsipeptide dendra is depicted in Scheme 1. A C-protected amino acid or peptide is coupled to a tartaric acid derivative **1** with one unprotected carboxylic group. The configuration at the corresponding stereogenic centers of both the amino acid and tartaric acid derivatives can be freely chosen. The orthogonal protecting groups PG and PG' are alternatively removed to yield the carboxylic acid **3** or the diol **4**. The coupling of these two units leads to the dendron **5a**, which after deprotection to the acid **5b** and coupling with **4** is transferred to the dendron **6**. The latter two steps are successively repeated for the synthesis of higher generation dendra. The construction of the higher generation dendra can in principle also be accomplished by using a divergent approach, which involves the repetitive deprotection of PG' and subsequent coupling with **3**. However, no matter which approach is followed, two prerequisites have to be provided: 1) efficient and mild esterification reactions for the synthesis of **5**, **6**, and their higher analogues are required in order to prevent epimerization at the amino acid or tartaric acid units and 2) a set of two orthogonal protecting groups PG' and PG'' must be found.

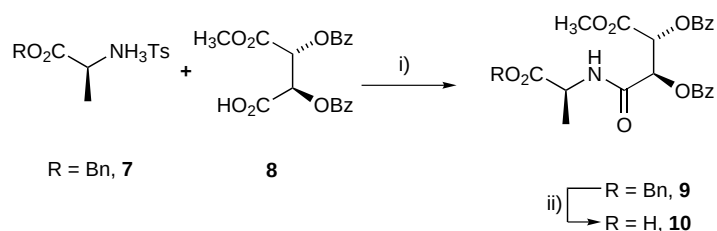
As a first example commercially available (*L*)-alaninebenzylester-*p*-tosylate **7** was used as the amino acid unit. The mono-deprotected tartaric acid derivative **8** was prepared according to a literature procedure.^[17] Formation of the coupling product **9** was accomplished by reaction of **7** with **8** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) at 0 °C

[a] Prof. Dr. A. Hirsch, Dipl.-Chem. J. Kress, Dipl.-Chem. A. Rosner
Institut für Organische Chemie, der Universität Erlangen-Nürnberg
Henkestr. 42, 91054 Erlangen (Germany)
Fax: (+49) 9131-8526864
E-mail: hirsch@organik.uni-erlangen.de



Scheme 1. General concept for the convergent syntheses of depsipeptide dendra consisting of tartaric acid moieties as branching units and peptides as spacer units.

in CH_2Cl_2 (Scheme 2). The removal of the benzylic protecting groups by catalytic hydrogenation afforded the acid **10**. Coupling reactions of **10** with simple alcohols such as ethanol via the corresponding acyl chloride of **10** showed that epimerization occurred at the stereogenic center of the alanine moiety.



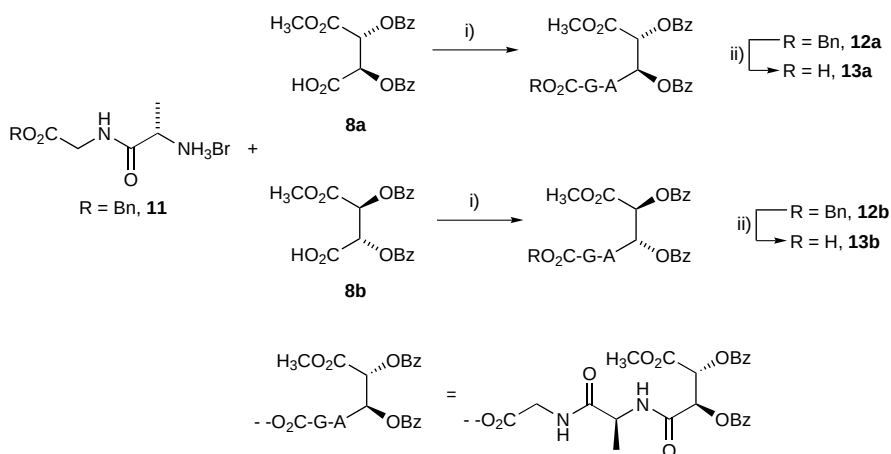
Scheme 2. Synthesis of the acid **10**: i) NEt_3 , DCC, CH_2Cl_2 , 0°C , 52%; ii) dioxane, H_2 , Pd-C, 100%. Bn = benzyl, Bz = benzoyl.

To avoid the problem of epimerization at a_1 within the peptide chain (a_1 in Scheme 1) we decided to use achiral glycine as the C terminus in order to “protect” neighboring stereogenic centers of chiral amino acids from stereoeimerization. At the same time we switched to milder coupling procedures namely the Steglich reaction.^[18] As a first example we used the dipeptide **11** obtained from the corresponding Z-protected mother compound^[19] according to a literature procedure^[20] and allowed it to react with mono-deprotected tartaric acids (Scheme 3). In addition to the building block **8a**, which was made from natural tartaric acid with (*R,R*)-configuration, the corresponding unnatural (*S,S*)-enantiomer **8b** was used for the subsequent coupling step. The deprotection leading to **13a,b** was carried out in analogy to that of **9**.

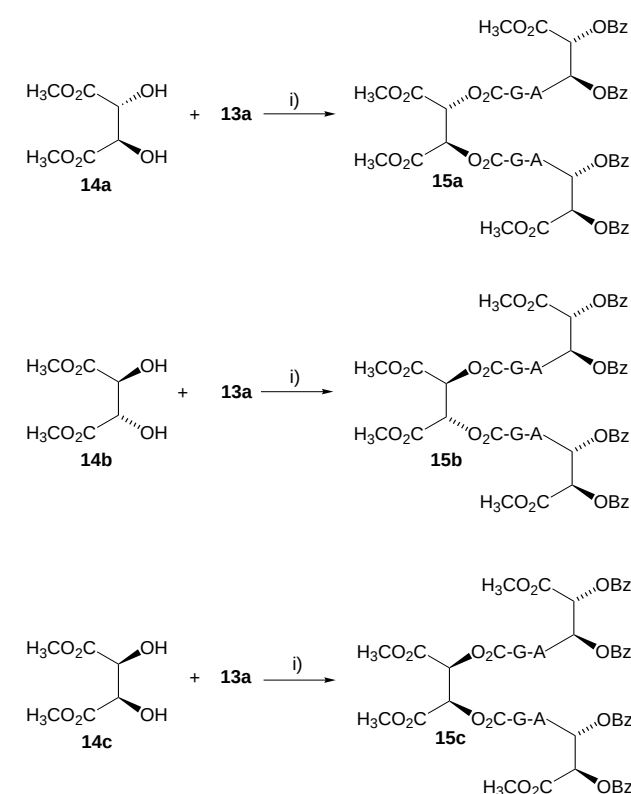
Carboxylic acid **13a** was then successfully coupled with the three stereoisomeric derivatives of dimethyltartrate (*R,R*)-**14a**, (*S,S*)-**14b**, and *meso*-**14c** by means of the Steglich reaction in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) (Scheme 4). Compounds **14a** and **14b** are commercially available, the *meso*-isomer **14c** was prepared according to a literature procedure.^[21] Other

procedures like the Steglich reaction without DMAP or coupling via the acyl chloride gave lower yields or no product at all. The products **15a**, **15b**, and **15c** are first-generation dendrimers with a chiral core (**15a,b**), chiral spacers (dipeptide unit), and chiral branching units (tartaric acid moieties). Purification was achieved by flash chromatography (FC) on silica gel. As eluent a mixture of toluene/EtOAc = 3:5 was successfully used. The products **15a,b,c** were fully characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis. Considering that the problem of epimerization could be solved, the yields of 54–56% are satisfactory. However, the yields are not good enough to envisage a divergent approach for the synthesis of higher generation dendrimers.

For the synthesis of higher generation dendra it was necessary to create a building block like **4** with two free alcohol groups. Since the acid-protecting benzyl group (Bn) and the alcohol-protecting benzoyl group (Bz) of **12** are not



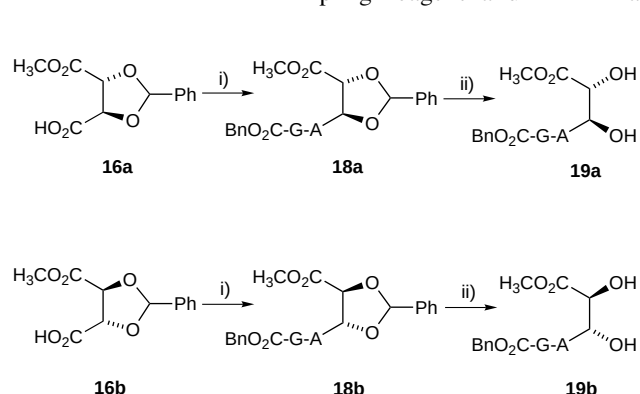
Scheme 3. Syntheses of the carboxylic acids **13a,b**: i) NEt_3 , DCC, CH_2Cl_2 , 0°C , 53–58 %; ii) dioxane, H_2 , Pd-C, 100 %.



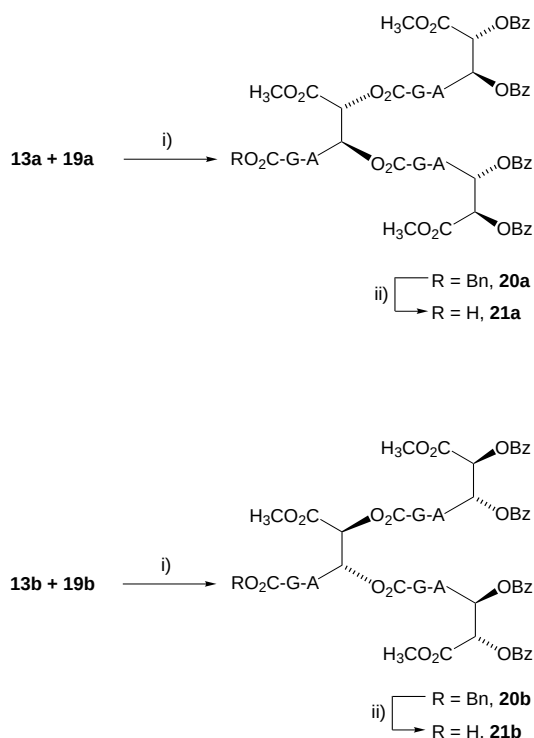
Scheme 4. Synthesis of the first-generation dendrimers **15a,b,c**: i) dioxane, DCC, DMAP, RT, 51–56 %.

orthogonal a new building block had to be developed. The benzylidene acetals **18a,b** seemed to be an appropriate choice (Scheme 5). They were prepared from the known benzylidene acetals **16a,b**^[22] and hydrobromide **11** by using the same reaction conditions as described previously. Purification of **18a,b** was accomplished by flash chromatography. In fact, **18a,b** were isolated as a mixture of diastereomers, since the starting materials **16a,b** are each a mixture of two diastereomers, which differ only in the configuration of the stereogenic centers at the acetal moiety. However, this was not a serious drawback, since cleavage of the acetal is the next step.

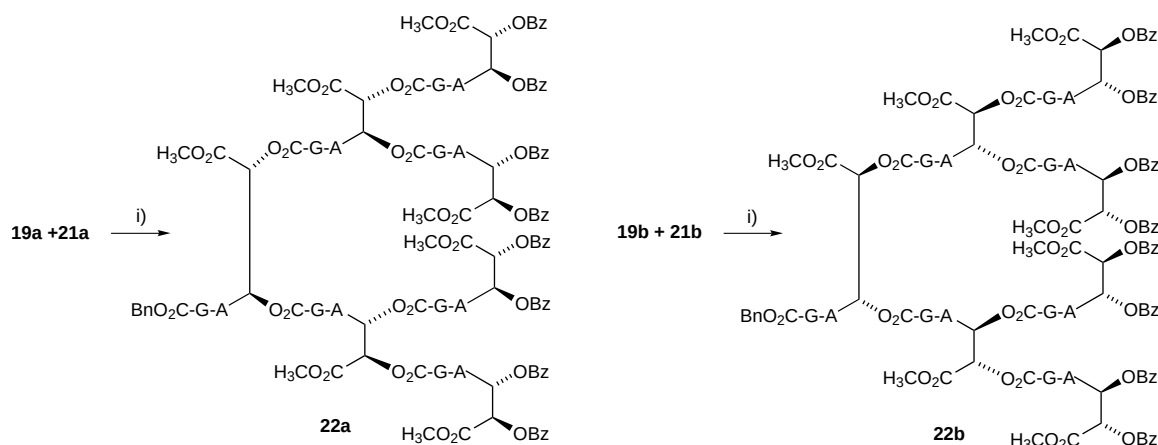
The acetal deprotection was accomplished by the action of trifluoroacetic acid (TFA) upon **18a,b** in the presence of some water at 0°C . The diols **19a,b** were released in yields of about 85 % after recrystallization from EtOAc (Scheme 5). The Bn groups were not attacked under these conditions. Now the scene was set for the synthesis of the unsymmetrical second-generation dendra **20a,b** (Scheme 6). The diols **19a,b** were coupled with the carboxylic acids **13a,b** at room temperature, with DCC as a coupling reagent and DMAP as



Scheme 5. Syntheses of the diols **19a,b**: i) NEt_3 , DCC, CH_2Cl_2 , 0°C , 51 %; ii) TFA, H_2O , 0°C , 83 %.

