Hydroxy-Functionalized Dendritic Building Blocks

Andrea Ingerl, Ingo Neubert, Rainer Klopsch, and A. Dieter Schlüter*

Institut für Organische Chemie, Freie Universität Berlin,
Takustraße 3, D-14195 Berlin, Germany
Fax: (internat.) + 49(0)30/838-3357
E-mail: adschlue@chemie.fu-berlin.de

A convenient and practical multi-gram procedure for the synthesis of second- (G2; **4a**, **5a**, **5d**) and third-generation (G3; **6a**) dendrons with orthogonally protected functional groups in the periphery (hydroxy) and at the focal point (carboxylic acid) is described. It uses the amply available first-generation dendrons with amine and carboxylic ester functions (**1**) and tetrahydropyranyl-protected hydroxy and carboxylic acid functions (**2b**, **3**), respectively, which are connected via amides by peptide methods. Purification is either done by recrystallization or simple filtration through silica gel and yields the products as analytically pure materials on a several-gram scale (even for G3). The dendrons' protective groups are proven to be orthogonal (500-MHz NMR) which makes them useful components (building blocks) of a future dendron construction kit for a versatile synthesis of, for example, dendronized polymers.

Introduction

The goal of a current, long-term project are macromolecules structurally characterized by a polymeric backbone which dendritic fragments (dendrons) are attached to via anchor groups[1]. Some of these macromolecules may be considered as molecular objects with a cylindrical shape[2][3]. In order to be able to engineer the properties of this intriguing class of macromolecules[4] it would be important (a) to be able to modify their interior structure[5] and (b) to have access to surface-functionalized representatives[6]. For this aim it is important to make available in a synthetically facile way a variety of dendritic building blocks, which differ not only in flexibility and polarity of their main structure, but also in their functional-group pattern at both focal point and periphery. As a continuation of previously reported hydroxy-[7] and amine-functionalized dendron building blocks[8][9], we describe here the synthesis of two orthogonally protected G2[10] dendrons and one G3 dendron with hydroxy functional groups at the periphery[11]. One of the G2 dendrons is prepared with and without a spacer unit at the focal point. The dendrons are constructed so that not all consecutive repeat units are identical which opens access to layered dendrimers.

Results and Discussion

The syntheses described here are based on dendrons **1**, **2**, and **3** which have either unprotected amino (**1**) or tetrahydropyranyl-(THP-)protected hydroxy functions (**2**, **3**) in the periphery and ester (**1**, **2a**) or carboxylic acid functions (**2b**, **3**) at the focal point. Dendrons **1**[9] and **3**[7] are available on a 100-g scale. THP-protected dendron **2a** was obtained from methyl 3,5-dihydroxybenzoate and THP-protected 3-chloropropanol[12] (Scheme 1). In order to achieve high yields of desired double alkylated product, the reaction was performed in refluxing diethyl ketone and also gave **2a** on a 100-g scale in 80% yield after simple filtration through silica gel. Saponification of the ester function of **2a** proceeded very cleanly and gave the corresponding carboxylic acid **2b** in 90% yield.

Scheme 1. G1 building blocks and synthesis of **2**

Reagents and conditions: a) diethyl ketone, K$_2$CO$_3$, nBu$_4$NI, 18-C-6, reflux, 80 h (80%); b) methanol, KOH, reflux, 20 h, (90%).

Scheme 2. Synthesis and deprotection of G2 dendron **4a**

$$2 \times \textbf{2b} + \textbf{1} \xrightarrow{a} \textbf{4a}$$

4a: X = CH$_3$, Y = THP
4b: X = H, Y = THP
4c: X = CH$_3$, Y = H
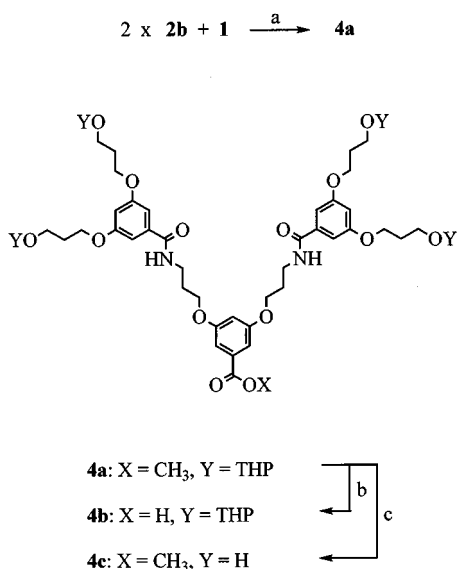
Reagents and conditions: a) 1. THF, CDI, 40°C, 24 h, 2. CH$_2$Cl$_2$, **1**, DBU, r. t., 24h, (50%); b) methanol, KOH, reflux, 20 h, (70%); c) 1. THF, HCl/methanol, r. t., 4 h, 2. THF, HCl/methanol, r. t., 10 h, (70%).

Scheme 3. Synthesis and deprotection of G2 dendrons **5a/5d**

$$2 \times \textbf{3} + \textbf{1} \xrightarrow{a}$$

5a: X = CH$_3$, Y = THP
5b: X = H, Y = THP
5c: X = CH$_3$, Y = H
5d: X = NHCH$_2$-p-C$_6$H$_4$-CO$_2$CH$_3$, Y = THP
5e: X = NHCH$_2$-p-C$_6$H$_4$-CO$_2$H, Y = THP
5f: X = NHCH$_2$-p-C$_6$H$_4$-CO$_2$CH$_3$, Y = H

5f

Reagents and conditions: a) 1. CH$_2$Cl$_2$, HOBT, **1**, DBU, r. t., 30 min, 2. EDC, r. t., 14 h, (89%); b) methanol/water, KOH, reflux, 3 h, (95%); c) 2 × (THF, HCl/methanol, r. t., 12 h) (80%); d) 1. CH$_2$Cl$_2$, HOBT, methyl 4-(aminomethyl)benzoate·HCl, DBU, r. t., 30 min, 2. EDC, r. t., 14 h (89%); e) methanol/water, KOH, reflux, 5 h (75%); f) 2 × (THF, HCl/methanol, r. t., 12 h) (95%).

