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ARTICLE

Strategies for penicillin V dendronization with cationic carbosilane dendrons and study of antibacterial properties

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Abstract: Strategies to synthesize a cationic carbosilane dendron containing the antibiotic penicillin V potassium salt (PenVK) at the focal point are discussed. The preparation of such a compound requires the use of systems with no donor atoms such as N or S in their framework, because their presence favours the rupture of the penicillin β-lactam ring. The antibacterial activity of the new dendron containing ammonium groups, at the periphery, and the PenV moiety, at the focal point, against gram-positive *Staphylococcus aureus* strains was evaluated. These results were compared with those obtained for free PenVK, a related cationic dendron without a penicillin moiety at the focal point, and also compared with an equimolar mixture of this last dendron with free PenV. The data obtained indicate that, on one hand, the conjugation or interaction of PenV with cationic dendrons reduces its activity in comparison with free PenVK. On the other hand, the penicillin dendron is able to release the antibiotic in the presence of esterease, due to the breaking of the ester bond in this derivative.

Key words: dendritic molecules, carbosilane dendrons, antibacterial, penicillin, antibiotic.

Résumé : Il est question dans le présent article de stratégies pour synthétiser un dendron de carbosilane cationique contenant en son point focal le sel potassique de la pénicilline V (PenVK), un antibiotique. La préparation d'un tel composé requiert l'emploi de systèmes dont la structure est dépourvue de donneurs d'atomes, tels que l'azote (N) ou le soufre (S), car ceux-ci causent la rupture du cycle β-lactame de la pénicilline. L'activité antimicrobienne de ce nouveau dendron dotés de groupes ammonium en périphérie et du groupement PenV au point focal a été évaluée en présence de souches de *Staphylococcus aureus* à gram positif. Nous avons comparé ces résultats à ceux qui ont été obtenus pour la PenVK libre, pour un dendron cationique apparenté sans groupement pénicilline au point focal, ainsi que pour un mélange équimolaire de ce dernier dendron avec la PenV libre. Les données obtenues indiquent que l'activité de la PenV conjuguée aux dendrons cationiques ou en présence de ceux-ci est réduite par rapport à celle de la PenVK libre. Par ailleurs, nous avons montré qu'en présence d'estérase, le dérivé pénicilline-dendron est capable de libérer l'antibiotique par clivage de sa liaison ester. [Traduit par la Rédaction]

Mots-clés : molécules dendritiques, dendrons de carbosilane, antibactérien, pénicilline, antibiotique.

Introduction

The widespread use and misuse of antibiotics have favored the appearance of antibiotic-resistant bacteria,[1–3] creating a major public health concern.[4] The problem is worsened by the ability of bacteria to create biofilms,[5] which are involved in the majority of infection diseases caused by bacteria.[6] Thereby, the need of finding compounds with non-specific antibacterial activity to fight resistance and (or) reduce antibiotic dependence is a priority.[7,8]

The bacterial cell walls are formed with negative lipoproteins and divalent cations such as Mg^{2+} and Ca^{2+} acting as glue.[9] Thus, quaternary ammonium salts (QAS) have become popular antimicrobials due to their ability to replace these cations and destroy the cell wall.[9–11] Another advantage of some QAS is their solubility in water, which allows them to kill bacteria in water solution.[12] The incorporation of QAS to polymers generates polycations that present a high surface charge. The multivalency of these polyammonium macromolecules such as polymers,[13] hyperbranched polymers,[14] and dendrimers[15,16] increases the activity with respect to monofunctional molecules.[7,13,17]

Dendrimers and dendrons are multibranched macromolecules designed step by step, which leads to well-defined structures.[18–20] Dendrimers are spherical molecules, whereas dendrons are cone-shaped molecules, presenting an extra active moiety, the focal point, that can be used to attach a second functionality or to dendronize materials. The well-known structures of these systems make it easier to establish structure–activity relationships. Several types of ammonium dendrimers, depending on their dendritic structure, have shown antibacterial properties.[21–25] Their activity is increased by the presence of hydrophobic chains, which enables their penetration into the phospholipid bilayer, leading to the disintegration of the bacterial membrane.[11,26] Regarding dendrons, antimicrobial studies are scarce,[27] and usually, they are associated to the generation of dendronized materials,[28–30] because the focal point is an excellent anchorage position for functionalization.

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Dendrimers have also been employed as drug carriers by electrostatic interaction between drugs and surface groups, conjugation of drug to dendrimer, or by encapsulation of drug inside a hyperbranched framework.[31,32] For example, it has been reported that some dendrimers enhance solubility and activity of antibiotics.[33–37] Moreover, a synergistic effect has been observed for some combinations of dendrimers with antibacterial properties and antibiotics.[38–40]

One type of dendrimers is based on carbosilane framework, which contains very low polar C–C and Si–C bonds.[41,42] The decoration of the surface of dendrimers with ammonium functions introduces antimicrobial properties and water solubility to these dendrimers.[43–46] Recently, we published an evaluation of antibacterial activity of cationic carbosilane dendrimers and dendrons by comparing generation, core of dendrimers, focal point of dendrons, and type of ammonium groups.[47] These results highlight the good activity obtained for low-generation systems (generation one for dendrimers and generation two for dendrons with six and four ammonium groups, respectively) against both gram-positive and gram-negative bacteria and also against resistant *S. aureus* strains. Moreover, these systems did not generate resistance after continuous treatments. We also reported the synergy produced after the combination of a cationic dendrimer with an amoebicide compound (chlorhexidine digluconate).[48]

Taking into account these results, we have considered the evaluation of cationic carbosilane dendrons of second generation as antibiotic carriers, as it could be expected that combination of biocide compounds with different modes of action could act synergistically.[49] As an antibiotic, we have chosen a penicillin derivative (penicillin V, PenV) for its simplicity and the presence of one carboxylate moiety. This anionic group will be used to interact electrostatically with the cationic dendrons[50] or to allow conjugation to the dendron employing an adequate group at the focal point.[51] The synthetic procedure to obtain the new dendrons and also the difficulties found to do it, their characterization, and antibacterial activity against *S. aureus* are discussed.

Experimental

General considerations

All reactions were carried out under inert atmosphere, and solvents were purified from appropriate drying agents when necessary. NMR spectra were recorded on a Varian Unity VXR-300 (300.13 (^{1}H), 75.47 (^{13}C) MHz) or on a Bruker AV400 (400.13 (1H), 100.60 (^{13}C), 40.56 (^{15}N), 79.49 (^{29}Si) MHz). Chemical shifts (δ) are given in ppm. ^{1}H and ^{13}C resonances were measured relative to internal deuterated solvent peaks considering TMS = 0 ppm; meanwhile, ^{29}Si resonances were measured relative to external TMS employing ^{1}H–^{29}Si HMBC experiments. When necessary, assignment of resonances was done from HSQC, HMBC, COSY, TOCSY, and NOESY NMR experiments. Thiol-ene reactions were carried out employing a HPK 125 W mercury lamp from Heraeus Noblelight with maximum energy at 365 nm, in normal glassware under an inert atmosphere. Elemental analyses were performed on a LECO CHNS-932. Mass spectra were obtained from an Agilent 6210. Compounds $HS(CH_2)_2NMe_2{\cdot}HCl$ 2,2′-dimethoxy-2-phenylacetophenone (DMPA), MeI, $HSiMe_2Cl$, $HSiMeCl_2$, $LiAlH_4$, $NaHCO_3$, penicillin V potassium salt (PenVK), platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex solution (Karstedt's catalyst), and porcine liver esterease were obtained from commercial sources. Compounds $NH_2G_n(NMe_2)_m$,[52] $[NH_2G_n(S\text{-}NMe_3)_m]^{m+1}$,[47] ClG_1V_2,[53] and ClG_1A_2[54] were synthesized as published.

Synthesis of selected compounds

The syntheses of all compounds are described in the Supplementary data, with only a selection mentioned herein.