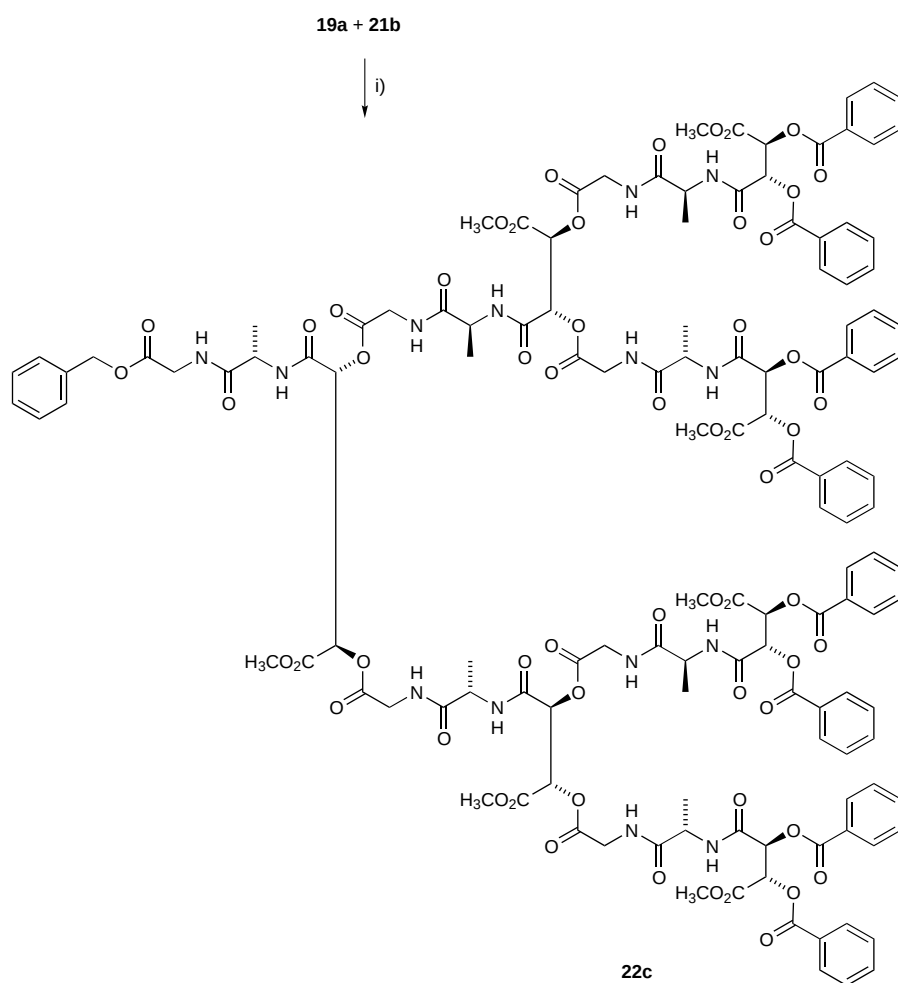


Scheme 6. Syntheses of the second-generation dendra **21a,b**: i) dioxane, DCC, DMAP, 60–65 %; ii) dioxane, H_2 , Pd-C, 100 %.



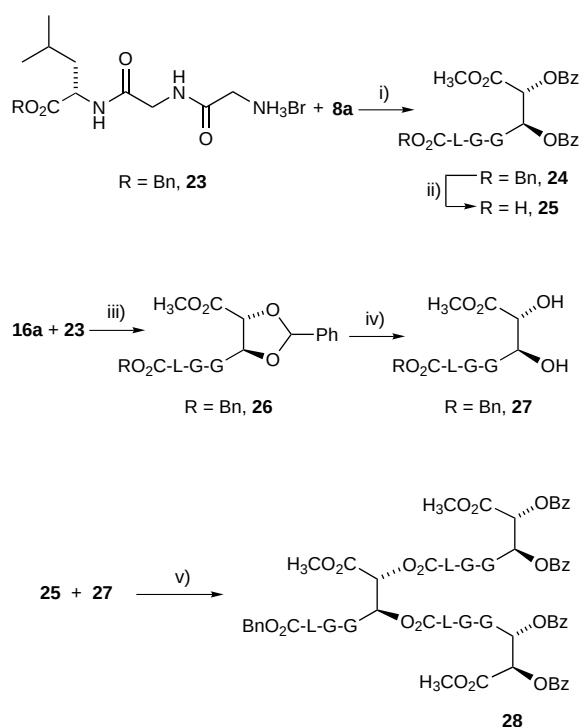
catalyst. After flash chromatography the pure benzylic esters **20a,b** were obtained in yields of 60–65 % as white solids.

Catalytic hydrogenation of the Bn-protected **20a,b** afforded the carboxylic acids **21a,b** in quantitative yields (Scheme 6). Not surprisingly, the NMR spectra are very similar to those of the precursors. The absence of the signals at $\delta = 5.1$ in the ¹H NMR and $\delta = 67$ in the ¹³C NMR confirmed the successful removal of the benzyl group. The mass spectra (FAB) revealed the principal peak at m/z 1279 [$M+\text{Na}$]⁺, the [$M+\text{Cs}$]⁺ peak at m/z 1389, and the [M]⁺ signal at m/z 1257. The third-generation dendra **22a,b,c** were prepared as sketched in Scheme 7. The yields were in the range between 7 and 15 % depending on the precise reaction conditions, especially the amount of DMAP used as a catalyst. The lower yield, relative to those achieved in the synthesis of the second-generation dendra, is probably due to steric hindrance. Because of the considerable polarity of the third-generation dendra **22**, their purification by chromatography turned out to be quite difficult. In fact, preparative HPLC was necessary to get the pure samples. Significantly, the retention times of the three diastereomers **22a,b,c**, which differ only at the stereochemistry of the tartaric acid units, can be very different. For example, retention times for **22a,b,c** on analytical HPLC (silica gel; CHCl₃/MeOH = 96.5:3.5 flow rate: 1 mL min⁻¹) were 8.1, 5.0, and 4.6 minutes, respectively.



Scheme 7. Syntheses of the third-generation dendra **22a,b,c**: i) dioxane, DCC, DMAP, 7–15 %.

The first example of the synthesis of a second-generation dendron with the tripeptide (L)-leucine-glycine-glycine as the spacer unit is outlined in Scheme 8. In the investigation of this synthesis we intended to find out whether there is any influence of the sterical demand of the C-terminal amino acid on the yield of the coupling reaction, and whether epimerization at the stereogenic center of the C terminus takes place under the Steglich esterification. For this purpose the hydrobromide **23** was prepared from the known Z-protected



Scheme 8. Synthesis of the second-generation dendron **28**: i) NEt_3 , DCC, CH_2Cl_2 , 0°C , 44%; ii) THF, H_2 , Pd-C, 100%; iii) NEt_3 , DCC, CH_2Cl_2 , 0°C , 46%; iv) TFA, H_2O , 0°C , 45%; v) THF, DCC, DMAP, 9%.

precursor^[23] by deprotection with HBr/HOAc .^[20] The subsequent steps were carried out in analogy to those of the second-generation dendra **20** and **21**. Whereas the yields for the syntheses of the key building blocks **25** and **27** are satisfactory, the final coupling to the depsipeptide dendron **28** were less efficient. This is obviously due to the bulky isobutyl group in the proximity of the reaction center. All couplings proceeded without epimerization at the stereogenic center of the leucine moiety. This leads to the conclusion that this concept for the synthesis of depsipeptide dendrimers tolerates the use of chiral amino acids as C termini but requires as little sterical hindrance as possible, for example, small C termini and peptides of a sufficient length in order to efficiently synthesize higher generation dendra.

All depsipeptide dendrimers and their precursor building blocks were completely characterized by NMR and IR spec-

troscopy, mass spectrometry, elemental analysis, and by their specific and molar optical rotations $[\alpha]_D$ and $[\Phi]_D$, respectively. FAB mass spectrometry turned out to be the method of choice for these systems. As a representative example the FAB spectrum of **22c** is shown in Figure 1. The base peak m/z 2860 corresponds to $[M+\text{H}]^+$. Important fragments are m/z 2435 $[M-426+\text{H}]^+$, 1678 $[M-1182]^+$, and 729 $[728+\text{H}]^+$. The smaller peaks on the right side of the base peaks at m/z 2882 and m/z 2992 are due to $[M+\text{Na}]^+$ and $[M+\text{Cs}]^+$, respectively.

A characteristic feature of these chiral dendritic systems is that, with the exception of the C_2 symmetric compounds **15a** and **15b**, all C and H atoms are topologically different even if they originate from identical locations within a set of free constituting precursors. This is reflected by the splitting of the signals of the various sets of groups in the NMR spectra. As an example three characteristic regions within the ^{13}C NMR spectrum of **22a**, namely, the carbonyl C-atoms ($\delta = 165-174$), the methylene C-atoms of the glycine units ($\delta = 40.9-41.7$), and the methine C-atoms of the alanine moieties ($\delta = 48.4-49.2$) are depicted in Figure 2. All the corresponding sets of seven topologically different C-atoms of both the glycine and alanine units give rise to seven resolved signals, and 32 signals for the 36 topologically different carbonyl C atoms are resolved.

The region between $\delta = 5.5-6.2$ in the ^1H NMR spectra of **22a,b,c** is an example of characteristic fingerprints caused only by the different stereochemistry of such chiral dendra

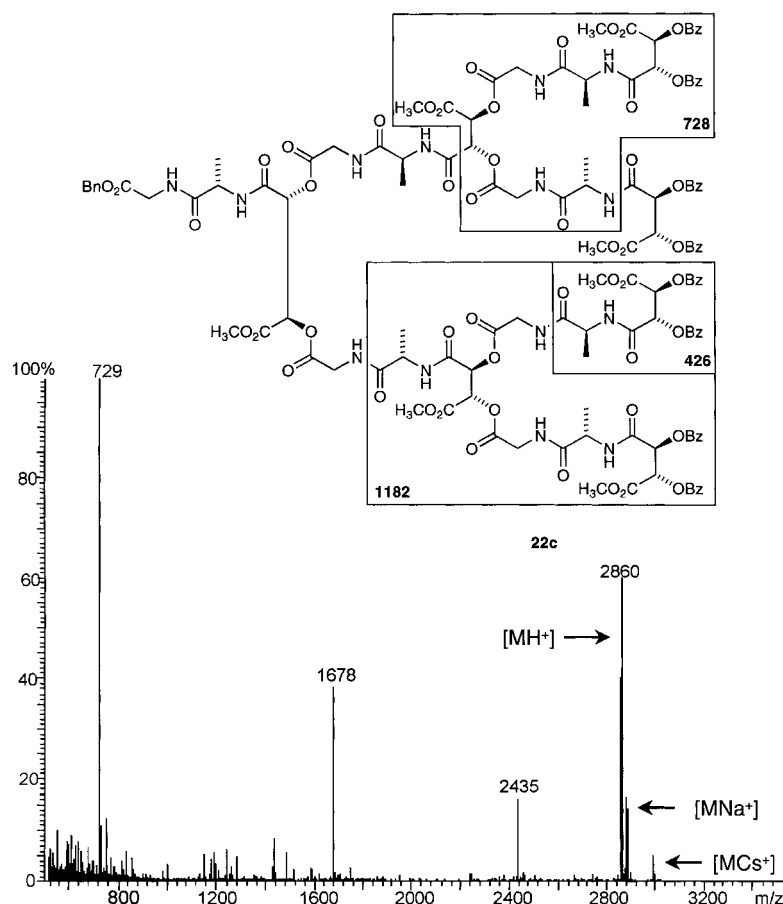


Figure 1. FAB mass spectrum of **22c**.

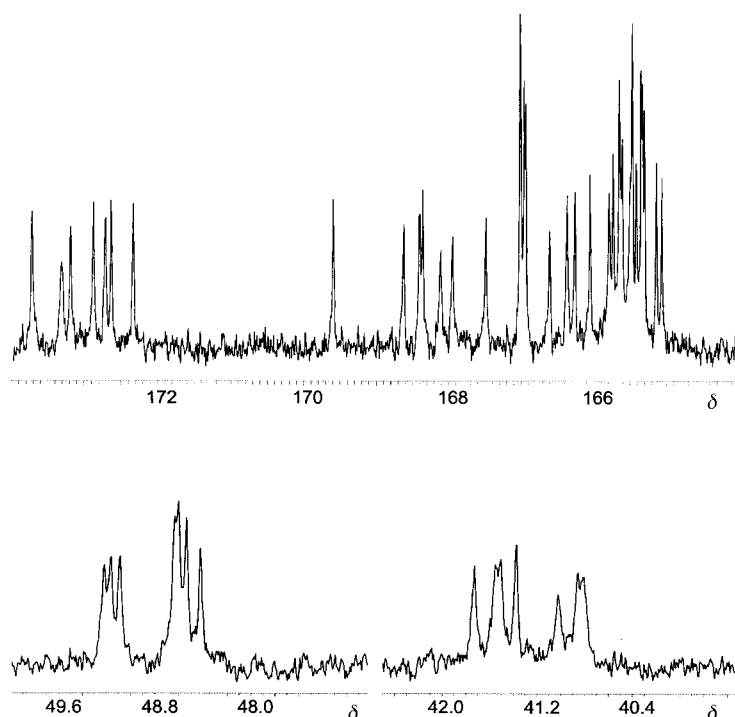


Figure 2. ^{13}C NMR spectrum (125.7 MHz, CDCl_3) of **22a** for the ranges from $\delta = 164\text{--}174$ ($\text{C}=\text{O}$), $\delta = 46\text{--}50$ (CH alanine), and $\delta = 40\text{--}42$ (CH_2 glycine).