Hydroxy-functionalized, THP-protected G2 dendrons **4a** and **5a** were prepared by combining hydroxy-G1-carboxylic acids **2b** and **3**, respectively, with diamine **1** (Scheme 2). The acids were used in a slight excess (1.1 equiv. per amine function)[13] and activated prior to use with carbonyl diimidazole (CDI)[14] or ethyl[(dimethylamino)propyl]carbodiimide/hydroxybenzotriazole (EDC/HOBT)[15] (see below). Diamine **1**, which is obtained as a dihydrochloride was deprotonated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane. By employing DBU instead of the normally applied tertiary amines like triethylamine or di(isopropyl)ethylamine use of DMF as a cosolvent is avoided, which otherwise can not be completely removed from these highly polar compounds. G2 dendrons **4a** and **5a** were obtained in optimized yields of 50% and 79%, if activation of the acids was carried out by CDI. If EDC/HOBT was used instead, the yield of **4a** could not be improved beyond 50%, whereas the yield of **5a** reproducibly reached 89%. All byproducts of the EDC/HOBT procedure are water soluble and were therefore easily removed from the reaction mixture. This fact is important in view of our goal to make the dendrons easily available on a multigram scale.

Both G2-carboxylic esters **4a** and **5a** were selectively deprotected to the corresponding acids **4b** and **5b** by saponification with potassium hydroxide in methanol or methanol/water. While the former is a viscous oil, the latter is a solid. Dendron **4b** was obtained in a 70% yield (losses during work-up), **5b** crystallized from methanol/chloroform (95% yield).

In the context of the outlined project it was important to synthesize (a) the second-generation dendron **5d**, which differs from **5a** by a spacer unit and (b) the third-generation dendron **6a**. As spacer for **5d**, methyl 4-(aminomethyl)ben-

zoate was selected. Its attachment to **5b** was conveniently done by the EDC method and gave **5d** on a 20-g scale in 89% yield despite the fact that a chromatographic separation (filtration; silica gel) had to be carried out. G1-diamine **1** and THP-protected G2-carboxylic acid **4b** were used for the construction of G3 dendron **6a** (Scheme 3), whereby **1** served as the inner part. CDI coupling gave **6a** in 80% yield. **6a** contains six amide bonds instead of two as in **4b** which rendered its purification more difficult. From the many solvent combinations tried for the chromatographic separation (filtration), only an ethyl acetate/10% acetone mixture gave fully satisfactory results with regard to isolated quantity over time and effort required.
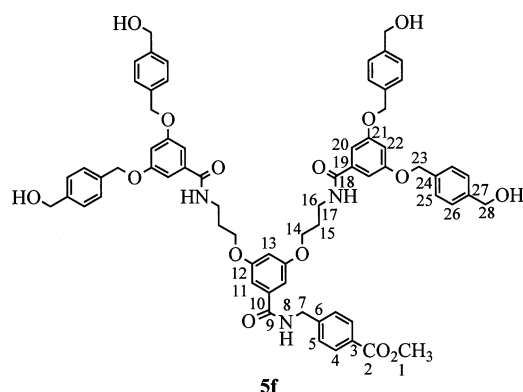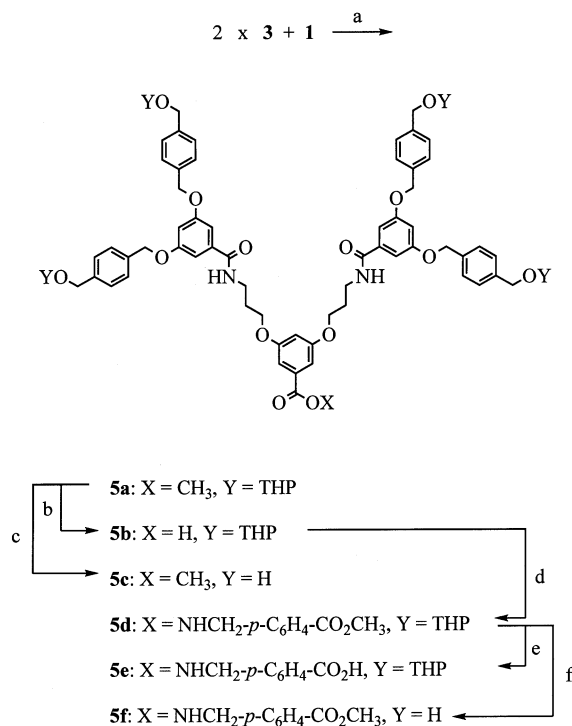
Scheme 4. Synthesis and deprotection of G3 dendron **6a**

$$2 \times 4b + 1 \xrightarrow{a} 6a$$

6a: X = CH₃, Y = THP

6b: X = H, Y = THP

6c: X = CH₃, Y = H
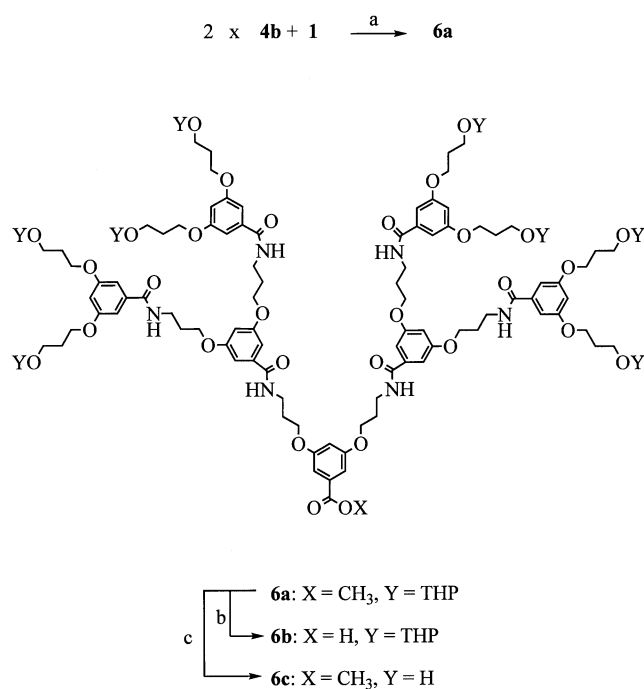
Reagents and conditions: a) 1. THF, CDI, 40 °C, 24 h, 2. CH₂Cl₂, **3**, DBU, r. t., 24 h (80%); b) methanol, KOH, reflux, 20 h (75%); c) 1. THF, HCl/methanol, r. t., 4 h, 2. THF, HCl/methanol, r. t., 10 h (70%).