$ClG_1(Si\text{-}NMe_2)_2$ (11)

An excess of allyl-dimethylamine (0.21 mL, 1.76 mmol) and two drops of Karsted's catalyst were added to a solution of $ClG_1(SiH)_2$ (**6**) (0.145 g, 0.44 mmol) in THF (2 mL). The reaction mixture was heated at 80 °C in a sealed ampoule under inert atmosphere for one night and then evaporated to dryness to remove the solvent and residual allyl-dimethylamine. Afterwards, hexane (10 mL) was added, and the solution was filtered through active carbon and dried under vacuum to yield **11** as a pale yellow oil (0.194 g, 88%).

^{1}H NMR ($CDCl_3$): δ –0.06 (s, 12 H, $SiMe_2$), 0.04 (s, 3 H, $SiMe$), 0.44 (t, J_a = 8.4 Hz, 4 H, $SiCH_2CH_2CH_2N$), 0.57 (m, 10 H, $SiCH_2CH_2CH_2Si$ and $ClCH_2CH_2CH_2Si$), 1.29 (m, 4 H, $SiCH_2CH_2CH_2Si$), 1.42 (m, 4 H, $SiCH_2CH_2CH_2N$), 1.72 (m, 2 H, $ClCH_2CH_2$), 2.19 (m, 16 H, CH_2NMe_2), 3.47 (t, J_b = 6.9 Hz, 2 H, $ClCH_2$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ –5.2 ($SiMe$), –3.4 ($SiMe_2$), 11.6 ($ClCH_2CH_2CH_2Si$), 12.8 ($SiCH_2CH_2CH_2N$), 18.3, 18.5 and 20.0 ($SiCH_2CH_2CH_2Si$), 22.1 ($SiCH_2CH_2CH_2NMe_2$), 27.7 ($ClCH_2CH_2$), 45.5 ($-NMe_2$), 48.1 ($ClCH_2$), 63.4 (CH_2NMe_2). MS: $[M + H]^+$ = 493.4 uma (calcd = 493.4 uma). Anal. Calcd for $C_{24}H_{57}ClN_2Si_3$ (493.43 g/mol): C, 58.42; H, 11.64; N, 5.68; Exp.: C, 58.89; H, 11.57; N, 5.81.

$ClG_1(Si\text{-}NMe_3I)_2$ (13)

A mixture of **11** (0.220 g, 0.44 mmol) and MeI (0.11 mL, 1.76 mmol) in THF (50 mL) were stirred for 16 h. Afterward, volatiles were removed under vacuum, and the remaining solid was washed with Et_2O (50 mL), obtaining **13** as a white solid (0.300 g, 87%).

^{1}H NMR (DMSO-d_6): δ –0.07 (s, 3 H, $SiMe$), 0.00 (s, 12 H, $SiMe_2$), 0.38 and 0.56 (m, 14 H, $SiCH_2$), 1.31 (m, 4 H, $SiCH_2CH_2CH_2Si$), 1.62 (m, 6 H, $CH_2CH_2N^+$ and $ClCH_2CH_2$), 3.05 (s, 18 H, $-NMe_3^+$), 3.25 (t, J_a = 7.8 Hz, 4 H, CH_2N^+), 2.58 (t, J_b = 6.5 Hz, $ClCH_2$). ^{13}C{^{1}H} NMR (DMSO-d_6): δ –5.6 ($SiMe$), –3.9 ($SiMe_2$), 10.6 ($SiCH_2CH_2CH_2N^+$), 16.4–17.4 ($SiCH_2CH_2CH_2Si$), 18.6 ($CH_2CH_2N^+$), 26.7 ($ClCH_2CH_2$), 47.8 ($ClCH_2$), 51.6 ($-NMe_3^+$), 67.4 ($SiCH_2CH_2CH_2NMe_3^+$).[29] Si-NMR (DMSO-d_6): δ 2.1 ($SiMe$), 2.4 ($SiMe_2$). ESI: (776.21 g/mol) q = 1 (649.31 $[M–I]^+$). Anal. Calcd for $C_{26}H_{63}ClI_2N_2Si_3$ (777.31 g/mol): C, 40.17; H, 8.17; N, 3.60; Exp.: C, 40.78; H, 8.39; N, 3.93.

$(PenV)G_1(Si\text{-}NMe_3I)_2$ (15)

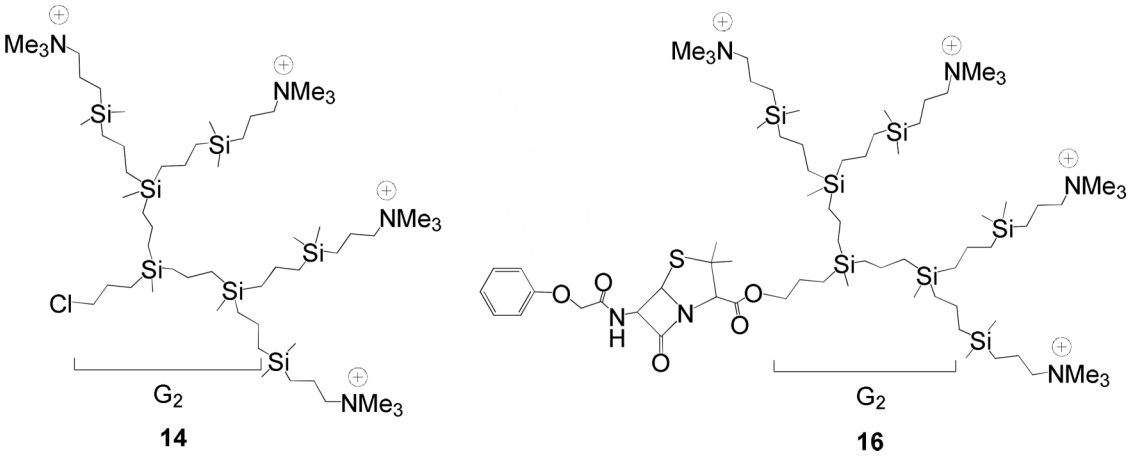
To a solution of **14** (0.050 g, 0.06 mmol) in dry DMF, PenVK (0.027 g, 0.07 mmol) was added in the presence of ether crown 18C6 (0.002 g, 0.01 mmol) and a catalytic amount of NaI. The mixture was heated at 80 °C in a sealed ampoule under argon atmosphere for 40 h, after which volatiles were removed. After washing the residues with water, this dendron was obtained as a very hygroscopic white solid (0.062 g, 89%).

^{1}H NMR ($CDCl_3$): δ 0.00 (s, 12 H, $SiMe_2$), 0.04 (s, 3 H, $SiMe$), 0.57 (m, 14 H, $SiCH_2$), 1.29 (m, 4 H, $SiCH_2CH_2CH_2Si$), 1.48 (s, 3 H, CMe_2), 1.58 (s, 3 H, CMe_2), 1.70 (m, 6 H, $CH_2CH_2N^+$ and OCH_2CH_2), 3.41 (s, 18 H, $-NMe_3^+$), 3.63 (m, 4 H, CH_2N^+), 4.08 (t, J_a = 8.4 Hz, 2 H, $(CO)OCH_2$), 4.43 (s, 1 H, $CH(CMe_2)$), 4.53 (s, 2 H, OCH_2CO), 5.56 (d, J_b = 4.3 Hz, 1 H, CHS), 5.70 (m, 1 H, $NHCH$), 6.90 (d, J_c = 7.6 Hz, 2 H, CH_{Ar}), 7.01 (t, J_d = 7.4 Hz, 1 H, CH_{Ar}), 7.30 (m, 2 H, CH_{Ar}). ^{13}C{^{1}H} NMR ($CDCl_3$): δ –5.0 ($SiCH_3$), –3.2 ($SiMe_2$), 9.9 (CH_2Si), 11.4 ($SiCH_2CH_2CH_2N^+$), 17.9, 18.0, and 18.3 ($SiCH_2CH_2CH_2Si$), 19.8 ($CH_2CH_2N^+$), 23.2 (OCH_2CH_2), 26.8 and 32.0 ($SCMe_2$), 53.7 ($-NMe_3^+$), 58.0 ($NHCH$), 64.7 ($SCMe_2$), 67.1 (CH_2N^+), 67.7 (OCH_2CO), 68.4 ($COOCH_2$), 69.5 (CHS), 70.5 ($CHCOO$), 114.7 (CH_{Ar}), 122.4 (CH_{Ar}), 129.8 (CH_{Ar}), 156.8 (CO_{Ar}), 167.6, 167.8, and 173.0 (C=O). ESI: (1090.32 g/mol) q = 1 (963.42 $[M–I]^+$), q = 2 (418.26 $[M–2I]^{2+}$). Anal. Calcd for $C_{42}H_{80}I_2N_4O_5SSi_3$ (1091.24 g/mol): C, 46.23; H, 7.39; N, 5.13; Exp.: C, 45.94; H, 7.07; N, 4.43.