(Figure 3). In this range the CH resonances of the tartaric acid units are localized. Two main sections show up: a down-field part, whose integration accounts for eight protons, and a high-field part, which is due to six protons. The H atoms of the

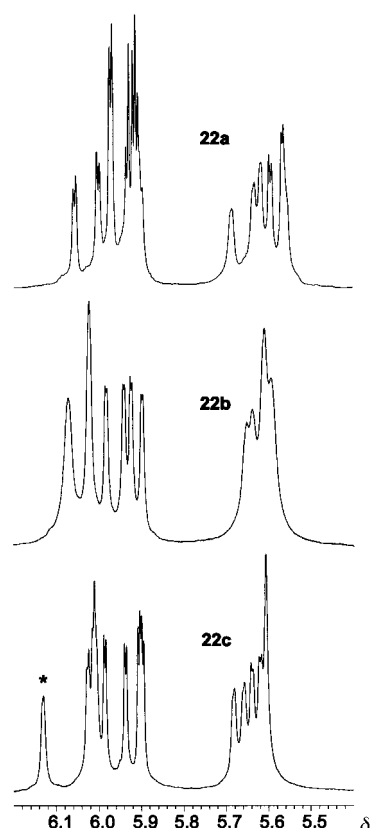


Figure 3. ^1H NMR (500 MHz, CDCl_3) of **22a**, **22b**, and **22c** for the range from $\delta = 5.4\text{--}6.2$ (CH tartaric acid).

outer shell resonate in the down-field part, whereas the high-field resonances are caused by the inner two sets of methine protons. For the whole region 14 doublets are expected; these are not completely resolved. The patterns for these signals are very different for each diastereomer. The comparison of **22b** with **22c** is particularly instructive. These two compounds differ only at the configuration of the inner tartaric acid moiety (*S,S* for **22b**, *R,R* for **22c**). In compound **22c** one proton (marked with a *) of the outer tartaric acid units, along with the Bz groups, undergoes a significant down-field shift, even though it is in a position very remote from the location of stereochemistry differences.

Specific optical rotations $[\alpha]_D$ and the molar optical rotations $[\Phi]_D$ are shown in Table 1. To check whether there was a concentration dependence the measurements were carried out at two different concentrations.

With the exception of building block **12a**, whose chiroptical data show a pronounced concentration dependence of unknown nature, the optical rotations of the other building blocks and dendritic systems are basically independent of the concentration. Further inspection of Table 1 shows that no folding phenomena owing to the formation of chiral secondary structures can be detected, since in a first approximation the molar optical rotation of a larger dendritic system like **22** represents the sum of those of the constituting building blocks like **20**. The contributions to the optical rotations are mainly due to the tartaric acid building blocks, whereas the alanine units exhibit only a minor influence. For example, the two diastereomers **22a** and **22b**, whose tartaric acid skeletons behave like a pair of enantiomers, have almost the same molar rotations but with opposite sign.

Table 1. Optical rotational values $[\alpha]_D$ and molar optical rotations $[\Phi]_D$ for the dendrons **12**, **13**, **20**, **21**, **22** and the dendrimers **15a,b,c**.

	$c_1^{[a]}$	$[\alpha]_D^{[b]}$	$[\Phi]_D^{[c]}$	$c_2^{[a]}$	$[\alpha]_D^{[b]}$	$[\Phi]_D^{[c]}$	solvent
12a	0.414	−45.65	−270	0.590	−94.92	−561	CHCl_3
12b	0.414	+64.98	+384	0.590	+66.10	+390	CHCl_3
20a	0.785	−59.87	−807	1.047	−62.37	−840	CHCl_3
20b	0.314	+66.88	+901	0.523	+69.98	+943	CHCl_3
22a	0.260	−65.77	−1881	0.520	−67.12	−1920	CHCl_3
22b	0.715	+68.53	+1960	0.953	+68.63	+1963	CHCl_3
22c	0.715	+68.53	+1960	0.953	+61.89	+1770	CHCl_3
15a	1.000	−62.00	−709	1.331	−58.60	−670	CHCl_3
15b	1.000	−46.30	−529	1.333	−47.93	−548	CHCl_3
15c	1.000	−54.00	−617	1.333	−55.50	−634	CHCl_3
13a	0.318	−79.25	−468	0.583	−91.42	−458	MeOH
13b	0.350	+59.14	+296	0.600	+56.00	+280	MeOH
21a	0.294	−77.21	−971	0.586	−76.79	−965	MeOH
21b	0.735	+32.25	+405	0.977	+31.12	+391	MeOH

[a] Concentration in 10 mg mL^{-1} . [b] Specific rotation in $10^{-1}\text{ deg cm}^2\text{ g}^{-1}$. [c] Molar rotation in $10\text{ deg cm}^2\text{ mol}^{-1}$.

Conclusion

We have disclosed a new concept of chiral dendrimers, which consist of tartaric acid moieties as branching units and peptides as spacers. We synthesized a first series of such depsipeptide dendrimers including third-generation dendra using a convergent approach. The corresponding dendritic systems contain up to 21 stereogenic centers within the chiral peptide or the building blocks derived from tartaric acid. This impressively demonstrates the scope of this concept, since just the variation of the chiral-pool building blocks, tartaric acid and amino acid, whose different stereoisomers are readily available, in principle allows for the formation of over two million stereoisomers of those third-generation dendra. The variation of just one stereogenic center can lead to a dramatic change of properties. The fact that also the length and the primary structure of the peptide can be varied demonstrates that ideal requirements for the development of libraries are met. First examples of depsipeptide mini libraries are introduced. We are now in the process of synthesizing higher generation dendra by using longer peptide spacers with small C termini. We intend to look systematically into the biological and catalytical properties of depsipeptide dendrimers by developing and screening combinatorial libraries of this new type of peptoids.

Experimental Section

^1H NMR and ^{13}C NMR spectra were recorded on JEOL GX400, JEOL EX400, and JEOL A500 spectrometers. Mass spectra were measured with Micromass Zab Spec (FAB) or Varian MAT (EI, 70 eV). IR spectra were recorded on Bruker Vector 22. HPLC (preparative) were measured with Shimadzu SIL 10A, SPD 10A, CBM 10A, LC 8A, FRC 10A (Nucleosil 100-5, Machery-Nagel). HPLC (analytical) were measured with Shimadzu CBM-10A, SPD-M10A, SIL-10A, LC-10AT (Nucleosil 100 Si, 5 m). TLC (Riedel-de Haën, silica gel 60 F₂₅₄). Materials and solvents were obtained from commercial suppliers and were used without further purification. Products were isolated by flash column chromatography (FC) (silica gel 60, particle size 0.04–0.063 nm, Merck) or recrystallization.

General procedure I for the amide formation: NEt₃ (1.4 mL, 10 mmol) was added to a suspension of 10 mmol of the hydrobromide or the tosylate in CH₂Cl₂ (150 mL) to release the amine. The solution was cooled to –5 °C. The equivalent amount of the carboxylic acid and (2.06 g, 10 mmol) of DCC were added all at once. The mixture was stirred for two hours at 0 °C and then overnight at room temperature. The white precipitate of dicyclohexylurea (DCU) was filtered, the CH₂Cl₂ layer was washed three times with a saturated solution of NaHCO₃ (500 mL) in water and dried over MgSO₄. After removal of the solvent the crude product was purified by FC.

General procedure II for the ester formation: The carboxylic acid (2.2 mmol) and then DCC (2.27 g, 1.1 mmol) and DMAP (10 mg) were added at room temperature to a solution of the diol (1 mmol) in dry dioxane or THF (150 mL). After 10 min the first DCU was formed. The solution was stirred for five hours. The precipitate (DCU) was filtered, the solvent removed, and the crude product purified by FC or HPLC.

General procedure III for the removal of the Bn ester: The Bn ester was dissolved in dioxane and 10 mass percent of Pd–C (10% Pd) were added. This suspension was subjected to hydrogenation until no more hydrogen was consumed. The Pd–C was filtered over aluminium oxide. The dioxane was evaporated and the product dried in vacuo.

General procedure IV for the removal of the benzylidene acetal: A suspension of the benzylidene acetal (10 mmol) in TFA (4 mL) and water (5 drops) was stirred at 0 °C until no starting material could be detected any

more (TLC control, 5 min). Then the reaction was quenched by the addition of water (50 mL). Solid NaHCO₃ was added in small portions to neutralize the solution. The crude product was extracted with EtOAc, the solvent was removed, and the residue recrystallized twice from EtOAc.

(2S,5R,6R)-1-Benzyl-7-methyl-5,6-bis(benzoyloxy)-2-methyl-4-oxo-3-azaheptanedicarboxylate (9): Compound **9** was synthesized according to general procedure I with the tosylate **7** (3.51 g) and the carboxylic acid **8** (3.72 g). FC with toluene/EtOAc = 4:1 (*R_f* = 0.58). Yield 2.8 g (52%) sticky solid; $[\alpha]_D^{20} = -68.7$ (*c* = 2.095, CHCl₃); ^1H NMR (400 MHz, CDCl₃, 24 °C, TMS): δ = 1.41 (d, 3J = 7.3 Hz, 3H; CH₃), 3.73 (s, 3H; OCH₃), 4.67 (dq, $^3J_1 = ^3J_2 = 7.1$ Hz, 1H; CH alanine), 5.08 (d, 2J = 12.3 Hz, 1H; CHH Bn), 5.14 (d, 2J = 12.3 Hz, 1H; CHH Bn), 5.94 (d, 3J = 2.2 Hz, 1H; CH tartaric acid), 6.13 (d, 3J = 2.2 Hz, 1H; CH tartaric acid), 7.05 (d, 3J = 7.1 Hz; NH), 7.26–7.36 (m, 5H; Bn), 7.40–7.64 (m, 6H; Bz), 8.08–8.14 (m, 4H; *o*-H of the Bz); ^{13}C NMR (100.5 MHz, CDCl₃, 24 °C, TMS): δ = 18.5 (CH₃), 48.1 (CH alanine), 52.9 (OCH₃), 67.3 (CH₂), 71.9, 73.6 (CH tartaric acid), 128.0, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 130.1, 130.1 (phenyl C), 133.6, 134.2, 135.0 (quaternary phenyl C), 164.7, 165.1, 165.3, 167.1, 172.2 (C=O); IR (KBr): $\tilde{\nu}$ = 3358, 2954, 1762, 1730, 1665, 1524, 1600, 1584, 1524, 756, 713 cm⁻¹; MS (70 eV, EI): *m/z* (%): 533 (58) [*M*]⁺, 398 (42), 355 (94), 105 (100) [C₇H₅O]⁺, 77 (61) [C₆H₅]⁺; C₂₉H₂₇NO₉ (533.57): calcd C 65.29, H 5.10, N 2.63; found: C 65.00, H 5.04, N 2.87.

(2S,5R,6R)-7-Methyl-5,6-bis(benzoyloxy)-2-methyl-4-oxo-3-azaheptanedicarboxylate (10): Compound **10** was synthesized according to general procedure III. Yield white solid (100%); $[\alpha]_D^{20} = -79.2$ (*c* = 1.540, CHCl₃); ^1H NMR (400 MHz, CDCl₃, 23 °C, TMS): δ = 1.41 (d, 3J = 7.3 Hz, 3H; CH₃), 3.72 (s, 3H; OCH₃), 4.62 (dq, $^3J_1 = ^3J_2 = 7.1$ Hz, 1H; CH alanine), 5.96 (d, 2J = 2.3 Hz, 1H; CH tartaric acid), 6.12 (d, 2J = 2.3 Hz, 1H; CH tartaric acid), 7.01 (d, 3J = 7.3 Hz, 1H; NH), 7.36–7.65 (m, 10H; Bz), 8.04–8.12 (m, 4H; *o*-H of the Bz group), 9.87 (br, 1H; CO₂H); ^{13}C NMR (100.5 MHz, CDCl₃, 23 °C, TMS): δ = 18.1 (CH₃), 48.0 (CH alanine), 53.0 (OCH₃), 71.8, 72.6 (CH tartaric acid), 128.2, 128.5, 128.6, 128.9, 130.0, 130.1 (phenyl C), 133.7, 134.2 (quaternary phenyl C), 164.8, 165.2, 165.7, 167.2 (C=O), 176.5 (CO₂H); IR (KBr): $\tilde{\nu}$ = 3400, 2954, 1738, 1652, 1585, 1493, 710 cm⁻¹; MS (70 eV, EI): *m/z* (%): 443 (7) [*M*]⁺, 412 (11) [*M* – CH₃O]⁺, 398 (41) [*M* – CO₂]⁺, 355 (70), 122 (23) [Ph – CO₂]⁺, 105 (100) [Ph – CO]⁺, 77 (100) [Ph]⁺; C₂₉H₂₁NO₉ (443.44): calcd C 59.59, H 4.77, N 3.16; found: C 59.41, H 4.88, N 3.01.

(5S,8R,9R)-1-Benzyl-10-methyl-8,9-bis(benzoyloxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (12a): Compound **12a** was synthesized according to general procedure I with the bromide **11** (3.17 g) and the carboxylic acid **8** (3.72 g). FC with toluene/EtOAc = 3:1 (*R_f* = 0.23). Yield 3.4 g (58%) white solid; $[\alpha]_D^{20} = -45.65$ (*c* = 0.414, CHCl₃); ^1H NMR (400 MHz, CDCl₃, 32 °C, TMS): δ = 1.36 (d, 3J (H,H) = 6.8 Hz, 3H; CH₃), 3.71 (s, 3H; OCH₃), 3.71 (dd, $^3J_1 = 5.1$, $^2J_2 = 15$ Hz, 1H; CHH glycine), 3.88 (dd, $^3J_1 = 5.6$ Hz, $^2J_2 = 14.2$, 1H; CHH glycine), 4.64 (dq, $^3J_1 = ^3J_2 = 7$ Hz, 1H; CH alanine), 5.06 (s, 2H; CH₂ Bn), 5.96 (d, 3J = 2.5 Hz, 1H; CH tartaric acid), 6.1 (d, 3J = 2.5 Hz, 1H; CH tartaric acid), 6.89 (dd, $^3J_1 = ^3J_2 = 5.4$ Hz, 1H; NH glycine), 7.29 (d, 3J = 1.7 Hz, 1H; NH alanine), 7.30–7.64 (m, 11H; Bn, Bz), 8.01–8.11 (m, 4H; *o*-H of the Bz group); ^{13}C NMR (100.5 MHz, CDCl₃, 32 °C, TMS): δ = 18.4 (CH₃), 41.1 (CH₂ glycine), 48.5 (CH alanine), 52.9 (OCH₃), 67.1 (CH₂ Bn), 71.9, 72.6 (CH tartaric acid), 128.2, 128.2, 128.3, 128.5, 128.6, 128.9 (phenyl C), 133.6, 134.2, 135.1 (quaternary phenyl C), 164.8, 165.1, 165.7, 167.0, 169.2, 171.7 (C=O); IR (KBr): $\tilde{\nu}$ = 3389, 2949, 1758, 1662, 1644, 1550, 1455, 1199, 1126, 912 cm⁻¹; MS (70 eV, EI): *m/z* (%): 590 (68) [*M*]⁺, 559 (57) [*M* – CH₃O]⁺, 483 (26) [*M* – C₇H₅O]⁺, 426 (100); C₃₁H₃₀N₂O₁₀ (590.63): calcd C 63.04, H 5.13, N 4.74; found: C 63.66, H 5.19, N 4.77.