The orthogonality of the protective-group pattern (THP/ester) is of importance for the dendrons' suitability as building blocks. Therefore the selective deprotection was examined in all the cases but specifically carefully in the most challenging one, the G3 dendron **6a**. Saponification of the ester function of **6a** was done with potassium hydroxide (3.5 equivalents, methanol, reflux) and gave **6b** virtually quantitatively. THP deprotection was achieved by treating **6a** twice with hydrochloric acid in methanol (2% v/v). After the second run, the hydroxy-dendron **6c** was obtained with a degree of deprotection exceeding 99%. The 500-MHz NMR spectra of **6a**, **6b**, and **6c** (Figure 1) illustrate the very high conversions achieved. Not only has the signal for the methyl ester in the spectrum of **6b** (Figure 1b) disappeared but the THP signals of **6a** in the spectrum of **6c** have also completely vanished (Figure 1c). It should also be noted at this point that the NMR spectra were taken from representative batches of material and do not give any indication of skeleton decomposition under deprotection conditions. Deprotection experiments with G2 dendrons **4a**, **5a**, and **5d** went completely analogously.

The structures of all dendrons were proved by ¹H- and ¹³C-NMR spectroscopy, mass spectrometry (FAB, Maldi-Tof), and elemental analysis. Correct data could not be obtained in all cases because of the dendrons' high polarity which rendered removal of last traces of solvent (NMR) even in high vacuum at elevated temperature difficult. In the case of **5f** the structure was further supported by NMR hetcorr experiments by which each and every signal could be assigned. The fact that the layered structure of **5f** gives

Figure 1. ¹H-NMR spectra of the orthogonally protected G3 dendron **6a** (a), at the focal point selectively deprotected carboxylic acid **6b** (b), and peripherially deprotected hydroxy dendron **6c** (c); all spectra (500 MHz) at room temperature, (a), (b) in CDCl₃, (c) in [D₄]methanol; signals for methyl ester (+) and solvents (*) are marked
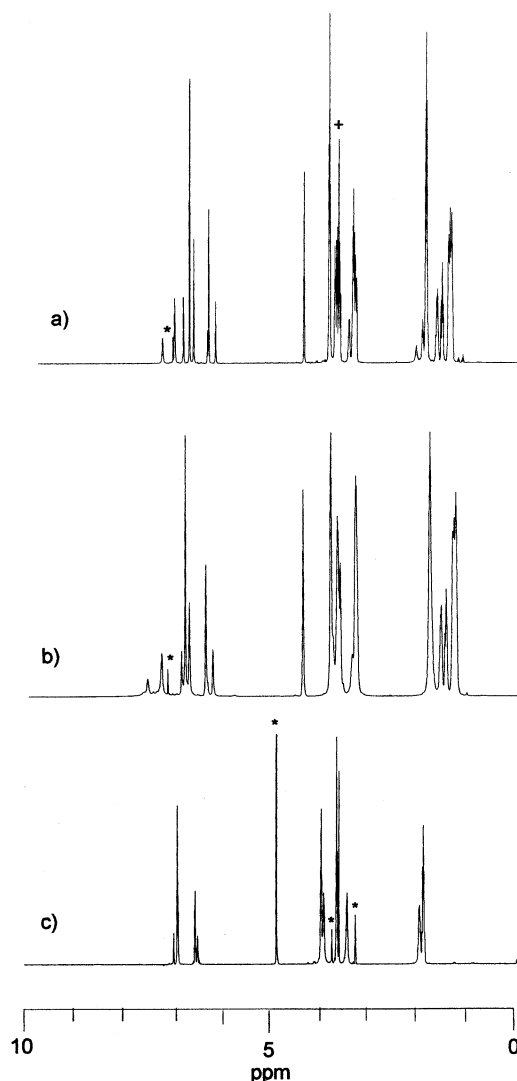
rise to individually identifiable sets of signals for each generation should open the possibility to also identify the structures of higher generation dendrons of the same type.

The reactions described in this paper were done on a several-gram scale. The fully protected second- and third-generation dendrons **4a**, **5a**, **5d**, **6a** which serve as starting material for further growth reactions were synthesized in batches of at least 20 g, which illustrates the feasibility of the chemistry developed. Compounds **4c**, **5c**, **5f**, and **6c** were prepared on a 0.5–2.0-g scale only to demonstrate the orthogonality of the protective groups pattern. A scale-up was not done because these dendrons cannot be involved in growth's schemes using amide bonds.

leg _Synthetische, mechanistische und reaktionstechnische Aspekte von Metallkatalysatoren_ for a postdoctoral stipend.

Experimental Section

All chemicals were purchased from Aldrich or Acros chimica and used without further purification. G1 dendrons were prepared according to literature procedures: **1**[9] and **3**[7]. Solvents: Dry THF was distilled from sodium using benzophenone as indicator for dryness. Dichloromethane was stored over sodium hydride and filtered before use. Analytical Equipment: a) NMR: AMX 500; b) MS: Varian MAT 112S, Varian MAT 711; EA: EA 240 Perkin Elmer. Because of the polarity of the compounds prepared it was difficult to obtain correct data from elemental analysis. For assignment of ^{1}H- and ^{13}C-NMR shifts of compounds **5a**−**5f** see numbering system shown in Scheme 3.

Methyl 3,5-Bis[3-(2-tetrahydropyranyloxy)propyloxy]benzoate (**2a**): A solution of 43.7 g (0.26 mol) of methyl 3,5-dihydoxybenzoate, 97.5 g (0.55 mol) of 3-(2-tetrahydropyranyloxy)propyl chloride[11], 108.4 g (0.78 mol) of potassium carbonate, 5 g of tetrabutyl ammonium iodide, and 5 g of 18-crown-6 in 1 l of diethyl ketone was refluxed for 80 h. After removal of the solvent, the oily residue was dissolved in 300 ml of ethyl acetate, washed with water (3 × 200 ml) and dried with magnesium sulfate. Chromatographic separation [silica gel, hexane/ethyl acetate (2:1, v/v)] furnished 94 g (80%) of **2a** as a viscous oil. − ^{1}H NMR (CDCl$_3$): δ = 1.5−1.9 (m, 12 H, THP-CH$_2$), 2.0 (q, 4 H, CH$_2$), 3.4−3.6 (m, 4 H, OCH$_2$), 3.7−3.9 (m, 7 H, CH$_3$, OCH$_2$), 4.1 (t, 4 H, ArOCH_2), 4.6 (t, 2 H, THP-CH), 6.6 (t, 1 H, ArH), 7.2 (d, 2 H, ArH). − ^{13}C NMR (CDCl$_3$): δ = 19.5, 25.4 (THP-CH$_2$), 29.5 (CH$_2$), 30.6 (THP-CH$_2$), 52.1 (CH$_3$), 62.2 (OCH$_2$), 63.8 (THP-OCH_2), 65.2 (ArOCH_2), 98.9 (THP-CH), 106.5, 107.7, 131.8 (ArC), 159.9 (OArC), 166.8 (COOH). − MS (70eV); _m/z_ (%): 452 (1.1) (HR: calcd. 452.241029; found 452.24395) [M$^+$], 85 (100) [THP$^+$].