DOSY NMR measurements

DOSY experiments were carried out on a Bruker Advance 400 at 25 °C. The values of midpoint between gradients (Δ) and gradient length (δ) were adjusted for free PenVK and for compound **14** in their solutions, and these values were later used in two different experiments for the mixture PenVK–**14**, not observing significant differences in the final result (Supplementary Fig. S6).

Fig. 1. Drawing of cationic dendrons of second generation $[XG_2(Si\text{-}NMe_3)_4]^{4+}$ (X = Cl, (**14**); X = PenV (**16**)).



Antibacterial methodology

Bacterial strains

Staphylococcus aureus (CECT 240, gram-positive bacteria) were obtained from the Spanish Type Culture Collection (CECT).

MIC and MBC

The minimal inhibitory concentration (MIC) of the products was measured in 96-well tray microplates by microdilution tray preparations following the international standard methods ISO 20776-1.[55] Assays were run in duplicate microplates and three different wells for each concentration analyzed in the microplate. Solutions of the products were prepared in the range of 0.25–1024 ppm adding in each well 100 μL of one of these solutions, 100 μL of double concentration Mueller Hinton (Scharlau, ref. 02–136), and 5 μL of a bacteria suspension of 2×10^7 CFU/mL. Microplates were incubated at 37 °C for 19 h using an ultra microplate reader ELx808iu (Bio-Tek Instruments), considering the MIC the minimal concentration for which no turbidity was observed. The minimal bactericidal concentration (MBC) was calculated by inoculating Petri dishes containing Mueller-Hinton agar with 3 μL of the samples used for MIC assessment. Samples were tested as droplets on the plates. Microbial growth on plates was monitored after 24 h of incubation at 37 °C. The MBC was determined as the minimal concentration at which no growth was detected.

Results and discussion

Synthesis and characterization of dendrons

To clarify the discussion of the compounds studied herein, the following nomenclature for dendrons has been used: $[XG_n(Y\text{-}Z)_m]$, where X refers to the focal point, G_n means carbosilane skeleton and generation (Fig. 1), Y indicates functionalization of the periphery by hydrosilylation (Y = Si) or hydrothiolation (Y = S), and Z and *m* correspond to the peripheral functional groups and their numbers on the surface, respectively.

Because the antibacterial results previously obtained by our group for carbosilane dendrons showed the best activity for second-generation derivatives containing a sulfur atom close to the surface of the dendron,[47] we have focused our efforts on obtaining a second-generation dendron with a PenV fragment at the focal point. Nonetheless, the reactions with the first-generation dendrons were carried out to find the adequate procedure and properly characterize the compounds.

Initially, we attempted to anchor the penicillin moiety by amide bond involving the carboxylic group of PenV and a primary amine at the focal point of the cationic dendron $NH_2G_1(S\text{-}NMe_3)_2]^{2+}$[47] or the related neutral derivative $NH_2G_1(S\text{-}NMe_2)_2$[52] (Scheme 1). However, the reaction of neutral PenV with these dendrons failed due to instability of the β-lactam ring toward the amino function, observing in the ^{1}H NMR spectra the disappearance of the original resonances belonging to this ring (data not shown). This instability of the β-lactam ring in the presence of $-NH_2$ functions has been exploited for the preparation of benzylpenicilloyl–dendrimer conjugates to evaluate penicillin allergy.[56]

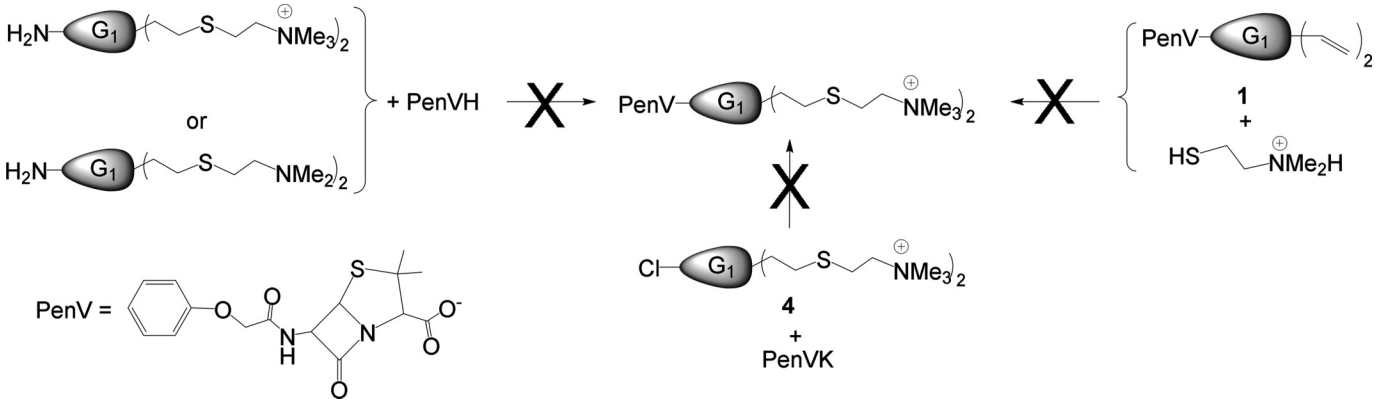
Alternatively, we proceeded to incorporate the PenV moiety to a vinyl dendron by direct reaction of the PenVK with the dendron containing a Br–C bond at the focal point, BrG_1V_2, in a similar way to other modifications introduced in these dendrons (Supplementary Scheme S1).[52] Thus, after reaction treatment and purification, the corresponding dendron $(PenV)G_1V_2$ (**1**) was obtained as a yellowish oil in good yield. The main NMR data that confirmed this transformation were the resonances corresponding to the CH_2 moiety of the new ester bond, observed at δ 4.16 ^{1}H NMR spectrum and at δ 65.4 ^{13}C NMR spectrum, respectively.

Unfortunately, subsequent modification of the periphery of **1** via thiol-ene addition failed, leading again to the rupture of the β-lactam ring, probably caused by a nucleophilic attack of the thiol function to the carbonyl carbon of this ring (Scheme 1).[57] Nevertheless, the halogen–PenV exchange seemed to be a promising procedure to obtain dendrons with a PenV unit at the focal point. Hence, we designed a cationic dendron with a Cl–C bond at the focal point and cationic peripheral functions at the periphery. The reason for the presence of a Cl–C bond instead of a Br–C bond is the clearly enhanced reactivity of the latter towards amines.