(5S,8S,9S)-1-Benzyl-10-methyl-8,9-bis(benzoyloxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (12b): Compound **12b** was synthesized according to the procedure used for **12a**. FC with toluene/EtOAc = 3:1 (*R_f* = 0.23). Yield 3.1 g (53%) white solid; $[\alpha]_D^{20} = 64.98$ (*c* = 0.414, CHCl₃); ^1H NMR (400 MHz, CDCl₃, 32 °C): δ = 1.30 (d, 3J = 7.2 Hz, 3H; CH₃), 3.72 (s, 3H; OCH₃), 3.99 (d, 5.0 Hz, 2H; CH₂ glycine), 4.61 (dq, $^3J_1 = ^3J_2 = 7.2$ Hz, 1H; CH alanine unit), 5.13 (s, 2H; CH₂ Bn group), 5.98 (d, 3J = 2.8 Hz, 1H; CH tartaric acid), 6.05 (d, 3J = 2.8 Hz, 1H; CH tartaric acid), 6.86 (dd, $^3J_1 = ^3J_2 = 5.5$ Hz, 1H; NH), 7.26 (m, 1H; NH), 7.30–7.63 (m, 11H; Bn, Bz), 8.06–8.10 (m, 4H; *o*-H of the Bz group); ^{13}C NMR (100.5 MHz, CDCl₃, 32 °C): δ = 18.5 (CH₃), 41.3 (CH₂ glycine), 48.7 (CH alanine), 52.9 (OCH₃), 67.2 (CH₂ Bn), 71.9, 72.8 (CH tartaric acid), 128.2, 128.3, 128.5, 128.6, 128.6, 128.8, 129.0, 129.9, 130.0 (phenyl C), 133.7, 134.1, 135.0

(quaternary phenyl C), 164.9, 165.0, 165.6, 167.0, 169.3, 171.7 (C=O); IR (KBr): $\tilde{\nu}$ = 3385, 3067, 2955, 1734, 1660, 1601, 1524, 1453, 1359, 1317, 1246, 1093, 1069, 1025, 712 cm⁻¹; MS (70 eV, EI): m/z (%): 590 (2) [M]⁺, 559 (2) [M - CH₃O]⁺, 355 (65), 105 (100) [PhCO]⁺; C₃₁H₃₀N₄O₁₀ (590.63): calcd C 63.04, H 5.13, N 4.74; found: C 63.10, H 5.19, N 4.72.

(5S,8R,9R)-10-Methyl-8,9-bis(benzoyloxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (13a): Compound **13a** was synthesized according to general procedure III. Yield white solid (100%); [α]_D²⁰ = -79.25 (c = 0.318, MeOH); ¹H NMR (400 MHz, CD₃OD, 22 °C): δ = 1.32 (d, ³ J = 7.1 Hz, 3H; CH₃), 3.73 (s, 3H; OCH₃), 3.74 (d, ² J = 17.8 Hz, 1H; CHH glycine), 3.84 (d, ² J = 17.8 Hz, 1H; CHH glycine), 4.50 (m, 1H; CH alanine), 5.97 (d, ³ J = 3.2 Hz, 1H; CH tartaric acid), 7.48–7.54, 7.62–7.67 (m, 6H; Bz), 8.06–8.11 (m, 4H, *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CD₃OD, 22 °C): δ = 18.3 (CH₃), 41.7 (CH₂ glycine), 50.1 (CH alanine), 53.5 (OCH₃), 73.2, 73.9 (CH tartaric acid), 129.3, 129.5, 129.8, 130.0, 130.9, 131.0 (phenyl C), 135.0, 135.1 (quaternary phenyl C), 166.59, 166.6, 167.4, 168.5, 172.5, 174.3 (C=O); IR (KBr): $\tilde{\nu}$ = 3386, 3068, 2956, 1732, 1656, 1533, 1453, 1317, 1248, 1095, 1025, 712 cm⁻¹; MS (FAB): m/z (%): 501 (100) [M]⁺, 426 (33), 379 (21) [M - PhCO₂H]⁺, 355 (46), 322 (28) [M - PhCO₂H - CO₂CH₃]⁺; C₃₄H₃₄N₂O₁₀ (500.50): calcd C 57.59, H 4.84, N 5.60; found: C 57.75, H 5.10, N 5.44.

(5S,8S,9S)-10-Methyl-8,9-bis(benzoyloxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (13b): Compound **13b** was synthesized according to the procedure used for **13a**. Yield white solid (100%); [α]_D²⁰ = +59.14 (c = 0.350, MeOH); ¹H NMR (400 MHz, CD₃OD, 32 °C): δ = 1.21 (d, ³ J = 6.6 Hz, 3H; CH₃), 3.67 (s, 3H; OCH₃), 3.81 (m, 2H; CH₂ glycine), 4.60 (m, 1H; CH alanine), 5.94 (d, ³ J = 2.8 Hz, 1H; CH tartaric acid), 5.97 (d, ³ J = 2.2 Hz, 1H; tartaric acid), 7.11 (m, 1H; NH), 7.39–7.58 (m, 6H; Bz), 7.63 (d, ³ J = 7.7 Hz, 1H; NH), 8.02–8.03 (d, ³ J = 7.7 Hz, 4H; *o*-H of the Bz group), 10.60 (br, 1H; acid proton); ¹³C NMR (100.5 MHz, CD₃OD, 32 °C): δ = 18.3 (CH₃), 41.1 (CH₂ glycine), 48.7 (CH alanine unit), 53.0 (OCH₃), 71.7, 72.7 (CH tartaric acid), 128.2, 128.5, 128.7, 129.0, 129.9, 130.0 (phenyl C), 133.8, 134.1, 135.0 (quaternary phenyl C), 165.0, 165.1, 166.0, 167.0, 171.3, 172.1, 172.4 (C=O); IR (KBr): $\tilde{\nu}$ = 3405, 2956, 1734, 1658, 1602, 1530, 1453, 1318, 1246, 1178, 1093, 1069, 1025, 711 cm⁻¹; MS (70 eV, EI): m/z (%): 501 (2) [M]⁺, 355 (100), 327 (27) [355 - CO]⁺, 105 (100) [PhCO]⁺; C₃₄H₃₄N₂O₁₀ (500.46) calcd C 57.60, H 4.83, N 5.60; found: C 57.70, H 4.96, N 5.57.

Tetramethyl(3R,4R,7S,13R,14R,20S,23R,24R)-4,23-bis(benzoyloxy)-7,20-dimethyl-1,5,8,11,16,19,22,26-octaaxo-1,26-diphenyl-2,12,15,25-tetraoxa-6,9,18,21-tetraaza hexacosane-3,13,14,24-tetracarboxylate (15a): Compound **15a** was synthesized according to general procedure II with the carboxylic acid **13a** (1.10 g) and (L)-tartaric acid dimethylester **14a** (0.18 g). FC with toluene/EtOAc = 3:5 (R_f = 0.33). Yield 0.62 g (54%) white solid; [α]_D²⁰ = -62.00 (c = 1.000, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 23 °C, TMS): δ = 1.34 (d, ³ J = 7.1 Hz, 3H; CH₃), 3.65 (s, 3H; OCH₃), 3.70 (s, 3H; OCH₃), 3.75 (dd, ³ J_1 = 5.4 Hz, ³ J_2 = 18.1 Hz, 2H; CHH), 3.92 (dd, ³ J_1 = 5.9 Hz, ³ J_2 = 18.1 Hz, 2H; CHH), 4.59 (dq, ³ J_1 = ³ J_2 = 7.3 Hz, 2H; CH alanine), 5.58 (s, 2H; CH central tartaric acid), 5.95 (d, ³ J_1 = 2.9 Hz, 2H; CH tartaric acid), 6.04 (d, ³ J_1 = 2.7 Hz, 2H; CH tartaric acid), 6.89 (dq, ³ J_1 = ³ J_2 = 5.7 Hz, 2H; NH), 7.14 (d, ³ J = 7.6 Hz, 2H; NH), 7.39–7.62 (m, 12H; phenyl rings), 8.02 (d, ³ J = 7.3 Hz, 4H; *o*-H of the Bz group), 8.05 (d, ³ J = 7.3 Hz, 4H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 23 °C, TMS): δ = 18.1 (CH₃), 40.9 (CH₂ glycine), 48.5 (CH alanine), 53.0, 53.2 (OCH₃), 71.0, 71.8, 72.7 (CH tartaric acid), 128.1, 128.6, 128.8, 130.0 (phenyl C), 133.7, 134.1 (quaternary phenyl C), 164.9, 165.2, 165.5, 165.9, 167.0, 167.9, 171.8 (C=O); IR (KBr): $\tilde{\nu}$ = 3388, 2957, 1734, 1675, 1602, 1521, 1453, 1247, 1174, 1094, 1070, 1025, 713, 687 cm⁻¹; MS (FAB): m/z (%): 1143 (39) [M]⁺, 718 (35) [M - 426]⁺ (see Figure 1), 355 (34); C₅₄H₅₄N₄O₂₄ (1143.12): calcd C 56.74, H 4.76, N 4.90; found: C 56.83, H 5.01, N 5.14.

Tetramethyl(3R,4R,7S,13S,14S,20S,23R,24R)-4,23-bis(benzoyloxy)-7,20-dimethyl 1,5,8,11,16,19,22,26-octaaxo-1,26-diphenyl-2,12,15,25-tetraoxa-6,9,18,21-tetraaza hexacosane-3,13,14,24-tetracarboxylate (15b): Compound **15b** was synthesized according to the procedure used for **15a**, but with (D)-dimethyl tartrate **14b** as diol. FC with toluene/EtOAc = 3:5 (R_f = 0.33). Yield 0.58 g (51%) white solid; [α]_D²⁰ = -46.30 (c = 1.000, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 23 °C): δ = 1.33 (d, ³ J = 6.3 Hz, 3H; CH₃), 3.71 (s, 3H; OCH₃), 3.74 (s, 3H; OCH₃), 3.85 (m, 4H; CH₂ glycine), 4.62 (dq, ³ J = ³ J_2 = 7.3 Hz, 2H; CH alanine), 5.66 (s, 2H; CH central tartaric acid), 5.99 (d, ³ J = 3.2 Hz, 2H; CH tartaric acid), 6.07 (d, ³ J = 3.2 Hz, 2H; CH tartaric acid), 7.00 (dq, ³ J_1 = ³ J_2 = 5.6 Hz, 2H; NH), 7.23 (d, ³ J = 7.6 Hz, 2H;

NH), 7.42–7.64 (m, 12H; phenyl rings), 8.07 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 25 °C): δ = 18.4 (CH₃), 41.1 (CH₂ glycine), 48.6 (CH alanine), 53.0, 53.3 (OCH₃), 71.7, 71.9, 72.5 (CH tartaric acid), 128.2, 128.6, 128.8, 130.1 (phenyl C), 133.7, 134.1 (quaternary phenyl C), 158.5, 165.0, 165.2, 165.6, 167.1, 167.8, 172.0 (C=O); IR (KBr): $\tilde{\nu}$ = 3406, 2957, 1763, 1733, 1670, 1602, 1529, 1452, 1317, 1248, 1177, 1095, 1071, 1025, 714 cm⁻¹; MS (FAB): m/z (%): 1275 (7) [M +Cs]⁺, 1143 (36) [M]⁺, 718 (100), 355 (65); C₅₄H₅₄N₄O₂₄ (1143.12): calcd C 56.74, H 4.76, N 4.90; found: C 56.81, H 4.65, N 4.67.