3,5-Bis-[3-(2-tetrahydropyranyloxy)propyloxy]benzoic Acid (**2b**): A solution of 8.3 g (18.4 mmol) methyl benzoate **2a** and 3.0 g (55 mmol) of potassium hydroxide in methanol was refluxed for 20 h. After removal of the solvent, the oily residue was dissolved in ethyl acetate, washed with water (3 × 100ml) and dried with magnesium sulfate. The removal of the solvent furnished 7.3 g (90%) of **2b** as colorless crystals, m.p. 35°C. − ^{1}H NMR (CDCl$_3$): δ = 1.3−1.8 (m, 12 H, THP-CH$_2$), 2.0 (q, 4 H, CH$_2$), 3.3−3.5 (m, 4 H, OCH$_2$), 3.6−3.8 (m, 4 H, OCH$_2$), 4.0 (t, 4 H, ArCOCH_2), 4.5 (t, 2 H, THP-CH), 6.6 (t, 1 H, ArH), 7.2 (d, 2 H, ArH), 9.0−11.5 (br., 1 H, OH). − ^{13}C NMR (CDCl$_3$): δ = 19.4, 25.3 (THP-CH$_2$), 29.5 (CH$_2$), 30.5 (THP-CH$_2$), 62.2 (OCH$_2$), 63.8 (THP-OCH_2), 65.1 (ArOCH_2), 98.8 (THP-CH), 107.2, 108.1, 131.3 (ArC), 159.9 (OAr), 171.0 (COOH). − MS (70eV); _m/z_ (%): 438 (7) [M$^+$], 85 (100) [THP$^+$]. − C$_{23}$H$_{34}$O$_8$ (438.5): calcd. C 63.00, H 7.81; found C 62.91, H 7.61.

Methyl 3,5-Bis{3-[3,5-bis[3-(2-tetrahydropyranyloxy)propyloxy]benzoylamino}benzoate (**4a**): A solution of 21.6 g (49.3 mmol) of benzoic acid **2b** and 8.7 g (53.7 mmol) of _N,N'_-carbonyldiimidazole (CDI) in 200 ml of dry THF was stirred at 40° C for 24 h. After cooling to 0°C and adding of 1 ml of water, a solution of 7.9 g (22.4 mmol) of bis(hydrochloride) **1** and 7.2 g (47 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 100 ml of dry dichloromethane was added and stirred for further 24 h. The solution was washed with water (3 × 100 ml) and dried with magnesium sulfate. Chromatographic separation [silica gel, hexane/ethyl acetate (1:3, v/v)] yielded 27 g (50%) of **4a** as a viscous oil. − ^{1}H NMR (CDCl$_3$): δ = 1.3−1.9 (m, 24 H, THP-CH$_2$), 2.0−2.2 (m, 12 H, CH$_2$), 3.4−3.6 (m, 12 H, OCH$_2$), 3.7−3.9 (m, 11 H,

OCH$_2$, CH$_3$), 4.0−4.1 (m, 12 H, ArOCH_2), 4.5 (t, 4 H, THP-CH), 6.5 (t, 2 H, ArH), 6.6 (t, 1 H, ArH), 6.8 (d, 4 H, ArH), 7.1 (d, 2 H, ArH). − ^{13}C NMR (CDCl$_3$): δ = 19.5, 25.3 (THP-CH$_2$), 28.9, 29.5 (CH$_2$), 30.6 (THP-CH$_2$), 37.7 (CH$_2$-NH), 52.2 (CH$_3$), 62.3 (OCH$_2$), 63.8 (THP-OCH_2), 65.2, 66.5 (ArOCH_2), 98.9 (THP-CH), 104.4, 105.3, 106.6, 107.8, 132.0, 136.6 (ArC), 159.6, 160.2 (OAr), 166.5 (_C_OOCH$_3$), 167.4 (CONH). − FAB-MS; _m/z_ (%): 1123 (10) [M$^+$], 787 (81) [M$^+$ − 4THP]. − C$_{60}$H$_{86}$N$_2$O$_{18}$ (1123.3): calcd. C 64.15, H 7.72, N 2.49; found C 64.01, H 7.34, N 2.30.

3,5-Bis{3-[3,5-bis-[3-(2-tetrahydropyranyloxy)propyloxy]benzoylamino]propyloxy}benzoic Acid (**4b**): A solution of 10.3 g (9.2 mmol) of methyl benzoate **4a** and 1.5 g (27.5 mmol) of potassium hydroxide in methanol was refluxed for 20 h. After removal of the solvent, the oily residue was dissolved in ethyl acetate, washed with water (3 × 100 ml) and dried with magnesium sulfate. The removal of the solvent furnished 7.1 g (70%) of **4b** as a viscous oil. − ^{1}H NMR (CDCl$_3$): δ = 1.3−1.8 (m, 24 H, THP-CH$_2$), 1.9−2.2 (m, 12 H, CH$_2$), 3.4−3.6 (m, 12 H, OCH$_2$), 3.7−3.9 (m, 8 H, OCH$_2$), 4.0−4.1 (m, 12 H, ArOCH_2), 4.5 (t, 4 H, THP-CH), 6.4 (t, 2 H, ArH), 6.5 (t, 1 H, ArH), 6.8 (d, 4 H, ArH), 7.0 (s, 2 H, NH), 7.1 (d, 2 H, ArH), 7.8−9.0 (br., 1 H, OH). − ^{13}C NMR (CDCl$_3$): δ = 19.5, 25.3 (THP-CH$_2$), 28.8, 29.5 (CH$_2$), 30.5 (THP-CH$_2$), 37.8 (CH$_2$-NH), 62.3 (OCH$_2$), 63.9 (THP-OCH_2), 65.1, 66.6 (ArOCH_2), 98.9 (THP-CH), 104.3, 105.4, 106.3, 108.2, 132.0, 136.4 (Ar), 159.6, 160.1 (OAr), 167.5 (CONH), 168.4 (COOH). − FAB-MS; _m/z_ (%): 1107 (51) [M$^+$ − H]. − C$_{59}$H$_{84}$N$_2$O$_{18}$ (1109.3): calcd. C 63.88, H 7.63, N 2.53; found C 63.83, H 7.32, N 2.41.