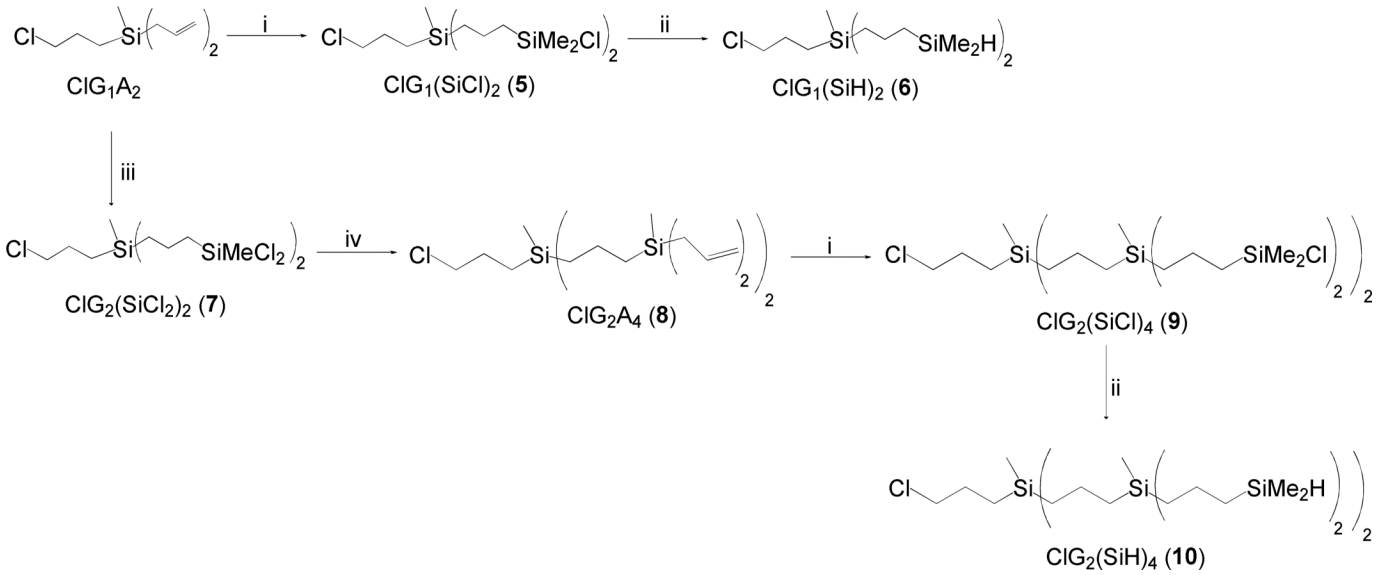
For the synthesis of this new dendron (Supplementary Scheme S2), we started from ClG_1V_2[53] and carried out a thiol-ene addition with cysteamine hydrochloride ($HS(CH_2)_2NMe_2{\cdot}HCl$) under UV irradiation, obtaining $[ClG_1(S\text{-}NMe_2H)_2]^{2+}$ (**2**) as a white solid. The formation of this compound was confirmed by NMR spectroscopy: the resonances of the vinyl groups disappeared in both ^{1}H NMR and ^{13}C NMR spectra; the new chain formed $Si(CH_2)_2S$ presented in the ^{1}H NMR two multiplets at δ 0.87 ($SiCH_2$) and at 2.60 (CH_2S) and in the ^{13}C NMR two signals at δ 13.5 ($SiCH_2$) and at 26.0 (CH_2S); and the resonances of the new chain introduced $S(CH_2)_2NMe_2H$ were also observed. Next, basic treatment of **2** led to the neutral dendron $ClG_1(S\text{-}NMe_2)$ (**3**) that was obtained as a yellowish oil. The ^{1}H NMR spectrum showed a clear shifting of the NMe_2 groups from δ 2.73 in **2** to δ 2.24 in **3**. Finally, addition of MeI to **3** afforded the cationic dendron $[ClG_1(S\text{-}NMe_3)_2]^{2+}$ (**4**), which was isolated as a pale yellow solid. In this case, the resonances of the Me_3N^+ groups were shifted to higher frequency, being observed in the ^{1}H NMR spectrum at δ 3.07.

Again, the reaction of dendron $[ClG_1(S\text{-}NMe_3)_2]^{2+}$ (**4**) with PenVK (Scheme 1) did not render the desired dendron, once again observing the rupture of the β-lactam ring by means of modification

Scheme 1. Failed attempts to obtained penicillin (PenV) functionalized dendrons containing sulfur atoms.



Scheme 2. Synthesis of carbosilane dendrons containing peripheral Si–H bonds and a Cl–C bond at the focal point $ClG_n(SiH)_m$ (n = 1, m = 2 (**6**); n = 2, m = 4 (**10**)). (*i*) $HSiMe_2Cl$, 60 °C, [Pt], 4 h; (*ii*) $LiAlH_4$, Et_2O, 0 °C to room temperature, 16 h; (*iii*) $HSiMeCl_2$, 60 °C, [Pt], 4 h; (*iv*) BrMg(allyl), Et_2O, 0 °C to room temperature, 16 h.



of their resonances in the ^{1}H NMR spectrum. In this case, this β-lactam ring probably suffered a nucleophilic attack of the thioether function. It is important to note that this reaction requires heating over 80 °C.

To bypass all these drawbacks in the synthesis of a cationic carbosilane dendron containing a PenV moiety, we moved to modification of the dendron surface by hydrosilylation processes instead of thiol-ene addition, with the aim to avoid the presence of any donor atom in the final dendron. This methodology successfully allowed us to prepare cationic dendrons with PenV at the focal point.

Thus, starting from ClG_1A_2[54] and using typical reactions for the preparation of carbosilane dendritic systems (hydrosilylation, alkenylation, and Cl–H substitution; Scheme 2),[58] we obtained dendrons with a Cl–C bond at the focal point and Si–H peripheral groups $ClG_n(SiH)_m$ (n = 1, m = 2 (**6**); n = 2, m = 4 (**10**)). Treatment of these derivatives with allyldimethylamine in the presence of Karstedt's catalyst[59] afforded the neutral dendrons $ClG_n(Si\text{-}NMe_2)_m$ (n = 1, m = 2 (**11**); n = 2, m = 4 (**12**) (Scheme 3). NMR spectroscopy clearly showed the incorporation of the new propylene chain ($Si(CH_2)_3N$) to the dendrimer structure by means of the resonances in the ^{1}H NMR spectra at δ ca. 0.44 ($SiCH_2$), 1.40 (CH_2), and 2.20 (CH_2N) and in the ^{13}C NMR spectra at δ ca. 12.8 ($SiCH_2$), 22.1 (CH_2), and 63.4 (CH_2N). These compounds were easily transformed into the cationic ones $[ClG_n(Si\text{-}NMe_3)_m]^{m+}$ (n = 1, m = 2 (**13**); n = 2, m = 4 (**14**) by addition of MeI (Scheme 3; Fig. 1). The typical shifting to higher frequency of the methyl (MeN) resonances was observed in the ^{1}H NMR spectra (Supplementary Figs. S1 and S2). Subsequent heating of **13** and **14** with PenVK yielded the goal dendrons $[(PenV)G_n(Si\text{-}NMe_3)_m]^{m+}$ (n = 1, m = 2 (**15**); n = 2, m = 4 (**16**) (Scheme 3; Fig. 1), which were isolated in good yields as highly hygroscopic pale yellow solids. The solubility was generation dependent, being G1 dendron soluble in chlorinated solvents, alcohols, and DMSO but not in water, whereas G2 dendron was soluble in water and other highly polar solvents but not in chlorinated solvents. NMR (Figs. 2 and 3), MS (Supplementary Fig. S3), and elemental analysis were in accordance with this formulation. The main NMR data confirming formation of these dendrons were the resonances associated to the ester fragment. The CH_2O group was observed at about δ 4.1 and δ 67 in the ^{1}H and ^{13}C spectra, respectively, and the corresponding carbon atom of the carbonyl group at about δ 173 in the ^{13}C spectra. Furthermore, the binding of PenV to the dendron was confirmed by DOSY NMR, showing the joint diffusion of both moieties (Supplementary Fig. S3), in comparison with the mixture of PenV and dendron **14** (Supplementary Fig. S6). The formation and stability of the dendrons containing the PenV moi-

Scheme 3. Synthesis of dendrons $[(PenV)G_n(Si\text{-}NMe_3)_m]^{m+}$ (n = 1, m = 2 (**15**); n = 2, m = 4 (**16**)) with PenV at the focal point and cationic peripheral groups derived by hydrosilylation. (*i*) (allyl)NMe_2, 60 °C, [Pt]; (*ii*) MeI, THF, room temperature, 16 h; (*iii*) PenVK, ether crown 18C6, NaI, DMF, 80 °C, 40 h.