Tetramethyl(3R,4R,7S,13R,14S,20S,23R,24R)-4,23-bis(benzoyloxy)-7,20-dimethyl-1,5,8,11,16,19,22,26-octaaxo-1,26-diphenyl-2,12,15,25-tetraoxa-6,9,18,21-tetraaza hexacosane-3,13,14,24-tetracarboxylate (15c): Compound **15c** was synthesized according to the procedure used for **15a**, but with (*meso*)-dimethyl tartrate **14c** as diol. FC with toluene/EtOAc = 3:5 (R_f = 0.30). Yield 0.64 g (56%) white solid; [α]_D²⁰ = -54.00 (c = 1.000, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 32 °C): δ = 1.34 (m, 6H; CH₃), 3.71 (s, 3H; OCH₃), 3.72 (s, 3H; OCH₃), 3.74 (s, 3H; OCH₃), 3.75 (s, 3H; OCH₃), 3.85 (m, 3H; CH₂ glycine), 3.94 (dd, ³ J_1 = 6.1 Hz, ³ J_2 = 18.2 Hz, 1H; CH₂ glycine), 4.62 (dq, ³ J_1 = ³ J_2 = 7.2 Hz, 1H; CH alanine), 4.69 (dq, ³ J_1 = ³ J_2 = 7.2 Hz, 1H; CH alanine), 5.51 (d, ³ J = 2.2 Hz, 1H; CH tartaric acid), 5.59 (d, ³ J = 2.8 Hz, 1H; CH tartaric acid), 5.97 (d, ³ J = 2.8 Hz, 1H; CH tartaric acid), 5.99 (d, ³ J = 3.3 Hz, 1H; CH tartaric acid), 6.01 (d, ³ J = 3.3 Hz, 1H; CH tartaric acid), 6.02 (d, ³ J = 2.8 Hz, 1H; CH tartaric acid), 7.33 (m, 2H, 2 NH), 7.40–7.63 (m, 14H; phenyl rings, 2 NH), 8.06 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 32 °C): δ = 17.7, 18.4 (CH₃), 40.9 (2 × CH₂ glycine), 48.4, 48.5 (CH alanine), 52.8, 52.9, 52.9, 53.0 (OCH₃), 70.8, 71.1 (CH tartaric acid), 71.7, 72.7 (4 × CH tartaric acid), 128.2, 128.4, 128.5, 128.6, 128.7, 129.9, 130.0 (phenyl C), 133.6, 133.7, 134.0 (quaternary phenyl C), 164.9, 164.94, 165.4, 165.5, 165.7, 165.8, 166.9, 167.0, 167.76, 167.80, 172.2, 172.3 (C=O), 165.2 (2 × C=O); IR (KBr): $\tilde{\nu}$ = 3406, 2958, 1765, 1734, 1674, 1602, 1585, 1452, 1317, 1249, 1178, 1095, 1070, 1025, 803, 713 cm⁻¹; MS (FAB): m/z (%): 1275 (25) [M +Cs]⁺, 1143 (39) [M]⁺, 718 (100) [M - 426]⁺ (see Figure 1), 355 (58); C₅₄H₅₄N₄O₂₄ (1143.12): calcd C 56.74, H 4.76, N 4.90; found: C 56.31, H 4.94, N 4.84.

(5S,8R,9R)-1-Benzyl-10-methyl-8,9-(phenylmethylenedioxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (18a): Compound **18a** was synthesized according to general procedure I with the hydrobromide **11** (3.17 g) and the acid **16a** (2.52 g). FC with toluene/EtOAc = 1:1 (R_f = 0.46). Yield 2.40 g (51%) white solid; mixture of two diastereomers; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 1.34 (d, ³ J = 6.8 Hz, 3H; CH₃), 1.44 (d, ³ J = 7.1 Hz, 3H; CH₃), 3.77 (s, 3H; OCH₃), 3.82 (s, 3H; OCH₃), 4.09 (m, 4H; CH₂ of the two glycine), 4.62 (dq, ³ J_1 = ³ J_2 = 7.1 Hz, 1H; CH alanine), 4.73 (dq, ³ J_1 = ³ J_2 = 7.3 Hz, 1H; CH alanine), 4.77 (d, ³ J = 3.9 Hz, 1H; CH tartaric acid), 4.89 (d, ³ J = 4.6 Hz, 1H; CH tartaric acid), 4.94 (d, ³ J = 3.6 Hz, 1H; CH tartaric acid), 5.00 (d, ³ J = 3.7 Hz, 1H; CH tartaric acid), 5.16 (m, 4H; CH₂ Bn), 6.01, 6.14 (s, 2H; CH acetal), 7.06–7.57 (m, 26H; phenyl rings and four NH); ¹³C NMR (100.5 MHz, CDCl₃, 25 °C, TMS): δ = 18.0, 18.2 (CH₃), 41.3 (CH₂ glycine), 48.4, 48.5 (CH alanine), 52.8 (OCH₃), 67.1, 67.2 (CH₂ Bn group), 77.2, 77.9, 77.98, 78.14 (CH tartaric acid), 106.1, 106.4 (CH acetal), 127.0, 127.2, 128.4, 128.5, 128.6, 128.7, 130.1, 130.2 (phenyl C), 135.0, 135.16, 135.2 (quaternary phenyl C), 169.2, 169.5, 169.56, 169.60, 170.4, 171.7, 172.2 (C=O); IR (KBr): $\tilde{\nu}$ = 3424, 2929, 1764, 1736, 1644, 1541, 1451, 1240, 1218, 1111, 1028, 752, 697 cm⁻¹; MS (FAB): m/z (%): 471 (100) [M]⁺, 225 (36); C₂₄H₂₆N₂O₈ (470.478): calcd C 61.27, H 5.57, N 5.95; found: C 62.16, H 5.90, N 6.04.

(5S,8S,9S)-1-Benzyl-10-methyl-8,9-(phenylmethylenedioxy)-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (18b): Compound **18b** was synthesized according to general procedure I with the hydrobromide **11** (3.17 g) and the acid **16b** (2.52 g). FC with toluene/EtOAc = 1:1 (R_f = 0.30). Yield 2.22 g (47%) white solid; mixture of two diastereomers; ¹H NMR (400 MHz, CDCl₃, 23 °C): δ = 1.13 (d, ³ J = 6.1 Hz, 3H; CH₃), 1.16 (d, ³ J = 7.1 Hz, 3H; CH₃), 3.71 (s, 3H; OCH₃), 3.79 (s, 3H; OCH₃), 3.98 (m, 4H; CH₂ glycine), 4.42 (m, 1H; CH alanine), 4.56 (m, 1H; CH alanine), 4.69 (d, ³ J = 3.2 Hz, 1H; CH tartaric acid), 4.80 (d, ³ J = 4.6 Hz, 1H; CH tartaric acid), 4.88 (d, ³ J = 4.4 Hz, 1H; CH tartaric acid), 5.00 (d, ³ J = 3.2 Hz, 1H; CH tartaric acid), 5.08 (s, 2H; CH₂ Bn), 5.09 (s, 2H; CH₂ Bn), 6.71–6.85 (m, 4H; NH), 7.19–7.48 (m, 20H, phenyl rings); ¹³C NMR (100.5 MHz, CDCl₃, 23 °C): δ = 17.3, 18.2 (CH₃), 41.3 (CH₂ glycine), 48.4, 48.6 (CH alanine), 52.8 (OCH₃), 67.2, 67.3 (CH₂ Bn group), 77.1, 77.9, 78.0, 78.1 (CH tartaric acid), 106.1, 106.2 (CH acetal), 126.5, 127.0, 128.4, 128.5, 128.6, 130.1 (phenyl C), 135.2, 135.6 (quaternary phenyl C), 169.1, 169.4, 169.43,

170.1 (C=O); IR (KBr): $\tilde{\nu}$ = 3306, 3276, 2927, 1733, 1641, 1552, 1443, 1242, 1228, 1154, 1016, 757, 698 cm⁻¹; MS (70 eV, EI): m/z (%): 470 (2) [M]⁺, 411 (4) [M - CO₂CH₃]⁺, 278 (48) [M - PhCO₂]⁺, 91 (100) [PhCH₂]⁺; C₂₈H₂₆N₂O₈ (470.478): calcd C 61.27, H 5.57, N 5.95; found: C 60.69, H 5.62, N 5.96.

(5S,8R,9R)-1-Benzyl-10-methyl-8,9-dihydroxy-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (19a): Compound **19a** was synthesized according to general procedure IV. Yield 82% white solid; [α]_D²⁰ = +27.5 (*c* = 1.020, MeOH); ¹H NMR (400 MHz, CD₃OD, 21 °C): δ = 1.39 (d, ³*J* = 7.3 Hz, 3H; CH₃), 3.77 (s, 3H; OCH₃), 3.94 (d, ²*J* = 17.6 Hz, 1H; CHH glycine), 3.99 (d, ²*J* = 17.6 Hz, 1H; CHH glycine), 4.45 (d, ³*J* = 2.2 Hz, 1H; CH tartaric acid), 4.49 (m, 1H; CH alanine), 4.56 (d, ³*J* = 2.2 Hz, 1H; CH tartaric acid), 4.85 (br; OH), 5.15 (s, 2H; CH₂ Bn), 7.34 (m, 7H; phenyl ring and NH); ¹³C NMR (100.5 MHz, CD₃OD, 21 °C): δ = 18.1 (CH₃), 42.0 (CH₂ glycine), 48.4 (CH alanine), 52.8 (OCH₃), 67.9 (CH₂ Bn), 73.9, 74.3 (CH tartaric acid), 129.3, 129.5 (phenyl C), 137.1 (quaternary phenyl C), 170.9, 173.7, 173.8, 175.0 (C=O); IR (KBr): $\tilde{\nu}$ (cm⁻¹) = 3350, 3291, 3118, 2950, 1758, 1645, 1575, 1550, 1412, 1388, 1276, 1199, 1126, 1078, 912, 736, 697; MS (70 eV, EI): m/z (%): 382 (4) [M]⁺, 190 (100); C₁₇H₂₂N₂O₈ (382.41): calcd C 53.39, H 5.81, N 7.33; found: C 53.86, H 6.12, N 7.22.

(5S,8S,9S)-1-Benzyl-10-methyl-8,9-dihydroxy-4,7-dioxo-5-methyl-3,6-diazadecanedicarboxylate (19b): Compound **19b** was synthesized according to the procedure used for **19a**, but with **18b** as the starting material. Yield 79% white solid; [α]_D²⁰ = -65.30 (*c* = 0.268, MeOH); ¹H NMR (400 MHz, CD₃OD, 32 °C): δ = 1.38 (d, ³*J* = 7.2 Hz, 3H; CH₃), 3.76 (s, 3H; OCH₃), 3.95 (d, ²*J* = 17.6 Hz, 1H; CHH glycine), 4.03 (d, ²*J* = 17.6 Hz, 1H; CHH glycine), 4.43 (d, ³*J* = 2.2 Hz, 1H; CH tartaric acid), 4.48 (dq, ³*J*₁ = ³*J*₂ = 7.1 Hz, 1H; CH alanine), 4.58 (d, ³*J* = 2.2 Hz, 1H; CH tartaric acid), 4.85 (s; OH from the product and the solvent), 5.15 (s, 2H; CH₂ Bn), 7.30–7.35 (m, 7H; phenyl ring and NH); ¹³C NMR (100.5 MHz, CD₃OD, 32 °C): δ = 18.6 (CH₃), 42.1 (CH₂ glycine), 48.4 (CH alanine), 52.7 (OCH₃), 67.9 (CH₂ Bn), 73.5, 74.3 (CH tartaric acid), 129.30, 129.31, 129.5 (phenyl C), 137.1 (quaternary phenyl C), 170.9, 173.4, 174.0, 175.1 (C=O); IR (KBr): $\tilde{\nu}$ = 3369, 3265, 3085, 2929, 1736, 1659, 1554, 1532, 1456, 1440, 1374, 1337, 1290, 1225, 1117, 1065, 1025, 968, 870, 758, 700 cm⁻¹; MS (70 eV, EI): m/z (%): 382 (4) [M]⁺, 190 (100), 91 (100) [C₇H₇]⁺; C₁₇H₂₂N₂O₈ (382.41): calcd C 53.39, H 5.81, N 7.33; found: C 53.62, H 5.85, N 7.35.

Trimethyl(3R,4R,7S,13R,14R,20S,23R,24R)-4,23-bis(benzoyloxy)-14-[[[(1S)-2-[[2-(benzyloxy)-2-oxoethyl]amino]-1-methyl-2-oxoethyl]amino]carbonyl]-7,20-dimethyl-1,5,8,11,16,19,22-heptaaxo-1-phenyl-2,12,15,25-tetraoxa-6,9,18,21-tetraazahexacosane-3,13,24-tricarboxylate (20a): Compound **20a** was synthesized according to general procedure II with the diol **19a** (0.38 g) and the carboxylic acid **13a** (1.10 g). FC with toluene/EtOAc = 1:2 (*R*_f = 0.20). Yield 0.88 g (65%) white solid; [α]_D²⁰ = -59.87 (*c* = 0.785, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 1.26 (m, 6H; CH₃), 1.37 (d, ³*J* = 7.1 Hz, 3H; CH₃), 3.60 (s, 3H; OCH₃), 3.65 (s, 3H; OCH₃), 3.72 (s, 3H; OCH₃), 3.52–3.85, 4.01–4.15 (m, 6H; CH₂ glycine), 4.49 (dq, ³*J*₁ = ³*J*₂ = 7.3 Hz, 1H; CH alanine), 4.70 (dq, ³*J*₁ = ³*J*₂ = 7.6 Hz, 1H; CH alanine), 4.75 (dq, ³*J*₁ = ³*J*₂ = 7.1 Hz, 1H; CH alanine), 5.07 (s, 2H; CH₂ Bn), 5.70 (d, ³*J*₁ = 2.7 Hz, 1H; CH tartaric acid), 5.73 (d, ³*J*₁ = 2.7 Hz, 1H; CH tartaric acid), 6.00 (d, ³*J*₁ = 3.4 Hz, 1H; CH tartaric acid), 6.02 (d, ³*J*₁ = 3.2 Hz, 1H; CH tartaric acid), 6.09 (d, ³*J*₁ = 3.4 Hz, 1H; CH tartaric acid), 6.15 (d, ³*J*₁ = 3.4 Hz, 1H; CH tartaric acid), 7.21–7.84 (m, 23H; phenyl rings and NH), 8.02–8.09 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 25 °C, TMS): δ = 17.5, 18.1, 18.8 (CH₃), 41.2, 41.3, 41.7 (CH₂ glycine), 48.5, 48.6, 49.2 (CH alanine), 52.9, 52.96, 53.0 (OCH₃), 67.2 (CH₂ Bn), 71.4, 71.8, 71.9, 72.2, 72.7 (CH tartaric acid), 128.2, 128.3, 128.40, 128.44, 128.5, 128.6, 128.7, 128.8, 130.0, 130.1, (phenyl C), 133.75, 133.8, 134.0, 134.1, 135.0 (quaternary phenyl C), 165.2, 165.3, 165.36, 165.4, 165.6, 165.7, 165.8, 166.5, 166.9, 167.0, 167.5, 168.3, 169.6, 172.5, 172.9, 173.7 (C=O); IR (KBr): $\tilde{\nu}$ = 3388, 3069, 2956, 1734, 1669, 1602, 1525, 1453, 1248, 1178, 1095, 1070, 1025, 713 cm⁻¹; MS (FAB): m/z (%): 1479 (100) [M +Cs]⁺, 1347 (9) [M]⁺; C₆₅H₆₆N₆O₂₆ (1347.37): calcd C 57.95, H 4.94, N 6.24; found: C 57.60, H 4.87, N 5.68.