Methyl 3,5-Bis{3-[3,5-bis(3-hydroxypropyloxy)benzoylamino]propyloxy}benzoate (**4c**): 10 ml of a 2% HCl solution in methanol was added to a solution of 1.0 g (0.9 mmol) of methyl benzoate **4a** in 20 ml of THF and stirred for 4 h. The solution was washed with water (3 × 100 ml) and the solvent was removed. The oily residue was dissolved in THF, and treated with 20 ml of a 2% HCl solution in methanol and stirred for further 10 h. The solution was washed with water (3 × 150 ml), dried with magnesium sulfate, and concentration yielded 0.5 g (70%) of **4c** as a highly viscous oil. − ^{1}H NMR ([D$_4$]MeOH): δ = 1.9 (m, 8 H, CH$_2$), 2.1 (m, 4 H, CH$_2$), 3.5 (m, 4 H, OCH$_2$), 3.7 (t, 8 H, OCH$_2$), 3.8 (s, 3 H, CH$_3$), 4.0−4.1 (m, 12 H, ArOCH$_2$), 4.6 (s, OH, H$_2$O), 6.6 (t, 2 H, ArH), 6.7 (t, 1 H, ArH), 6.9 (d, 4 H, ArH), 7.1 (d, 2 H, ArH), 8.5 (t, NH). − ^{13}C NMR ([D$_4$]MeOH): δ = 30.1, 33.3 (CH$_2$), 38.4 (CH$_2$NH), 59.5 (CH$_3$), 59.5 (CH$_2$OH), 66.0, 67.2 (ArOCH_2), 105.5, 106.8, 107.3, 108.8, 133.0, 137.6 (ArC), 161.4, 161.6 (OAr), 168.2 (_C_OOCH$_3$), 170.0 (CONH). − FAB-MS; _m/z_ (%): 787 (5.6) [M$^+$].

Methyl 3,5-Bis{3-{3,5-bis[3-[3,5-bis[3-(2-tetrahydropyranyloxy)propyloxy]benzoylamino]propyloxy]benzoylamino}propyloxy}benzoate (**6a**): A solution of 28.9 g (26 mmol) of benzoic acid **4b** and 4.4 g (27.3 mmol) of CDI in 300 ml of dry THF was stirred at 40° C for 24 hours. After cooling to 0°C and adding of 1 ml of water a solution of 4.6 g (13 mmol) of bis(hydrochloride) **1** and 3.9 ml (26 mmol) of DBU in 70 ml of dry dichloromethane was added and stirred for further 24 h. The solution was washed with water (3 × 100 ml) and dried with magnesium sulfate. Chromatographic separation (silica gel, ethyl acetate/10% acetone) yielded 26 g (80%) of **6a** as a colorless powder, m.p. 72−74°C. − ^{1}H NMR (CDCl$_3$): δ = 1.3−1.8 (m, 48 H, THP-CH$_2$), 1.9−2.1 (m, 28 H, CH$_2$), 3.4−3.6 (m, 28 H, OCH$_2$), 3.7−3.9 (m, 27 H, OCH$_2$, CH$_3$), 4.0−4.1 (m, 20 H, ArOCH$_2$), 4.5 (t, 8 H, THP-CH), 6.3 (t, 2 H, ArH), 6.5 (t, 3 H, ArH), 6.6 (t, 1 H, ArH), 6.8 (d, 4 H, ArH), 6.9 (d, 8 H, ArH), 7.0 (d, 2 H, ArH), 7.3 (br., 4 H, NH), 7.5 (br., 2 H, NH). − ^{13}C NMR (CDCl$_3$): δ = 19.5, 25.3 (THP-CH$_2$), 28.9, 29.5 (CH$_2$), 30.5 (THP-CH$_2$), 37.3 (CH$_2$NH), 52.1 (CH$_3$), 62.3 (OCH$_2$),

63.8 (THP-OCH$_2$), 65.0, 65.7, 66.5 (ArOCH$_2$), 98.9 (THP-CH), 104.2, 105.5, 106.7, 107.2, 107.6, 132.0, 136.4 (ArC), 159.5, 159.6, 160.0 (OAr), 166.6 (COOCH$_3$), 167.2, 167.5 (CONH). − FAB-MS; m/z (%): 2487 (0.2) [M$^+$ + Na], 1793 (2.5) [M$^+$ − 8 THP]. − Maldi-Tof; m/z: 2488.4 [M$^+$ + Na], 1793.2 [M$^+$ − 8 THP]. − C$_{132}$H$_{186}$N$_6$O$_{38}$ (2464.9): calcd. C 64.32, H 7.61, N 3.41; found C 63.98, H 7.36, N 3.15.

3,5-Bis{3-{3,5-bis[3-[3,5-bis[3-(2-tetrahydropyranyloxy)-propyloxy]benzoylamino]propyloxy]benzoylamino}propyloxy}benzoic Acid (**6b**): A solution of 5.0 g (2 mmol) of methyl benzoate **6a** and 0.4 g (7 mmol) of potassium hydroxide in 70 ml of methanol was refluxed for 20 h. After removal of the solvent, the oil was dissolved in ethyl acetate, washed with water (3 × 100 ml) and dried with magnesium sulfate. Complete removal of the solvent furnished 3.7 g (75%) of **6b** as a colorless powder, m.p. 85−88°C. − ^{1}H NMR (CDCl$_3$): δ = 1.3−1.8 (m, 48 H, THP-CH$_2$), 1.9−2.1 (m, 28 H, CH$_2$), 3.3−3.6 (m, 28 H, OCH$_2$), 3.7−3.9 (m, 24 H, OCH$_2$), 4.0−4.1 (m, 20 H, ArOCH$_2$), 4.5 (t, 8 H, THP-CH), 6.3 (t, 2 H, ArH), 6.5 (t, 5 H, ArH), 6.8 (d, 4 H, ArH), 6.9 (d, 8 H, ArH), 7.3 (s, 4 H, NH), 7.6 (d, 2 H, ArH). − ^{13}C NMR (CDCl$_3$): δ = 19.5, 25.7 (THP-CH$_2$), 28.6, 28.8, 29.4 (CH$_2$), 30.5 (THP-CH$_2$), 37.4, 37.5 (CH$_2$NH), 62.3 (OCH$_2$), 63.8 (THP-OCH$_2$), 65.7, 66.1, 66.8 (ArOCH$_2$), 98.8 (THP-CH), 104.3, 104.4, 105.4, 106.4, 107.8, 131.9, 136.2 (ArC), 159.5, 159.6, 160.0 (OAr), 167.4, 167.7 (CONH), 171.2 (COOH). − Maldi-Tof ; m/z: 2475.3 [M$^+$ + Na], 1781.3 [M$^+$ − 8 THP]. − C$_{131}$H$_{184}$N$_6$O$_{38}$ (2450.9): calcd. C 64.20, H 7.57, N 3.43; found C 63.28, H 7.43, N 3.20.