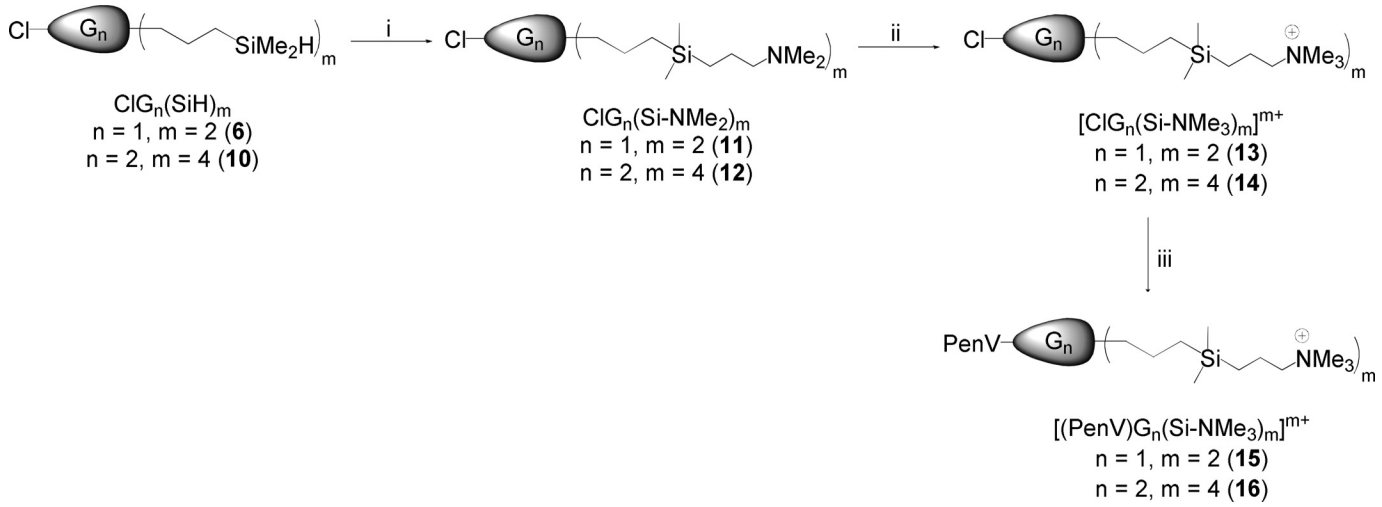
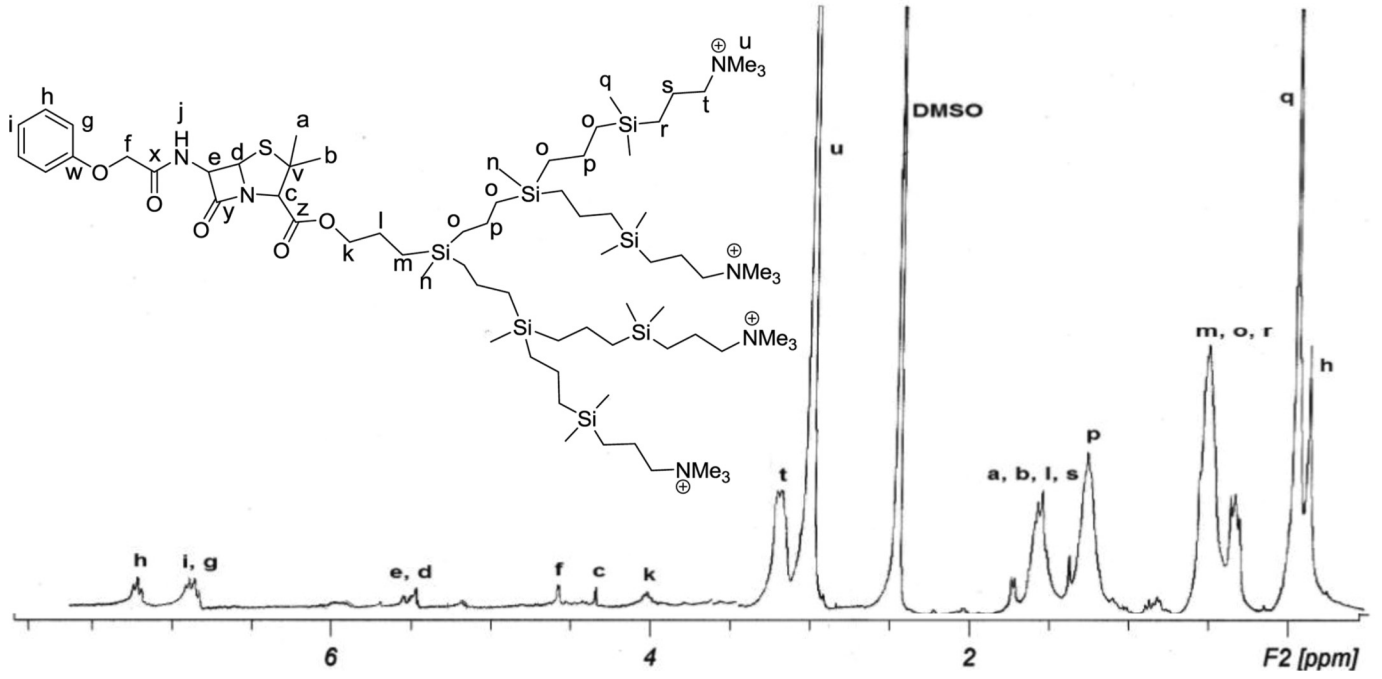


Fig. 2. ^1H NMR of $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**) in DMSO-D6.



ety **14** and **16** following this route confirms that the presence of donor atoms such as S or N in the dendron structure was responsible of β-lactam ring degradation.

Antibacterial activity

For the study of the biocidal capacity of dendrons, *S. aureus* was chosen as a model of gram-positive bacteria, as penicillin is a specific antibiotic for this type of bacteria. Figure 1 depicts drawings of cationic dendrons employed for the assays. To ascertain the effect of the PenV moiety in dendron $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**), a comparative study of the antibacterial activity of this dendron with its parent compound $[ClG_2(Si\text{-}NMe_3)_4]^{4+}$ (**14**) and an equimolecular mixture of PenVK salt plus dendron **14** was carried out. Table 1 summarizes the MIC and MBC of these dendrons.

The data obtained point out the following facts: (*i*) there were slight differences in the antibacterial response of dendrons with or without PenV at the focal point $[ClG_2(Si\text{-}NMe_3)_4]^{4+}$ (**14**) and $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**); (*ii*) there was much lower activity of the PenV fragment in **16** than that of the free PenV; and (*iii*) a MIC for the stoichiometric mixture of PenVK and **14** was similar to that obtained for free PenVK, whereas the MBC increased to 0.78 ppm (with respect to PenV), which was much higher than that of free PenVK.

The decrease of the bactericide activity (MBC) of the mixture PenVK–**14** compared with free PenVK could be explained in terms of availability of the antibiotic, because PenV is an anionic compound capable of interacting with the cationic dendron[50] and, thus, likely to diminish its availability. Comparison of the diffusion coefficients of free PenVK and PenVK in an equimolecular

Fig. 3. ^{13}C NMR of $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**) in DMSO-D6.