Trimethyl(3S,4S,7S,13S,14S,20S,23S,24S)-4,23-bis(benzoyloxy)-14-[[[(1S)-2-[[2-(benzyloxy)-2-oxoethyl]amino]-1-methyl-2-oxoethyl]amino]carbonyl]-7,20-dimethyl-1,5,8,11,16,19,22-heptaaxo-1-phenyl-2,12,15,25-tetraoxa-6,9,18,21-tetraazahexacosane-3,13,24-tricarboxylate (20b): Compound **20b** was synthesized according to general procedure II with the diol **19b** (0.38 g) and the carboxylic acid **13b** (1.10 g). FC with toluene/EtOAc = 1:2 (*R*_f = 0.15). Yield 0.70 g (52%) white solid; [α]_D²⁰ = +66.88 (*c* = 0.314,

CHCl₃); ¹H NMR (400 MHz, CDCl₃, 32 °C): δ = 1.24 (d, ³*J* = 7.2 Hz, 3H; CH₃), 1.28 (d, ³*J* = 7.1 Hz, 3H; CH₃), 1.31 (d, ³*J* = 7.1 Hz, 3H; CH₃), 3.42 (s, 3H; OCH₃), 3.65 (s, 3H; OCH₃), 3.72 (s, 3H; OCH₃), 3.80–3.87 (m, 3H; CHH glycine), 4.05–4.20 (m, 2H; CH₂ glycine), 4.27–4.36 (m, 2H; CHH glycine and CH alanine), 4.58 (dq, ³*J*₁ = ³*J*₂ = 7.1 Hz, 1H; CH alanine), 4.66 (dq, ³*J*₁ = ³*J*₂ = 7.7 Hz, 1H; CH alanine), 5.09 (s, 2H; CH₂ Bn), 5.59 (d, ³*J*₁ = 2.8 Hz, 1H; CH tartaric acid), 5.63 (d, ³*J*₁ = 2.8 Hz, 1H; CH tartaric acid), 5.88 (d, ³*J*₁ = 2.8 Hz, 1H; CH tartaric acid), 6.00 (d, ³*J*₁ = 2.2 Hz, 1H; CH tartaric acid), 6.02 (d, ³*J*₁ = 2.8 Hz, 1H; CH tartaric acid), 6.20 (d, ³*J*₁ = 2.2 Hz, 1H; CH tartaric acid), 6.66 (br, 1H; NH), 7.13–7.61 (m, 17H; phenyl rings and 5 NH), 7.99–8.04 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 32 °C): δ = 17.7, 18.2, 18.6 (CH₃), 40.8, 41.3, 41.7 (CH₂ glycine), 48.1, 48.7, 48.9 (CH alanine), 52.9 (2 ×), 53.0 (OCH₃), 67.2 (CH₂), 71.1, 71.7, 71.8, 72.5, 72.7, 73.0 (CH tartaric acid), 128.2, 128.3, 128.4, 128.44, 128.5, 128.6, 128.64, 128.8, 128.81, 129.0, 129.9, 129.96 (phenyl C), 133.8, 134.0, 134.1, 135.0 (quaternary phenyl C), 164.6, 164.8, 164.9, 165.1 (2 ×), 165.8, 166.5, 166.7, 167.1, 167.8, 168.0, 169.9, 171.7, 171.8, 173.0 (C=O); IR (KBr): $\tilde{\nu}$ = 3387, 2931, 1736, 1671, 1601, 1522, 1453, 1246, 1178, 1093, 1069, 1025, 713 cm⁻¹; MS (FAB): m/z (%): 1347 (45) [M]⁺, 922 (24), 729 (20), 355 (52), 307 (100); C₆₅H₆₆N₆O₂₆ (1347.37): calcd C 57.95, H 4.94, N 6.24; found: C 58.11, H 5.02, N 6.20.

(4R,5R,8S,14R,15R,18S)-4,5-Bis(benzoyloxy)-15-[(2-[(2S,3R)-2-(benzyloxy)-3,4-dimethoxy-4-oxobutanoyl]amino]propanoyl]amino]acetyl]oxy)-14-(methoxycarbonyl)-8,18-dimethyl-3,6,9,12,16,19-hexaaxo-2,13-dioxo-7,10,17,20-tetraazadocosan-22-oic acid (21a): Compound **21a** was synthesized according to general procedure III. Yield white solid (100%); [α]_D²⁰ = -77.21 (*c* = 0.294, MeOH); ¹H NMR (400 MHz, CDCl₃, 19 °C): δ = 1.30 (m, 6H; CH₃), 1.37 (d, ³*J* = 7.3 Hz, 3H; CH₃), 3.69 (s, 3H; OCH₃), 3.73 (s, 6H; OCH₃), 3.77–3.94 (m, 7H; CH₂ glycine, CH alanine), 4.45 (m, 2H; CH alanine), 5.66 (d, ³*J* = 2.9 Hz, 1H; CH tartaric acid), 5.67 (d, ³*J* = 2.9 Hz, 1H; CH tartaric acid), 5.98 (m, 4H; CH tartaric acid), 7.46–7.66 (m, 12H; phenyl rings), 8.04–8.09 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 20 °C): δ = 17.4, 17.9, 18.5 (CH₃ alanine), 40.9, 41.2, 41.7 (CH₂ glycine), 48.6, 48.7, 49.0 (CH alanine), 53.0, 53.1 (OCH₃), 71.2, 71.7, 71.8, 72.3, 72.5, 72.7 (CH tartaric acid), 128.2, 128.3, 128.5, 128.6, 128.61, 128.7, 128.8, 129.9, 130.0 (phenyl C), 133.8, 134.0 (quaternary phenyl C), 165.1, 165.3, 165.7, 165.9, 166.6, 166.9, 167.5, 168.6, 172.4, 173.1, 173.6 (C=O); IR (KBr): $\tilde{\nu}$ = 3377, 3070, 2956, 1734, 1671, 1602, 1528, 1453, 1248, 1178, 1095, 1070, 1025, 713, 687 cm⁻¹; MS (FAB): m/z (%): 1389 (100) [M +Cs]⁺, 1279 (80) [M +Na]⁺, 1257 (84) [M]⁺, 832 (57) [M +H-426]⁺, 729 (24) [see Figure 1], 426 (29) [see Figure 1], 355 (79); C₅₈H₆₀N₆O₂₆ (1257.24): calcd C 55.41, H 4.81, N 6.69; found: C 55.26, H 4.90, N 6.61.

(4S,5S,8S,14S,15S,18S)-4,5-Bis(benzoyloxy)-15-[(2-[(2S)-2-[(2R,3R)-2-(benzyloxy)-3,4-dimethoxy-4-oxobutanoyl]amino]propanoyl]amino]acetyl]oxy)-14-(methoxycarbonyl)-8,18-dimethyl-3,6,9,12,16,19-hexaaxo-2,13-dioxo-7,10,17,20-tetraazadocosan-22-oic acid (21b): Compound **21b** was synthesized according to general procedure III. Yield white solid (100%); [α]_D²⁰ = +32.25 (*c* = 0.735, MeOH); ¹H NMR (400 MHz, CDCl₃, 32 °C): δ = 1.13 (d, ³*J* = 7.2 Hz, 3H; CH₃), 1.20 (d, ³*J* = 7.2 Hz, 3H; CH₃), 1.24 (d, ³*J* = 7.2 Hz, 3H; CH₃), 3.66 (s, 3H; OCH₃), 3.67 (s, 3H; OCH₃), 3.68 (s, 3H; OCH₃), 3.71–4.61 (a series of broad signals, 9H; CH₂ glycine, CH alanine), 5.61 (br, 2H; CH tartaric acid), 5.89 (d, ³*J* = 2.2 Hz, 1H; CH tartaric acid), 6.00 (br, 2H; CH tartaric acid), 6.11 (br, 1H; CH tartaric acid), 7.07 (br, 1H; NH), 7.24–7.57 (m, 12H; phenyl rings), 7.69 (br, 1H; NH), 8.01 (m, 8H; *o*-H of the Bz group); ¹³C NMR (100.5 MHz, CDCl₃, 32 °C): δ = 17.6, 18.3, 18.4 (CH₃), 40.8, 41.2, 41.3 (CH₂ glycine), 48.3, 48.7, 48.9 (CH alanine), 53.0 (OCH₃), 71.2, 71.8, 72.2, 72.6 (CH tartaric acid), 128.4, 128.5, 128.6, 128.7, 128.8, 129.9 (phenyl C), 133.8, 133.9, 134.0 (quaternary phenyl C), 164.9, 165.0, 165.1, 165.2, 165.9, 166.3, 166.6, 167.1, 167.2, 168.0, 171.2, 172.4, 172.5, 173.0 (C=O); IR (KBr): $\tilde{\nu}$ = 3389, 3072, 2956, 1735, 1667, 1602, 1529, 1453, 1246, 1178, 1097, 1094, 1025, 713 cm⁻¹; MS (FAB): m/z (%): 1257 (43) [M]⁺, 832 (16) [M - 426+H]⁺, 729 (26), 426 (34), 355 (100); C₅₈H₆₀N₆O₂₆ (1257.24): calcd C 55.41, H 4.81, N 6.69; found: C 55.15, H 5.10, N 6.13.

Third-generation dendron 22a: DCC (0.167 g, 8 mmol) and DMAP (0.01 g, 0.08 mmol) were added all at once to a solution of **21a** (1.018 g, 0.8 mmol) and **19a** (0.132 g, 0.3 mmol) in dioxane (20 mL). After 15 minutes a white precipitate of DCU was formed. After stirring for an additional five hours at room temperature the precipitate was filtered, the solvent was removed in vacuo, and the crude product was prepurified by FC (CHCl₃/MeOH = 30:1). A second purification was carried out by means of HPLC

(Nucleosil, 14 mL min⁻¹, retention time 8.72 min, CHCl₃/MeOH = 97:3). Yield 0.08 g (8%) white solid; $[\alpha]_D^{20} = -65.77$ ($c = 0.260$, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 45 °C, TMS): $\delta = 1.21-1.28$ (m, 21 H; CH₃), 3.46, 3.53, 3.57, 3.62, 3.63, 3.64, 3.65 (7 s, 21 H; OCH₃), 3.66–4.65 (m, 21 H; CH₂ glycine, CH alanine), 4.99 (d, ³*J* = 13 Hz, 1 H; CHH Bn), 5.01 (d, ³*J* = 13 Hz, 1 H; CHH Bn), 5.56–5.68 (m, 6 H; CH tartaric acid), 5.90–5.97 (m, 6 H; CH tartaric acid), 6.00 (d, ³*J* = 3.5 Hz, 1 H; CH tartaric acid), 6.05 (d, ³*J* = 3.0 Hz, 1 H; CH tartaric acid), 7.10–7.81 (m, 43 H; phenyl rings, NH), 7.96–8.14 (m, 16 H; *o*-H of the Bz group); ¹³C NMR (125.65 MHz, CDCl₃, 45 °C, TMS): $\delta = 16.4, 16.5, 16.6, 16.7, 17.1, 17.7, 17.9$ (CH₃ alanine), 39.9, 40.0, 40.1, 40.5, 40.6, 40.7, 40.8 (CH₂ glycine), 47.6, 47.7, 47.8, 48.2, 48.3 (2 ×) (CH alanine), 51.9, 52.0, 52.0 (OCH₃), 66.1 (CH₂ Bn), 70.3, 70.4, 70.5, 70.9 (2 ×), 71.0, 71.0, 71.4, 71.5, 71.7, 71.8, 71.8, 71.9, 72.0 (CH tartaric acid), 127.2, 127.5, 127.5, 127.5, 127.6, 127.6, 127.8, 127.8, 129.0, 129.0, 129.1 (phenyl C), 132.7, 132.7, 132.8, 133.0 (br), 134.3 (quaternary phenyl C), 164.2, 164.2, 164.4, 164.4 (2 ×), 164.4, 164.5, 164.5, 164.6, 164.7 (2 ×), 164.8, 164.8, 164.9, 165.1, 165.3, 165.4, 165.6, 166.0, 166.1, 166.1, 166.6, 167.0, 167.2, 167.4, 167.4, 167.7, 168.6, 171.4, 171.6, 171.7, 172.0, 172.2, 172.3, 172.6 (C=O); IR (KBr): $\tilde{\nu} = 3420, 2957, 1736, 1671, 1524, 1453, 1247, 1178, 1094, 1070, 1025, 713$ cm⁻¹; MS (FAB): *m/z* (%): 2993 (48) [M+Cs+H]⁺, 2861 (83) [M]⁺, 2436 (100), 1679 (39), 729 (76); C₁₃₃H₁₃₈N₁₄O₅₈ · 2 MeOH (2924.691): calcd C 55.44, H 5.03, N 6.70; found: C 55.07, H 5.03, N 6.70.