Methyl 3,5-Bis{3-{3,5-bis[3-[3,5-bis(3-hydroxypropyloxy)benzoylamino]propyloxy]benzoylamino}propyloxy}benzoate (**6c**): 5 ml of a 2% HCl solution in methanol was added to a solution of 1.0 g (0.4 mmol) of methyl benzoate **6a** in THF and stirred for 4 h. The solution was washed with water (3 × 100 ml) and the solvent was removed. The oily residue was dissolved in THF, and treated with 20 ml of a 2% HCl solution in methanol and stirred for further 10 h. The solution was washed with water (3 × 150 ml), dried with magnesium sulfate, and evaporation yields 0.5 g (70%) of **6c** as a highly viscous oil. − ^{1}H NMR ([D$_4$]MeOH): δ = 1.9 (m, 16 H, CH$_2$), 2.0 (m, 12 H, CH$_2$), 3.5 (m, 12 H, OCH$_2$), 3.7 (t, 16 H, CH$_2$OH), 3.9 (s, 3 H, CH$_3$), 4.0 (m, 12 H, ArOCH$_2$), 4.1 (m, 16 H, ArOCH$_2$), 4.9 (s, OH, H$_2$O), 6.4 (t, 1 H, ArH), 6.5 (t, 6 H, ArH), 6.9 (d, 12 H, ArH), 7.0 (s, 2 H, ArH). − ^{13}C NMR ([D$_4$]MeOH): δ = 30.1, 33.2 (CH$_2$), 38.2 (CH$_2$NH), 52.8 (CH$_3$), 59.5 (HOCH$_2$), 66.0, 67.0, 68.1 (ArOCH$_2$), 100.0, 105.4, 105.6, 106.7, 107.2, 108.8, 132.8, 137.5 (ArC), 161.3, 161.4, 161.6 (OAr), 168.2 (COO), 169.7, 169.8 (CONH). − FAB-MS: m/z (%): 1793 (0.5) [M + H$^+$].

Methyl 3,5-Bis(3-{3,5-bis[4-(2-tetrahydropyranyloxymethyl)-benzyloxy]benzoylamino}propyloxy)benzoate (**5a**): A solution of benzoic acid **3** (21.38 g, 38 mmol) and hydroxybenzotriazole (6.58 g, 43 mmol) in dry dichloromethane (600 ml) was stirred for 10 min at ambient temperature. Bis(hydrochloride) **1** (6.04 g, 17 mmol) and DBU (13.1 g, 86 mmol, 12.9 ml) were added and the reaction mixture was stirred until the reactands have completely dissoved. Then 1-[3-(dimethylamino)propyl]ethylcarbodiimide hydrochloride (EDC) (8.24 g, 43 mmol) was added. The solution was allowed to stir for 14 h at ambient temperature, then diluted with 200 ml of dichloromethane and washed with sat. sodium hydrogen carbonate, citric acid (20% in water) and brine. The organic layer was dried with magnesium sulfate and then concentrated. Column chromatography of the oily residue (silica gel, dichloromethane/5% methanol) furnished **5a** (20.7 g, 15.1 mmol, 89%) as a colourless solid, m.p. 89−95°C. − ^{1}H NMR ([D$_7$]DMF): δ = 1.40−1.62 (m, 16 H,

THP), 1.69 (m, 4 H, THP), 1.79 (m, 4 H, THP), 2.09 (quint, 4 H, 15-H), 3.51 (m, 4 H, THP), 3.59 (dt, 4 H, 16-H), 3.85 (m, 4 H, THP), 3.87 (s, 3 H, CH$_3$), 4.15 (t, 4 H, 14-H), 4.49 (d, 4 H, 28a-H), 4.72 (t, 4 H, THP), 4.75 (d, 4 H, 28b-H), 5.18 (s, 8 H, 23-H), 6.83 (t, 1 H, 13-H), 6.90 (t, 2 H, 22-H), 7.14 (d, 2 H, 11-H) 7.29 (d, 4 H, 20-H) 7.42 (d, 8 H, 26-H), 7.50 (d, 8 H, 25-H), 8.69 (t, 2 H, 17-H). − ^{13}C NMR ([D$_7$]DMF): δ = 19.9 (THP), 26.0 (THP), 29.8 (C-15), 31.3 (THP), 37.3 (C-16), 52.6 (CH$_3$), 62.2 (C-28), 66.6 (C-14). 68.8 (THP), 70.3 (C-23), 98.4 (THP), 105.2 (C-13), 106.6 (C-22), 107.0 (C-20), 128.4 (C-25/C-26), 132.6 (C-11), 137.0 (C-24), 137.5 (C-10), 137.8 (C-19), 139.2 (C-27), 160.6 (C-21), 160.9 (C-12), 166.9 (C-9), 168.0 (C-18). − MS (FAB$^+$); m/z (%): 1503 (2.25) [M$^+$ + Cs].