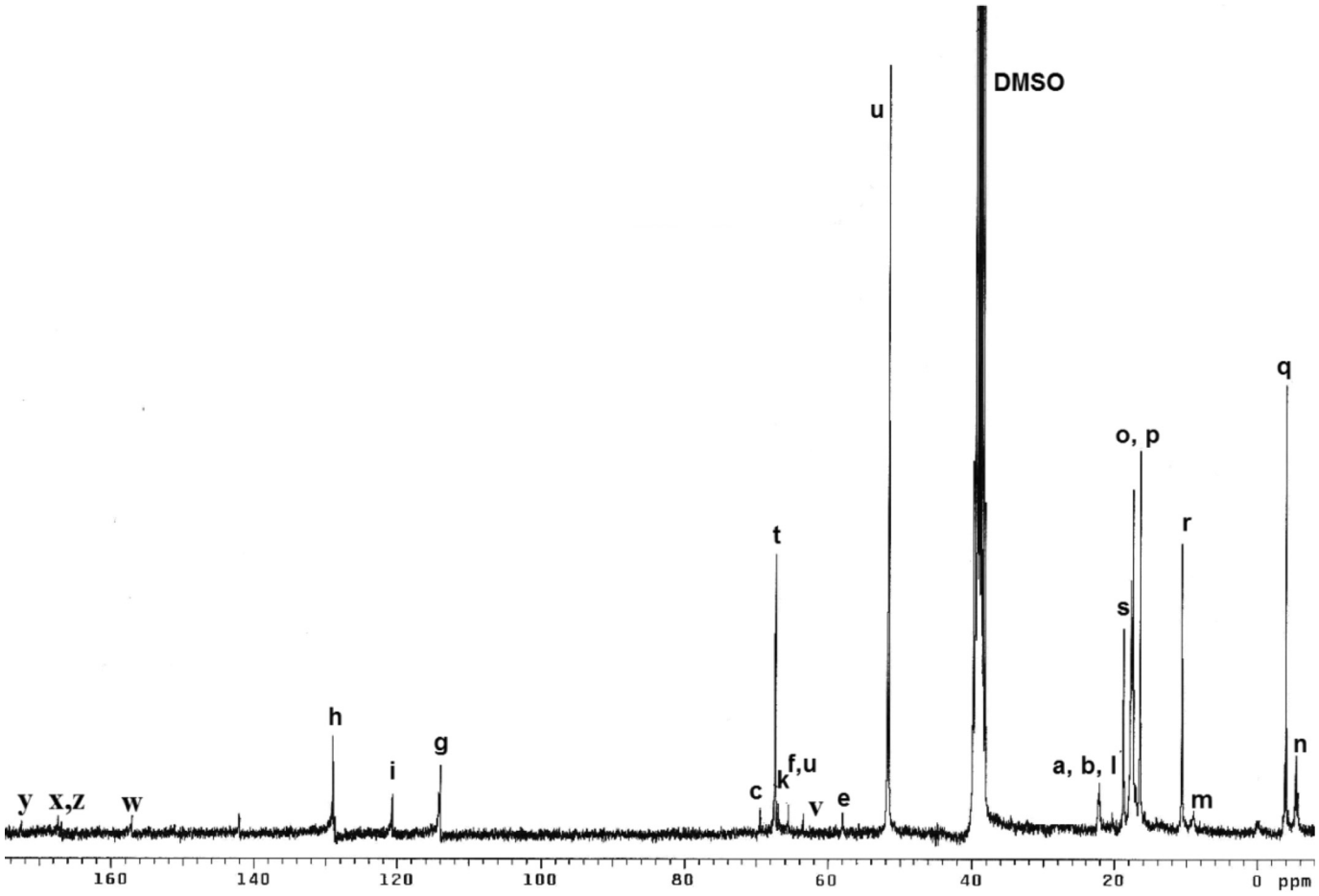


Table 1. Antibacterial activity of PenV, dendrons $[XG_2(Si\text{-}NMe_3)_4]^{4+}$ (X = Cl, **14**; PenV, **16**), and equimolecular mixture of PenVK and **14** against *S. aureus.*

	MIC		MBC	
	ppm	$[NR_3^+]$	ppm	$[NR_3^+]$
PenVK	0.016	—	0.031	—
14	8	20	8	20
PenVK–**14**	0.012[a]	0.14	0.78[a]	9
16	2.91[a]	33	2.91[a]	33
16–esterease	0.95[a]	3.70	0.95[a]	3.70

Note: $[NR_3^+]$ refers to the μmol/L concentration of ammonium groups.

[a]refers to ppm concentration of PenV.

mixture with dendron $[ClG_2(Si\text{-}NMe_3)_4]^{4+}$ (**14**) by DOSY 2D NMR experiments showed that this coefficient is clearly smaller when the dendron is present. This means that diffusion of PenVK is affected by the dendron, supporting the assessment of interaction between both systems (Supplementary Fig. S6). Although in our case the dendron–PenV interaction seems to difficult the action of the antibiotic, it has been reported that electrostatic interaction between β-lactam antibiotics and a polymer containing cationic cobaltocenium units exhibit synergistic effects against methicillin resistant *S. aureus* by efficiently inhibiting activity of β-lactamase and effectively lysing bacterial cells.[60]

In the case of dendron $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**) with a covalently bonded PenV, the higher inhibitory and bactericidal concentration values with respect to free PenVK are probably due to the fact that the ester bond is not adequately split in solution. The activity of PenV requires the availability of the carboxylate moiety, which also favours its stability, as the formation of the ester bond to conjugate penicillin to the dendron alters the crucial equilibrium between stability and activity of the β-lactam ring.[61] Thus, the presence of this ester bond triggers the reactivity of the ring, thereby affecting their activity.

With the aim of facilitating the release of the penicillin fragment by rupture of the ester bond, we tested the antibacterial activity of dendron $[(PenV)G_2(Si\text{-}NMe_3)_4]^{4+}$ (**16**) in the presence of porcine liver esterase. For this experiment, we initially added one unit of esterase per ester bond. From the first moment, the activity increased (MIC = 0.95 ppm and MBC = 0.95 ppm, with respect to the concentration of PenV), confirming the splitting of the ester bond. However, the obtained values were different from those for free PenV in the absence of dendron. This may be due to the electrostatic interactions of free PenV with the dendron or also to partial degradation of penicillin previous to its release from dendron. Addition of excess esterase did not affect the behavior observed in this experiment.

Conclusions

Carbosilane cationic dendrons with a penicillin moiety at the focal point can be obtained, employing the carboxylate group of penicillin (PenV) to be attached to the dendron. However, the synthetic protocol requires avoiding the presence of donor atoms or groups to avoid degradation of the β-lactam ring, which is responsible for the penicillin activity.

Evaluation of the activity of this dendron (**16**) and of a mixture of cationic dendron (**14**) and free PenV revealed that both covalent

conjugation of PenV to the dendron or electrostatic interaction between PenV and the cationic dendron reduced penicillin activity. These phenomena can be ascribed to the blocking of the carboxylate group of penicillin, which also favours the hydrolysis of the β-lactam ring. Hydrolysis of the ester bond in dendron **16** with an esterase increases the activity, without reaching the values of free penicillin. However, the release of penicillin in this system could be useful to apply similar compounds in drug release of drugs where the carboxylate unit does not play a key role in its therapeutic action.

Supplementary data

Supplementary data, including complete experimental procedures and selected NMR spectra, are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2017-0059.