Third-generation dendron 22b: DCC (0.167 g, 8 mmol) and DMAP (0.02 g, 0.16 mmol) were added all at once to a solution of **21b** (1.018 g, 0.8 mmol) and **19b** (0.132 g, 0.3 mmol) in dioxane (20 mL). After 15 minutes a white precipitate of DCU was formed. After stirring for five hours at room temperature the precipitate was filtered, the solvent was removed in vacuo, and the crude was product prepurified by FC (CHCl₃/MeOH = 30:1). A second purification was carried out by means of HPLC (Nucleosil, 16 mL min⁻¹, retention time 15.86 min, CHCl₃/MeOH = 97.7:2.3). Yield 0.13 g (13%) white solid; $[\alpha]_D^{20} = +68.53$ ($c = 0.715$, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 24 °C): $\delta = 1.10-1.29$ (m, 21 H; CH₃), 3.32, 3.46, 3.63, 3.69 (4 s, 21 H; OCH₃), 3.89–4.67 (m, 21 H; CH₂ glycine, CH alanine), 5.07 (s, 4 H; CH₂ Bn), 5.61–5.65 (m, 6 H; CH tartaric acid), 5.90 (d, ³*J* = 2.5 Hz, 1 H; CH tartaric acid), 5.93 (d, ³*J* = 2.5 Hz, 1 H; CH tartaric acid), 5.95 (d, ³*J* = 2.0 Hz, 1 H; CH tartaric acid), 5.98 (d, ³*J* = 2.0 Hz, 1 H; CH tartaric acid), 6.05 (m, 4 H; CH tartaric acid), 7.14–7.72 (m, 43 H; phenyl rings, NH), 8.03 (m, 16 H; *o*-H of the Bz group); ¹³C NMR (125.65 MHz, CDCl₃, 24 °C): $\delta = 16.7, 17.3, 17.4, 18.5, 18.8, 19.0$ (CH₃), 40.9, 41.3, 41.4, 42.0 (CH₂ glycine), 48.3, 48.4, 48.5, 48.7, 49.0 (CH alanine), 52.9, 52.9, 53.1, 53.8 (OCH₃), 67.1 (CH₂ Bn), 71.0, 71.1, 71.3, 71.8, 71.8, 71.9, 72.1, 72.3, 72.6, 72.7, 72.8 (CH tartaric acid), 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.8, 129.9 (phenyl C), 133.5, 133.7, 133.9, 133.9, 134.0, 135.0 (quaternary phenyl C), 164.4, 164.6, 164.7, 164.8, 164.9, 165.0, 165.1, 165.2, 165.3, 165.7, 166.0, 166.2, 166.3, 166.6, 167.1, 167.2, 167.8, 167.9, 168.0, 168.4, 168.6, 169.7, 172.1, 172.6, 172.6, 172.9 (C=O); IR (KBr): $\tilde{\nu} = 3392, 3069, 2956, 1737, 1673, 1602, 1525, 1453, 1247, 1178, 1094, 1070, 1025, 714$ cm⁻¹; MS (FAB): *m/z* (%): 2992 (1) [M+Cs]⁺, 2860 (46) [M+H]⁺, 2435 (9), 1678 (28), 729 (100); C₁₃₃H₁₃₈N₁₄O₅₈ · 4 MeOH (2988.775): calcd C 55.06, H 5.19, N 6.56; found: C 54.72, H 5.06, N 6.37.

Third-generation dendron 22c: DCC (0.167 g, 8 mmol) and DMAP (0.03 g, 0.25 mmol) were added all at once to a solution of **21b** (1.018 g, 0.8 mmol) and **19a** (0.132 g, 0.3 mmol) in dioxane (20 mL). After 15 minutes a white precipitate of DCU was formed. After stirring for five hours at room temperature the precipitate was filtered, the solvent was removed in vacuo, and the crude product was prepurified by FC (CHCl₃/MeOH = 30:1). A second purification was carried out by means of HPLC (Nucleosil, 17 mL min⁻¹, retention time 7.37 min, CHCl₃/MeOH = 97:3). Yield 0.13 g (13%) white solid; $[\alpha]_D^{20} = +68.53$ ($c = 0.715$, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 25 °C): $\delta = 1.14-1.30$ (m, 21 H; CH₃), 3.38, 3.64, 3.68, 3.69, 3.691 (5 s, 21 H; OCH₃), 3.75–4.67 (m, 21 H; CH₂ glycine, CH alanine), 5.61–5.68 (m, 6 H; CH tartaric acid), 5.90 (d, ³*J* = 2.5 Hz, 1 H; CH tartaric acid), 5.91 (d, ³*J* = 2.5 Hz, 1 H; CH tartaric acid), 5.94 (d, ³*J* = 2.5 Hz, 1 H; CH tartaric acid), 5.99 (d, ³*J* = 2.0 Hz, 1 H; CH tartaric acid), 6.01 (m, 2 H; CH tartaric acid), 6.03 (d, ³*J* = 2.0 Hz, 1 H; CH tartaric acid), 6.13 (s, 1 H; CH tartaric acid), 7.25–7.70 (m, 43 H; phenyl rings, NH), 8.02 (m, 16 H; *o*-H of the Bz group); ¹³C NMR (125.65 MHz, CDCl₃, 25 °C): $\delta = 17.0, 17.5, 18.5, 18.6, 18.7, 18.8$ (CH₃), 40.8, 40.9, 41.1, 41.3, 41.9 (CH₂ glycine), 48.2, 48.3, 48.3, 48.5, 48.6, 48.8 (CH alanine), 52.9, 52.9 (OCH₃), 67.1 (CH₂ Bn), 71.1, 71.1, 71.3, 71.5, 71.8, 71.9, 72.0, 72.2, 72.6, 72.7, 72.7 (CH tartaric acid), 128.1, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 128.7, 129.8 (phenyl C),

133.7, 133.9, 134.0, 135.0 (quaternary phenyl C), 164.6, 164.7, 164.9, 165.10, 165.1, 165.6, 165.7, 165.8, 166.2, 166.3, 166.5, 166.6, 167.1, 167.1, 167.2, 167.7, 167.8, 167.9, 168.1, 169.6, 172.3, 172.4, 172.6, 172.9, 173.3 (C=O); IR (KBr): $\tilde{\nu} = 3406, 2956, 1736, 1671, 1602, 1524, 1453, 1247, 1178, 1094, 1069, 1025, 714$ cm⁻¹; MS (FAB): *m/z* (%): 2992 (3) [M+Cs]⁺, 2882 (16) [M+Na]⁺, 2860 (100) [M+H]⁺, 2435 (14), 1678 (38), 729 (100); C₁₃₃H₁₃₈N₁₄O₅₈ · 4 MeOH (2988.775): calcd C 55.06, H 5.19, N 6.56; found: C 54.68, H 5.01, N 6.45.

(7S)-7-[(Benzyloxy)carbonyl]-2,5-dioxo-9-methyl-3,6-diazadecaneammoniumhydro bromide (23): *N*-Benzyloxycarbonyl-glycyl-glycyl-L-leucinbenzylester was deprotected as described.^[20] Yield (66%), yellow powder; ¹H NMR (400 MHz, CDCl₃, 32 °C, TMS): $\delta = 0.81-0.85$ (m, 6 H; CH₃), 1.52–1.84 (m, 3 H; CH₂, CH), 4.11–4.32 (m, 4 H; CH₂ glycine), 4.43–4.56 (m, 1 H; CH leucine), 4.98–5.21 (m, 2 H; CH₂ Bn), 7.28–7.41 (m, 5 H; phenyl rings), 7.72 (br, 3 H; NH₃⁺), 8.26 (br, 1 H; NH); ¹³C NMR (100.6 MHz, CDCl₃, 32 °C, TMS): $\delta = 21.6, 22.7$ (CH₃), 24.7 (CH), 39.8 (CH₂), 39.9, 42.8 (CH₂ glycine), 51.7 (CH leucine), 67.3 (CH₂ Bn), 128.4, 128.5, 128.8, 129.0 (phenyl C), 135.3 (quaternary phenyl C), 167.3, 170.6, 172.8 (C=O); MS (FAB): *m/z* (%): 671 (15) [M₂+H – HBr – Br]⁺, 336 (100) [M+H – Br]⁺.

13-Benzyl-3-methyl (3R,4R,13S)-4-(benzyloxy)-15-methyl-1,5,8,11-tetraoxo-1-phenyl-2-oxa-6,9,12-triazaheptadecane-3,13-dicarboxylate (24): Compound **24** was synthesized according to general procedure I with **23** (6.7 g, 10 mmol) and **8a** (3.72 g). FC with CHCl₃/MeOH = 40:1 (*R*_f = 0.36). Yield 3.0 g (44%) white powder; ¹H NMR (400 MHz, CDCl₃, 22.3 °C, TMS): $\delta = 0.83-0.85$ (m, 6 H; CH₃), 1.49–1.60 (m, 3 H; CH₂, CH leucine), 3.70 (s, 3 H; OCH₃), 3.78 (dd, ²*J* = 16.6 Hz, ³*J* = 5.4 Hz, 1 H; CHH glycine), 3.85 (dd, ²*J* = 16.7 Hz, ³*J* = 5.4 Hz, 1 H; CHH glycine), 3.94 (d, ³*J* = 5.1 Hz, 2 H; CH₂ glycine), 4.53–4.56 (m, 1 H; CH leucine), 5.08 (d, ²*J* = 12.2 Hz, 1 H; CHH Bn), 5.13 (d, ²*J* = 12.5 Hz, 1 H; CHH Bn), 5.98 (d, ³*J* = 2.9 Hz, 1 H; CH tartaric acid), 6.06 (d, ³*J* = 2.9 Hz, 1 H; CH tartaric acid), 6.86 (d, ³*J* = 8.1 Hz, 1 H; NH), 7.17 (t, ³*J* = 5.3 Hz, 1 H; NH), 7.26–7.59 (m, 12 H; phenyl rings, NH), 8.03–8.09 (m, 4 H; *o*-H of the Bz group); ¹³C NMR (100.6 MHz, CDCl₃, 23.8 °C, TMS): $\delta = 21.8, 22.7$ (CH₃), 24.8 (CH), 41.0 (CH₂), 42.8, 43.0 (CH₂ glycine), 51.0 (CH leucine unit), 53.0 (OCH₃), 67.1 (CH₂ Bn group), 71.8, 72.7 (CH tartaric acid), 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 130.0, 130.1, 130.3 (phenyl C), 133.7, 134.1, 135.3 (quaternary phenyl C), 165.2, 165.3, 166.7, 167.2, 168.5, 168.6, 172.7 (C=O); MS (FAB): *m/z* (%): 1379 (4) [M₂+H]⁺, 822 (10) [M+Cs]⁺, 690 (100) [M+H]⁺; C₃₆H₃₉N₃O₁₁ (689.72): calcd C 62.69, H 5.70, N 6.09; found: C 62.21, H 5.86, N 6.19.

(4R,5R,14S)-4,5-Bis(benzyloxy)-14-isobutyl-3,6,9,12-tetraoxo-2-oxa-7,10,13-triazapentadecan-15-oic acid (25): Compound **25** was synthesized according to general procedure III. Yield 100% white solid; ¹H NMR (400 MHz, [D₆]acetone, 22.4 °C): $\delta = 0.87-0.92$ (m, 6 H; CH₃), 1.59–1.75 (m, 3 H; CH₂, CH), 3.72 (s, 3 H; OCH₃), 3.76–3.98 (m, 4 H; CH₂ glycine), 4.43–4.48 (m, 1 H; CH leucine), 5.95 (d, ³*J* = 2.4 Hz, 1 H; CH tartaric acid), 6.12 (d, ³*J* = 2.7 Hz, 1 H; CH tartaric acid), 7.40 (d, ³*J* = 8.1 Hz, 1 H; NH), 7.52–7.72 (m, 7 H; phenyl rings, NH), 8.09–8.15 (m, 4 H; *o*-H of the Bz group, NH), 8.37 (br, 1 H; NH); ¹³C NMR (100.6 MHz, [D₆]acetone, 24.1 °C): $\delta = 21.8, 23.2$ (CH₃), 26.1 (CH), 41.4 (CH₂), 43.0, 43.6 (CH₂ glycine), 51.3 (CH leucine), 53.1 (OCH₃), 72.9, 73.5 (CH tartaric acid), 129.4, 129.5, 129.6, 129.7, 129.9, 130.6, 130.7, 130.8 (phenyl C), 134.6, 134.7 (quaternary phenyl C), 165.7, 165.9, 167.2, 167.9, 169.3, 169.6, 174.1 (C=O); MS (FAB): *m/z* (%): 638 (1) [M+K]⁺, 622 (14) [M+Na]⁺, 600 (100) [M+H]⁺; C₂₉H₃₃N₃O₁₁ (599.59): calcd C 58.09, H 5.55, N 7.01; found: C 57.83, H 5.80, N 6.53.