3,5-Bis(3-{3,5-bis[4-(2-tetrahydropyranyloxymethyl)benzyloxy]-benzoylamino}propyloxy)benzoic Acid (**5b**): A solution of potassium hydroxide (1.10 g, 19.7 mmol) in 60 ml of water was added to a solution of methyl benzoate **5a** (9.00 g, 6.56 mmol) in 180 ml of methanol. The solution was refluxed for 3 h. After cooling to 0°C, diluted acetic acid (21.0 mmol, 1.15 ml of glacial acetic acid in 30 ml of water) was added. The solution was concentrated to a volume of 90 ml and then extracted with dichloromethane. The combined organic layers were washed with sat. sodium hydrogen carbonate, citric acid (20% in water) and brine and dried with magnesium sulfate. The oily residue was purified by crystallization from methanol/chloroform to yield **5b** (8.42 g, 6.20 mmol, 95%), m.p. 95−99°C. − ^{1}H NMR ([D$_7$]DMF): δ = 1.36−1.95 (m, 24 H, THP) 2.09 (quint, 4 H, 15-H), 3.36−3.72 (m, 8 H, THP, 16-H), 3.85 (m, 4 H, THP), 4.15 (t, 4 H, 14-H), 4.49 (d, 4 H, 28a-H), 4.73 (m, 8 H, 28b-H, THP), 5.17 (s, 8 H, 23-H), 6.79 (t, 1 H, 13-H), 6.89 (t, 2 H, 22-H), 7.14 (d, 2 H, 11-H) 7.24 (d, 4 H, 20-H) 7.42 (d, 8 H, 26-H), 7.50 (d, 8 H, 25-H), 8.65 (t, 2 H, 17-H). − ^{13}C NMR ([D$_7$]DMF): δ = 19.9 (THP), 26.0 (THP), 29.8 (C-15), 31.1 (THP), 37.3 (C-16), 62.2 (C-28), 66.6 (C-14). 68.8 (THP), 70.3 (C-23), 98.4 (THP), 105.2 (C-13), 106.6 (C-22), 107.0 (C-20), 128.4 (C-25/C-26), 132.6 (C-11), 137.0 (C-24), 137.4 (C-10), 137.8 (C-19), 139.2 (C-27), 160.6 (C-21), 160.9 (C-12), 166.9 (C-9), 168.0 (C-18). − MS (FAB$^+$); m/z (%): 1490 (0.43) [M$^+$ + Cs].

Methyl 3,5-Bis-(3-{3,5-bis-[4-(hydroxymethyl)benzyloxy]benz-oylamino}propyloxy)benzoate (**5c**): A solution of methyl benzoate **5a** (2.00 g, 1.46 mmol) in 20 ml of tetrahydrofurane was treated with a solution of hydrochloric acid (4 ml) in 12 ml of methanol. The mixture was stirred at ambient temperature for 12 h and then concentrated. The residue was stirred with a second portion of deprotection mixture for another 12 h and again concentrated. Purification by column chromatography (silica gel, dichloromethane/10% methanol) furnished **5c** (1.29 g, 1.25 mmol, 86%) as a white solid which could be freeze-dried from dioxane, m.p. 132−138°C. − ^{1}H NMR ([D$_4$]MeOH): δ = 2.05 (quint, 4 H, 15-H), 3.50 (q, 4 H, 16-H), 3.80 (s, 3 H, CH$_3$), 4.10 (t, 4 H, 14-H), 4.65 (s, 8 H, 28-H), 5.18 (s, 8 H, 23-H), 6.80 (t, 1 H, 13-H), 6.85 (t, 2 H, 22-H), 7.10 (d, 2 H, 11-H) 7.20 (d, 4 H, 20-H) 7.35 (d, 8 H, 26-H), 7.50 (d, 8 H, 25-H), 8.60 (t, 2 H, 17-H). − ^{13}C NMR ([D$_4$]MeOH): δ = 28.7 (C-15), 36.3 (C-16), 52.3 (CH$_3$), 62.6 (C-28). 66.0 (C-14), 69.4 (C-23), 104.5 (C-13), 106.3 (C-20), 107.0 (C-22), 126.5 (C-25), 127.5 (C-26), 132.0 (C-11), 135.1 (C-24), 135.7 (C-10), 135.9 (C-19), 142.3 (C-27), 159.3 (C-21), 159.8 (C-12), 165.7 (C-18), 165.8 (C-9). − MS (FAB$^+$); m/z (%): 1490 (0.43) [M$^+$+Cs].

Methyl 4-[3,5-Bis(3-{3,5-bis[4-(2-tetrahydropyranyloxymethyl)-benzyloxy]benzoylamino}propyloxy)benzoylaminomethyl]benzoate (**5d**): A solution of benzoic acid **5b** (20.5 g, 15.1 mmol) and hydroxybenzotriazole (2.54 g, 16.6 mmol) in dry dichloromethane (600 ml) was stirred for 10 min. Methyl 4-(aminomethyl)benzoate

hydrochloride (3.35 g, 16.6 mmol) and DBU (5.2 g, 5.1 ml, 34.0 mmol) were added and the reaction mixture was stirred until the reactands hade completely dissoved. Then EDC (3.18 g, 16.6 mmol) was added. The solution was allowed to stir for 14 h, then diluted with 400 ml of dichloromethane and washed with sat. sodium hydrogen carbonate, citric acid (20% in water) and brine. The organic layer was dried with magnesium sulfate and then concentrated. Column chromatography of the oily residue (silica gel, dichloromethane/5% methanol) furnished **5d** (20.2 g, 13.4 mmol, 89%) as a colourless solid, m.p. 98−108°C. − ^{1}H NMR ([D$_7$]DMF): δ = 1.43−1.61 (m, 16 H, THP), 1.68 (m, 4 H, THP), 1.79 (m, 4 H, THP), 2.08 (quint, 4 H, 15-H), 3.51 (m, 4 H, THP), 3.57 (dt, 4 H, 16-H), 3.85 (m, 4 H, THP), 3.89 (s, 3 H, 1-H), 4.14 (t, 4 H, 14-H), 4.50 (d, 4 H, 28a-H), 4.65 (d, 2 H, 7-H), 4.71 (t, 4 H, THP), 4.75 (d, 4 H, 28b-H), 5.18 (s, 8 H, 23-H), 6.71 (t, 1 H, 13-H), 6.90 (t, 2 H, 22-H), 7.22 (d, 2 H, 11-H) 7.28 (d, 4 H, 20-H) 7.42 (d, 8 H, 26-H), 7.50 (d, 8 H, 25-H), 7.53 (d, 2 H, 5-H), 7.97 (d, 2 H, 4-H) 8.64 (t, 2 H, 17-H), 9.11 (t, 1 H, 8-H). − ^{13}C NMR ([D$_7$]DMF): δ = 19.9 (THP), 26.1 (THP), 29.6 (C-15), 31.1 (THP), 37.3 (C-16), 43.6 (C-7), 52.4 (C-1), 62.2 (C-28), 66.5 (C-14), 68.8 (THP), 70.3 (C-23), 98.4 (THP), 104.9 (C-13), 105.2 (C-22), 106.5 (C-11), 107.0 (C-20), 128.3 (C-5), 128.5 (C-25/C-26), 129.3 (C-3), 130.1 (C-4), 137.0 (C-24), 137.2 (C-10), 137.8 (C-19), 139.2 (C-27), 146.3 (C-6), 160.6 (C-21), 160.9 (C-12), 166.7 (C-2), 166.9 (C-9), 167.0 (C-18). − MS (FAB$^+$); *m/z* (%): 1637 (2.26) [M$^+$ + Cs]. − C$_{88}$H$_{101}$N$_3$O$_{19}$ (1504.8): calcd. C 70.24, H 6.77, N 2.79; found C 69.39, H 6.60, N 2.67.