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References

(1) Lode, H. M. *Clin. Microbiol. Infect.* **2009**, *15*, 212. doi:10.1111/j.1469-0691.2009.02738.x.
(2) Gonzales, F. P.; Maisch, T. *Drug News Perspect.* **2010**, *23*, 167. doi:10.1358/dnp.2010.23.3.1444225.
(3) Blair, J. M. A.; Webber, M. A.; Baylay, A. J.; Ogbolu, D. O.; Piddock, L. J. *Nat. Rev. Microbiol.* **2015**, *13*, 42. doi:10.1038/nrmicro3380.
(4) *Antimicrobial Resistance: Global Report on Surveillance* [online]; World Health Organization: Geneva, 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf.
(5) Donlan, R. M. *Emerg. Infect. Dis.* **2002**, *8*, 881. doi:10.3201/eid0809.020063.
(6) Bryers, J. D. In *Microbial Biofilms: Current Research and Applications*; Lear, G., Lewis, G. D., Eds.; Caister Academic Press: Poole, UK, 2012; pp. 25–42.
(7) Muñoz-Bonilla, A.; Fernández-García, M. *Prog. Polym. Sci.* **2012**, *37*, 281. doi:10.1016/j.progpolymsci.2011.08.005.
(8) Coates, A.; Hu, Y.; Bax, R.; Page, C. *Nat. Rev. Drug Discovery* **2002**, *1*, 895. doi:10.1038/nrd940.
(9) Clifton, L. A.; Skoda, M. W. A.; Le Brun, A. P.; Ciesielski, F.; Kuzmenko, I.; Holt, S. A.; Lakey, J. H. *Langmuir* **2015**, *31*, 404. doi:10.1021/la504407v.
(10) Tischer, M.; Pradel, G.; Ohlsen, K.; Holzgrabe, U. *ChemMedChem* **2012**, *7*, 22. doi:10.1002/cmdc.201100404.
(11) Panarin, E. F.; Solovskii, M. V.; Zaikina, N. A.; Afinogenov, G. E. *Makromol. Chem., Suppl.* **1985**, *9*, 25. doi:10.1002/macp.1985.020091985104.
(12) Tompkin, R. B. *Food Technol.* **1984**, *38*, 226.
(13) Dizman, B.; Elasri, M. O.; Mathias, L. J. *J. Appl. Polym. Sci.* **2004**, *94*, 635. doi:10.1002/app.20872.
(14) Osamura, T.; Ozawa, M.; Iwama, T. Patent JP2011037716A, 2011.
(15) Mintzer, M. A.; Dane, E. L.; O'Toole, G. A.; Grinstaff, M. W. *Mol. Pharmaceutics* **2012**, *9*, 342. doi:10.1021/mp2005033.
(16) Lazniewska, J.; Milowska, K.; Gabryelak, T. *WIREs Nanomed. Nanobiotechnol.* **2012**, *4*, 469. doi:10.1002/wnan.1181.
(17) Ikeda, T.; Hirayama, H.; Yamaguchi, H.; Tazuke, S.; Watanabe, M. *Antimicrob. Agents Chemother.* **1986**, *30*, 132. doi:10.1128/AAC.30.1.132.
(18) Newkome, G. R.; Shreiner, C. D. *Polymer* **2008**, *49*, 1. doi:10.1016/j.polymer.2007.10.021.
(19) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2719. doi:10.1002/pola.10301.
(20) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; Wiley-VCH: Weinheim, 2002. doi:10.1002/0470845821.
(21) Wang, B.; Navath, R. S.; Menjoge, A. R.; Balakrishnan, B.; Bellair, R.; Dai, H.; Romero, R.; Kannan, S.; Kannan, R. M. *Int. J. Pharm.* **2010**, *395*, 298. doi:10.1016/j.ijpharm.2010.05.030.
(22) Chen, C. Z.; Beck-Tan, N. C.; Dhurjati, P.; van Dyk, T. K.; LaRossa, R. A.; Cooper, S. L. *Biomacromolecules* **2000**, *1*, 473. doi:10.1021/bm0055495.
(23) Ciepluch, K.; Katir, N.; El Kadib, A.; Felczak, A.; Zawadzka, K.; Weber, M.; Klajnert, B.; Lisowska, K.; Caminade, A.-M.; Bousmina, M.; Bryszewska, M.; Majoral, J. P. *Mol. Pharmaceutics* **2012**, *9*, 448. doi:10.1021/mp200549c.
(24) Rasines, B.; Hernández-Ros, J. M.; de las Cuevas, N.; Copa-Patiño, J. L.; Soliveri, J.; Muñoz-Fernández, M. A.; Gómez, R.; de la Mata, F. J. *Dalton Trans.* **2009**, 8704. doi:10.1039/B909955G.
(25) Tulu, M.; Aghatabay, N. M.; Senel, M.; Dizman, C.; Parali, T.; Dulger, B. *Eur. J. Med. Chem.* **2009**, *44*, 1093. doi:10.1016/j.ejmech.2008.06.016.
(26) Chen, C. Z.; Cooper, S. L. *Biomaterials* **2002**, *23*, 3359. doi:10.1016/S0142-9612(02)00036-4.
(27) Janiszewska, J.; Sowińska, M.; Rajnisz, A.; Solecka, J.; Łącka, I.; Milewski, S.; Urbańczyk-Lipkowska, Z. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1388. doi:10.1016/j.bmcl.2011.12.051.
(28) Ghosh, S.; Banthia, A. K. *J. Biomed. Mater. Res., Part A* **2004**, *71A*, 1. doi:10.1002/jbm.a.30121.
(29) Moussodia, R.-O.; Balan, L.; Merlin, C.; Mustin, C.; Schneider, R. *J. Mater. Chem.* **2010**, *20*, 1147. doi:10.1039/B917629B.
(30) Öberg, K.; Ropponen, J.; Kelly, J.; Löwenhielm, P.; Berglin, M.; Malkoch, M. *Langmuir* **2013**, *29*, 456. doi:10.1021/la3041314.
(31) Kesharwani, P.; Jain, K.; Jain, N. K. *Prog. Polym. Sci.* **2014**, *39*, 268. doi:10.1016/j.progpolymsci.2013.07.005.
(32) Gillies, E. R.; Fréchet, J. M. J. *Drug Discovery Today* **2005**, *10*, 35. doi:10.1016/S1359-6446(04)03276-3.
(33) Sonawane, S. J.; Kalhapure, R. S.; Rambharose, S.; Mocktar, C.; Vepuri, S. B.; Soliman, M.; Govender, T. *Int. J. Pharm.* **2016**, *504*, 1. doi:10.1016/j.ijpharm.2016.03.021.
(34) Wrońska, N.; Felczak, A.; Zawadzka, K.; Poszepczyńska, M.; Różalska, S.; Bryszewska, M.; Appelhans, D.; Lisowska, K. *Molecules* **2015**, *20*, 19330. doi:10.3390/molecules201019330.
(35) Aghayari, M.; Salouti, M.; Kazemizadeh, A. R.; Zabihian, A.; Hamidi, M.; Shajari, N.; Moghtader, F. *Sci. Iran.* **2015**, *22*, 1330.
(36) Winnicka, K.; Wroblewska, M.; Wieczorek, P.; Sacha, P. T.; Tryniszewska, E. A. *Molecules* **2013**, *18*, 8607. doi:10.3390/molecules18078607.
(37) Felczak, A.; Zawadzka, K.; Wrońska, N.; Janaszewska, A.; Klajnert, B.; Bryszewska, M.; Appelhans, D.; Voit, B.; Lisowska, K. *New J. Chem.* **2013**, *37*, 4156. doi:10.1039/c3nj00760j.
(38) Ngu-Schwemlein, M.; Chin, S. F.; Hileman, R.; Drozdowski, C.; Upchurch, C.; Hargrove, A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1745. doi:10.1016/j.bmcl.2016.02.047.
(39) Michaud, G.; Visini, R.; Bergmann, M.; Salerno, G.; Bosco, R.; Gillon, E.; Richichi, B.; Nativi, C.; Imberty, A.; Stocker, A.; Darbre, T.; Reymond, J. L. *Chem. Sci.* **2016**, *7*, 166. doi:10.1039/C5SC03635F.
(40) Zhou, Y.-J.; Zhang, M.-X.; Hider, R. C.; Zhou, T. *FEMS Microbiol. Lett.* **2014**, *355*, 124. doi:10.1111/1574-6968.12465.
(41) van der Made, A. W.; van Leeuwen, P. W. N. M.; de Wilde, J. C.; Brandes, R. A. C. *Adv. Mater.* **1993**, *5*, 466. doi:10.1002/adma.19930050613.
(42) van der Made, A. W.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Chem. Commun.* 1992, 1400. doi:10.1039/C39920001400.
(43) Ortega, P.; Cobaleda, B. M.; Hernández-Ros, J. M.; Fuentes-Paniagua, E.; Sánchez-Nieves, J.; Tarazona, M. P.; Copa-Patiño, J. L.; Soliveri, J.; de la Mata, F. J.; Gómez, R. *Org. Biomol. Chem.* **2011**, *9*, 5238. doi:10.1039/c1ob05321c.
(44) Fuentes-Paniagua, E.; Hernández-Ros, J. M.; Sánchez-Milla, M.; Camero, M. A.; Maly, M.; Pérez-Serrano, J.; Copa-Patiño, J. L.; Sánchez-Nieves, J.; Soliveri, J.; Gómez, R.; de la Mata, F. J. *RSC Adv.* **2014**, *4*, 1256. doi:10.1039/C3RA45408H.
(45) Heredero-Bermejo, I.; Copa-Patiño, J. L.; Soliveri, J.; Fuentes-Paniagua, E.; de la Mata, F. J.; Gómez, R.; Pérez-Serrano, J. *Parasitol. Res.* **2015**, *114*, 473. doi:10.1007/s00436-014-4205-1.
(46) Heredero-Bermejo, I.; Copa-Patiño, J. L.; Soliveri, J.; García-Gallego, S.; Rasines, B.; Gómez, R.; de la Mata, F. J.; Pérez-Serrano, J. *Parasitol. Res.* **2013**, *112*, 961. doi:10.1007/s00436-012-3216-z.
(47) Fuentes-Paniagua, E.; Sánchez-Nieves, J.; Hernández-Ros, J. M.; Fernández-Ezequiel, A.; Soliveri, J.; Copa-Patiño, J. L.; Gómez, R.; de la Mata, F. J. *RSC Adv.* **2016**, *6*, 7022. doi:10.1039/C5RA25901K.
(48) Heredero-Bermejo, I.; Sánchez-Nieves, J.; Soliveri, J.; Gómez, R.; de la Mata, F. J.; Copa-Patiño, J. L.; Pérez-Serrano, J. *Int. J. Pharm.* **2016**, *509*, 1. doi:10.1016/j.ijpharm.2016.04.075.
(49) Cottarel, G.; Wierzbowski, J. *Trends Biotechnol.* **2007**, *25*, 547. doi:10.1016/j.tibtech.2007.09.004.
(50) Rasines, B.; Sánchez-Nieves, J.; Molina, I. T.; Guzmán, M.; Muñoz-Fernández, M. Á.; Gómez, R.; de la Mata, F. J. *New J. Chem.* **2012**, *36*, 360. doi:10.1039/C1NJ20374F.
(51) Perisé-Barrios, A. J.; Fuentes-Paniagua, E.; Sánchez-Nieves, J.; Serramía, M. J.; Alonso, E.; Reguera, R. M.; Gómez, R.; de la Mata, F. J.; Muñoz-Fernández, M. Á. *Mol. Pharmaceutics* **2016**, *13*, 3427. doi:10.1021/acs.molpharmaceut.6b00420.
(52) Fuentes-Paniagua, E.; Peña-González, C. E.; Galán, M.; Gómez, R.; de la Mata, F. J.; Sánchez-Nieves, J. *Organometallics* **2013**, *32*, 1789. doi:10.1021/om301217g.
(53) Downing, C. M.; Missaghi, M. N.; Kung, M. C.; Kung, H. H. *Tetrahedron* **2011**, *67*, 7502. doi:10.1016/j.tet.2011.07.068.
(54) Wolf, C.; Pirkle, W. H. *J. Chromatogr. A* **1998**, *799*, 177. doi:10.1016/S0021-9673(97)01063-7.
(55) *Clinical laboratory testing and in vitro diagnostic test systems – Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices – Part 1: Reference methods for the testing the in vitro activity of antimicrobial agents against bacteria involved in infectious diseases*; ISO 20776-1, 2016.
(56) Montañez, M. I.; Mayorga, C.; Torres, M. J.; Blanca, M.; Perez-Inestrosa, E. *Nanomedicine–Nanotechnol., Biol., Med.* **2011**, *7*, 682. doi:10.1016/j.nano.2011.07.008.
(57) Llinás, A.; Vilanova, B.; Muñoz, F.; Donoso, J. *J. Mol. Catal. A: Chem.* **2001**, *175*, 3. doi:10.1016/S1381-1169(01)00203-5.