(4R,5R,14S)-4,5-(phenylmethylenedioxy)-14-isobutyl-3,6,9,12-tetraoxo-2-oxa-7,10,13-triazapentadecan-15-oic acid (26): Compound **26** was synthesized according to general procedure I with **23** (10.41 g, 25 mmol) and **16a** (6.31 g, 25 mmol). FC with CHCl₃/EtOAc = 1:8 (*R*_f = 0.22). Yield 6.5 g (46%) white solid; mixture of two diastereomers; ¹H NMR (400 MHz, [D₆]acetone, 22.6 °C): $\delta = 0.87-0.91$ (m, 12 H; CH₃), 1.59–1.71 (m, 6 H; CH₂, CH leucine), 3.76 (s, 3 H; OCH₃), 3.80 (s, 3 H; OCH₃), 3.88–4.03 (m, 8 H; CH₂ glycine), 4.54–4.57 (m, 2 H; CH leucine), 4.84 (d, ³*J* = 3.9 Hz, 1 H; CH tartaric acid), 4.96 (d, ³*J* = 3.9 Hz, CH tartaric acid), 4.97 (d, ³*J* = 3.4 Hz, 1 H; CH tartaric acid), 4.99 (d, ³*J* = 3.4 Hz, 1 H; CH tartaric acid), 5.15 (s, 4 H; CH₂ Bn), 6.10 (s, 1 H; CH acetal), 6.12 (s, 1 H; CH acetal), 7.30–7.45 (m, 16 H; phenyl rings), 7.54 (br, 2 H; NH), 7.60–7.64 (m, 5 H; phenyl rings, NH), 7.81 (br, 1 H; NH), 8.23 (br, 1 H; NH); ¹³C NMR (100.6 MHz, [D₆]acetone, 24.4 °C): $\delta = 21.8, 23.1$ (CH₃), 25.3 (CH), 41.2

(CH₂), 42.9, 43.0, 43.4, 43.5 (CH₂ glycine), 51.5, 51.6 (CH leucine), 52.7, 52.8 (OCH₃), 67.0 (CH₂ Bn), 77.8, 78.5, 79.0, 79.5 (CH tartaric acid), 106.6, 106.9 (CH acetal), 128.2, 128.3, 128.6, 128.7, 128.8, 129.0, 129.3, 130.6, 130.8 (phenyl C), 136.6, 137.0, 137.1 (quaternary phenyl C), 169.4, 169.5, 169.6, 169.7, 170.2, 170.3, 170.6, 170.8, 171.2, 173.0 (C=O); MS (FAB): *m/z* (%): 1140 (12) [M₂+H]⁺, 570 (100) [M+H]⁺; C₂₉H₃₅N₃O₉·0.5H₂O (578.92): calcd C 60.20, H 6.27, N 7.26; found: C 60.24, H 6.18, N 7.32.

15-Methyl-(4S,13R,14R)-13,14-dihydroxy-4-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-5,8,11-triazapentadecane-15-carboxylate (27): Compound **27** was synthesized according to general procedure IV. Yield white solid, (45 %); ¹H NMR (400 MHz, [D₆]DMSO, 23.4 °C): δ = 0.81 (d, ³J = 6.4 Hz, 3H; CH₃), 0.87 (d, ³J = 6.4 Hz, 3H; CH₃), 1.46–1.56 (m, 3H; CH₂, CH leucine), 3.76 (d, ³J = 5.4 Hz, 2H; CH₂ glycine), 4.07 (d, ³J = 5.1 Hz, 1H; CH glycine), 4.10 (d, ³J = 5.1 Hz, 1H; CHH glycine), 4.30–4.38 (m, 3H; CH leucine, tartaric acid), 5.11 (s, 2H; CH₂ Bn), 7.30–7.39 (m, 5H; phenyl rings), 8.28 (d, ³J = 7.8 Hz, 1H; NH), 8.43 (t, ³J = 5.6 Hz, 1H; NH); ¹³C NMR (100.6 MHz, [D₆]DMSO, 24.8 °C): δ = 21.3, 22.7 (CH₃), 24.1 (CH), 40.1, 41.6 (CH₂ glycine), 48.6 (OCH₃), 50.4 (CH leucine), 65.9 (CH₂ Bn), 74.4 (CH tartaric acid), 127.8, 128.0, 128.4 (phenyl C), 135.9 (quaternary phenyl C), 165.7, 168.6, 169.5, 172.2, 174.2 (C=O); MS (FAB): *m/z* (%): 963 (4) [M₂+H]⁺, 614 (8) [M+Cs]⁺, 504 (9) [M+Na]⁺, 482 (100) [M+H]⁺; C₂₂H₃₁N₃O₉ (481.50): calcd C 54.88, H 6.49, N 8.73; found: C 55.23, H 6.64, N 8.71.

3,16,30-Trimethyl-(3R,4R,13S,16R,17R,20S,29R,30R)-4,29-bis(benzoyloxy)-13,20-diisobutyl-17-[(9S)-9-isobutyl-4,7,10-trioxo-12-phenyl-11-oxa-2,5,8-triazadodec-1-onyl]-1,5,8,11,14,19,22,25,28,32-decaoxo-1,32-diphenyl-2,15,18,31-tetraoxa-6,9,12,21,24,27-hexaazadotriacontane-3,16,30-tricarboxylate (28): DCC (0.65 g, 3.15 mmol) and DMAP (0.018 g, 0.15 mmol) were added to a solution of **27** (0.72 g, 1.5 mmol) and the acid **25** (1.89 g, 3.15 mmol) in dry THF (75 mL). After stirring overnight the precipitate was filtered, the solvent was removed, and the residue was dissolved in CH₂Cl₂. This solution was washed with HCl (1N) and dried over MgSO₄. After removal of the solvent the crude product was purified by FC (CHCl₃/MeOH = 30:1) and afterwards by means of HPLC (CHCl₃/MeOH = 96:4, flow = 20 mL min⁻¹, retention time = 6.7 min). Yield 0.23 g (9.4 %) white solid; ¹H NMR (400 MHz, [D₆]acetone, 22.7 °C): δ = 0.83–0.91 (m, 18H; CH₃), 1.56–1.69 (m, 9H; CH₂, CH leucine), 3.71 (s, 3H; OCH₃), 3.72 (s, 3H; OCH₃), 3.73 (s, 3H; OCH₃), 3.84–4.06 (m, 12H; CH₂ glycine), 5.11 (d, ³J = 12.5 Hz, 1H; CHH Bn), 5.15 (d, ³J = 11.0 Hz, 1H; CHH Bn), 5.64 (d, ³J = 2.0 Hz, 1H; CH tartaric acid), 5.72 (d, ³J = 2.2 Hz, CH tartaric acid), 5.96 (d, ³J = 2.4 Hz, 1H; CH tartaric acid), 5.97 (d, ³J = 2.7 Hz, 1H; CH tartaric acid), 6.11 (s, 1H; CH tartaric acid), 6.12 (s, 1H; CH tartaric acid), 7.23 (d, ³J = 7.3 Hz, 1H; NH), 7.30–7.74 (m, 23H; phenyl rings and 5 NH), 7.84 (d, ³J = 6.3 Hz, 1H; NH), 8.01 (t, ³J = 3.7 Hz, 1H; NH), 8.03–8.14 (m, 8H; *o*-H of the Bz group), 8.39 (t, ³J = 5.6 Hz, 1H; NH), 8.48 (t, ³J = 5.5 Hz, 1H; NH); ¹³C NMR (100.6 MHz, [D₆]acetone, 24.4 °C): δ = 21.4, 21.9, 22.0, 22.4, 22.7, 23.0 (CH₃), 23.1, 25.1, 25.3 (CH), 40.2, 41.0, 41.3 (CH₂), 42.9, 43.0, 43.2, 43.6, 43.7, 43.9 (CH₂ glycine), 51.6, 51.7, 52.3 (CH leucine), 53.1, 53.2, 53.3 (OCH₃), 67.1 (CH₂ Bn), 72.1, 72.8, 72.9, 73.4, 73.5, 73.6 (CH tartaric acid), 128.8, 129.0, 129.3, 129.6, 129.7, 129.8, 129.9, 130.7, 130.8 (phenyl C), 134.5, 134.6, 134.7, 134.8, 137.1 (quaternary phenyl C), 157.6, 165.7, 165.9, 166.8, 166.9, 167.2, 167.3, 167.4, 167.7, 167.9, 169.7, 169.8, 169.9, 171.1, 171.3, 172.2, 173.0 (C=O); MS (FAB): *m/z* (%): 1645 (100) [M+H]⁺, 1290 (4), 1233 (30), 1176 (40), 1063 (12), 582 (10), 469 (82), 412 (68), 355 (42); C₈₀H₉₃N₉O₂₉·H₂O (1662.68) calcd C 57.79, H 5.76, N 7.58; found: C 57.86, H 5.82, N 7.44.

Acknowledgments

This research project was supported by the Deutsche Forschungsgemeinschaft. We thank Dr. R. Waibel from the Institut für Pharmazie der Universität Erlangen-Nürnberg for measuring the optical rotations.

[1] E. Buhleier, W. Wehner, F. Vögtle, *Synthesis* **1978**, 155.

[2] For example: a) D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, 119, 119; *Angew. Chem. Int. Ed. Engl.* **1990**, 29,

- 119; b) N. Ardoin, D. Astruc, *Bull. Soc. Chim. Fr.* **1995**, 132, 875; c) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules*, 1st ed., VCH, Weinheim, **1996**; d) N. Feuerbacher, F. Vögtle, *Top. Curr. Chem.* **1998**, 197, 8; e) D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, 8, 1353; f) V. V. Narayanan, G. R. Newkome, *Top. Curr. Chem.* **1998**, 197, 19; g) J. P. Majoral, A.-M. Caminade, *Top. Curr. Chem.* **1998**, 197, 79; h) A.-D. Schlüter, *Top. Curr. Chem.* **1998**, 197, 165; i) M. Venturi, S. Serroni, A. Juris, S. Campagna, V. Balzani, *Top. Curr. Chem.* **1998**, 197, 193; j) M. Fischer, F. Vögtle, *Angew. Chem.* **1999**, 111, 934; *Angew. Chem. Int. Ed.* **1999**, 38, 884.
- [3] a) H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1997**, 3, 1563; b) D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz, H. Sellner, *Top. Curr. Chem.* **1998**, 197, 125.
- [4] a) J. A. Kremers, E. W. Meijer, *J. Org. Chem.* **1994**, 59, 4262; b) J. A. Kremers, E. W. Meijer, *React. Funct. Polym.* **1995**, 26, 137.
- [5] a) D. Seebach, J.-M. Lappiere, K. Skobridis, G. Greiveldinger, *Angew. Chem.* **1994**, 106, 457; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 440; b) D. Seebach, J.-M. Lappiere, G. Greiveldinger, K. Skobridis, *Helv. Chim. Acta* **1994**, 77, 1673.
- [6] a) J. R. Mc Elhanon, M.-J. Wu, M. Escobar, D. V. McGrath, *Macromolecules* **1996**, 29, 8879; b) J. R. Mc Elhanon, D. V. McGrath, *J. Am. Chem. Soc.* **1998**, 1647.
- [7] a) H.-F. Chow, C. C. Mak, *Tetrahedron Lett.* **1996**, 37, 5935; b) C. C. Mak, H.-F. Chow, *Chem. Commun.* **1996**, 1185; c) H.-F. Chow, C. C. Mak, *J. Chem. Soc. Perkin Trans. 1* **1997**, 91; d) H.-F. Chow, C. C. Mak, *Pure Appl. Chem.* **1997**, 69, 483.
- [8] H.-T. Chang, C.-T. Chen, T. Kondo, G. Siuzdak, K. B. Sharpless, *Angew. Chem.* **1996**, 108, 202; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 182.
- [9] a) P. R. Ashton, S. E. Boyd, C. L. Brown, S. A. Nepogodiev, E. W. Meijer, H. W. I. Peerlings, J. F. Stoddart, *Chem. Eur. J.* **1997**, 3, 975; b) N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1997**, 3, 1193.
- [10] G. R. Newkome, X. Lin, C. D. Weis, *Tetrahedron: Asymmetry* **1991**, 2, 957.
- [11] a) J. F. G. A. Jansen, H. W. I. Peerlings, E. M. M. de Brabander-van den Berg, E. W. Meijer, *Angew. Chem.* **1995**, 107, 1321; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1206; b) J. F. G. A. Jansen, H. W. I. Peerlings, E. M. M. de Brabander-van den Berg, E. W. Meijer, *Science* **1994**, 266, 1226.
- [12] T. K. Lindhorst, C. Kieburg, *Angew. Chem.* **1996**, 108, 2083; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1953; T. K. Lindhorst, *Nachr. Chem. Tech. Lab.* **1996**, 44, 1073.
- [13] a) D. Seebach, G. F. Herrmann, U. D. Lengweiler, W. Amreis, *Helv. Chim. Acta* **1997**, 80, 989; b) P. K. Murer, J.-M. Lappiere, G. Greiveldinger, D. Seebach, *Helv. Chim. Acta* **1997**, 80, 1648.
- [14] a) R. G. Denkwalter, J. F. Kolc, W. J. Lukasavage, U. S. Pat. 4,410,688, **1979**; b) R. G. Denkwalter, J. F. Kolc, W. J. Lukasavage, U. S. 4,360,646 **1982**; *Chem. Abs.* **1984**, 100, 103907p; c) R. G. Denkwalter, J. F. Kolc, W. J. Lukasavage, U. S. 4,289,872 **1981**; *Chem. Abs.* **1985**, 102, 79324q.
- [15] M. Schemjak, *Angew. Chem.*, **1960**, 10, 342.
- [16] L. Stryer, *Biochemistry*, 3rd ed., W. H. Freeman, New York, **1988**, 965.
- [17] J. Gawroński, K. Gawrońska, U. Rychlewska, B. Warżajtis, J. Rychlewski, M. Hoffmann, A. Szasecka, *Tetrahedron* **1997**, 53, 6113.
- [18] B. Neises, W. Steglich, *Angew. Chem.* **1978**, 90, 556; *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 522.
- [19] K. Ogata, S. Ishii, *Chem. Pharm. Bull.* **1967**, 15, 707.
- [20] M. Bodanszky, A. Bodanszky, *The Practice of Peptide Synthesis*, 2nd ed., Springer, Berlin, **1994**, 138.
- [21] T. K. M. Shing, E. K. W. Tam, V. W.-F. Tai, I. H. F. Chung, Q. Jiang, *Chem. Eur. J.*, **1996**, 2, 48.
- [22] W. R. Roush, L. Banfi, *J. Am. Chem. Soc.* **1988**, 110, 3979.
- [23] P. C. Crofts, J. H. H. Markes, H. N. Rydon, *J. Chem. Soc.* **1959**, 3610.

Received: April 14, 1999 [F1724]