4-[3,5-Bis(3-{3,5-bis[4-(2-tetrahydropyranyloxymethyl)-benzyloxy]benzoylamino}propyloxy)benzoylaminomethyl]benzoic Acid (**5e**): A solution of potassium hydroxide (2.47 g, 44.0 mmol) in 150 ml of water was added to a solution of methyl benzoate **5d** (13.2 g, 8.78 mmol) in 450 ml of methanol. The solution was refluxed for 5 h. After cooling to 0°C, diluted acetic acid (44.0 mmol, 2.52 ml of glacial acetic acid in 100 ml of water) was added. The solution was concentrated to a volume of 250 ml and then extracted with dichloromethane. The combined organic layers were washed with sat. sodium hydrogen carbonate, citric acid (20% in water) and brine and dried with magnesium sulfate. The oily residue was purified by column chromatography (silica gel, dichloromethane/10% methanol). For better solution behaviour **5e** (9.82 g, 6.59 mmol, 75%) could be freeze-dried from dioxane, m.p. 113−124°C. − ^{1}H NMR ([D$_7$]DMF): δ = 1.39−1.901 (m, 24 H, THP), 2.07 (quint, 4 H, 15-H), 3.36−3.72 (m, 8 H, THP, 16-H), 3.85 (m, 4 H, THP), 4.14 (t, 4 H, 14-H), 4.49 (d, 4 H, 28a-H), 4.65 (d, 2 H, 7-H), 4.74 (m, 8 H, 28b-H, THP), 5.17 (s, 8 H, 23-H), 6.71 (t, 1 H, 13-H), 6.89 (t, 2 H, 22-H), 7.22 (d, 2 H, 11-H) 7.27 (d, 4 H, 20-H) 7.42 (d, 8 H, 26-H), 7.50 (m, 10 H, 25-H, 5-H), 7.99 (d, 2 H, 4-H), 8.64 (t, 2 H, 17-H), 9.10 (t, 1 H, 8-H). − ^{13}C NMR ([D$_1$]CDCl$_3$): δ = 19.9 (THP), 26.1 (THP), 29.9 (C-15), 31.1 (THP), 37.3 (C-16), 43.6 (C-7), 62.2 (C-28), 66.5 (C-14), 68.8 (THP), 70.3 (C-23), 98.4 (THP), 104.8 (C-13), 105.2 (C-22), 106.5 (C-11), 107.0 (C-20), 128.1 (C-5), 128.4 (C-25/C-26), 128.5 (C-3), 130.3 (C-4), 137.0 (C-24), 137.3 (C-10), 137.8 (C-19), 139.2 (C-27), 146.0 (C-6), 160.6 (C-21), 160.9 (C-12), 166.7 (C-18), 166.8 (C-9), 172.1 (C-2). − MS (FAB$^-$); *m/z* (%): 1490 (5.61) [M$^-$ − H]. − C$_{87}$H$_{99}$N$_3$O$_{19}$ (1490.8): calcd. C 70.10, H 6.69, N 2.82; found C 69.19, H 6.43, N 2.37.

Methyl 4-[3,5-Bis(3-{3,5-bis[4-hydroxymethylbenzyloxy]benzoylamino}propyloxy)benzoylaminomethyl]benzoate (**5f**): A solution of methyl benzoate **5d** (3.01 g, 2.00 mmol) in 25 ml of tetrahydrofu-

ran was treated with a solution of hydrochloric acid (5 ml) in 15 ml of methanol. The mixture was stirred at ambient temperature for 12 h and then concentrated. The residue was stirred with a second portion of deprotection mixture for another 12 h and again concentrated. Purification by column chromatography (silica gel, dichloromethane/10% methanol) furnished **5f** (2.22 g, 1.95 mmol, 95%) as a white solid which could be freeze-dried from dioxane, m.p. 144−150°C. − ^{1}H NMR ([D$_7$]DMF): δ = 2.09 (quint, 4 H, 15-H), 3.58 (dt, 4 H, 16-H), 3.90 (s, 3 H, 1-H), 4.15 (t, 4 H, 14-H), 4.62 (d, 8 H, 28-H), 4.65 (d, 2 H, 7-H), 5.18 (s, 8 H, 23-H), 5.25 (t, 4 H, -OH), 6.72 (t, 1 H, 13-H), 6.90 (t, 2 H, 22-H), 7.22 (d, 2 H, 11-H) 7.29 (d, 4 H, 20-H) 7.42 (d, 8 H, 26-H), 7.47 (d, 8 H, 25-H), 7.55 (d, 2 H, 5-H), 7.98 (d, 2 H, 4-H) 8.65 (t, 2 H, NH), 9.11 (t, 1 H, NH). − ^{13}C NMR ([D$_7$]DMF): δ = 29.9 (C-15), 37.3 (C-16), 43.6 (C-7), 52.4 (C-1), 64.0 (C-28), 66.5 (C-14), 70.4 (C-23), 104.8 (C-13), 105.2 (C-22), 106.5 (C-11), 107.0 (C-20), 127.3 (C-26), 128.3 (C-5), 128.4 (C-25), 129.3 (C-3), 130.1 (C-4), 136.2 (C-24), 137.2 (C-10), 137.7 (C-19), 143.4 (C-27), 146.3 (C-6), 160.6 (C-21), 160.9 (C-12), 166.8 (C-18), 166.9 (C-9), 167.0 (C-2). − MS (FAB$^+$); *m/z* (%): 1168 (0.22) [M$^+$ + H]. − C$_{68}$H$_{69}$N$_3$O$_{15}$ (1168.3): calcd. C 69.91, H 5.95, N 3.60; found C 69.48, H 5.86, N 3.52.

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