(58) Sánchez-Nieves, J.; Ortega, P.; Muñoz-Fernández, M. Á.; Gómez, R.; de la Mata, F. J. *Tetrahedron* **2010**, *66*, 9203. doi:10.1016/j.tet.2010.09.063.
(59) Pedziwiatr-Werbicka, E.; Fuentes, E.; Dzmitruk, V.; Sánchez-Nieves, J.; Sudas, M.; Drozd, E.; Shakhbazau, A.; Shcharbin, D.; de la Mata, F. J.; Gómez-Ramírez, R.; Muñoz-Fernández, M. Á.; Bryszewska, M. *Colloids Surf., B* **2013**, *109*, 183. doi:10.1016/j.colsurfb.2013.03.045.
(60) Zhang, J.; Chen, Y.-P.; Miller, K. P.; Ganewatta, M. S.; Bam, M.; Yan, Y.; Nagarkatti, M.; Decho, A. W.; Tang, C. *J. Am. Chem. Soc.* **2014**, *136*, 4873. doi:10.1021/ja5011338.
(61) Mucsi, Z.; Chass, G. A.; Ábrányi-Balogh, P.; Jójárt, B.; Fang, D.-C.; Ramírez-Cuesta, A. J.; Viskolcz, B.; Csizmadia, I. G. *Phys. Chem. Chem. Phys.* **2013**, *15*, 20447. doi:10.1039/c3cp50868d.

For Supporting Information

Strategies for Penicillin V dendronization with cationic carbosilane dendrons and study of antibacterial properties

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S.1. Experimental Section

S.1.1. General Considerations. All reactions were carried out under inert atmosphere and solvents were purified from appropriate drying agents when necessary. NMR spectra were recorded on a Varian Unity VXR-300 (300.13 (^{1}H), 75.47 (^{13}C) MHz) or on a Bruker AV400 (400.13 (1H), 100.60 (^{13}C), 40.56 (^{15}N), 79.49 (^{29}Si) MHz). Chemical shifts (δ) are given in ppm. ^{1}H and ^{13}C resonances were measured relative to internal deuterated solvent peaks considering TMS = 0 ppm, meanwhile ^{29}Si resonances were measured relative to external TMS employing ^{1}H-^{29}Si HMBC experiments. When necessary, assignment of resonances was done from HSQC, HMBC, COSY, TOCSY and NOESY NMR experiments. Thiol-ene reactions were carried out employing a HPK 125 W mercury lamp from Heraeus Noblelight with maximum energy at 365 nm, in normal glassware under an inert atmosphere. Elemental analyses were performed on a LECO CHNS-932. Mass Spectra were obtained from an Agilent 6210. Compounds, $HS(CH_2)_2NMe_2 \cdot HCl$ (Acros), 2,2'-dimethoxy-2-phenylacetophenone (DMPA) (Aldrich), MeI (Aldrich), $HSiMe_2Cl$ (ABCR), $HSiMeCl_2$ (Aldrich), $LiAlH_4$ (Acros), K_2CO_3 (Panreac), penicillin V potassium salt (PenVK), platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex solution (Karsted's catalyst), porcine liver esterease (PLE) were obtained from commercial sources. Compounds $NH_2G_n(NMe_2)_m$,[1] $[NH_2G_n(S\text{-}NMe_3)_m]^{m+1}$,[2] ClG_1V_2,[3] and ClG_1A_2[4] were synthesized as published.

S.1.2. Synthesis of compounds.

$PenG_1V_2$ (1). PenVK (0.177 g, 0.46 mmol) and BrG_1V_2 (0.119 g, 0.46 mmol) were heated (80 ºC) in a sealed ampoule in DMF in presence of 18C6 (0.012 g, 0.04 mmol) and catalytic amounts of NaI overnight. Then, volatiles were removed and a CH_2Cl_2/H_2O(NaCl) extraction was performed and the organic phase was dried over $MgSO_4$ and SiO_2. Finally, dendron **1** (0.157 g, 64 %) was obtained after removing the volatiles.

^{1}H-NMR ($CDCl_3$): δ -0.02 (s, 3 H, Si*Me*), 0.56 (t, J_a = 8.5 Hz, 2 H, SiCH_2), 1.38 (m, 4 H, CH_2CH_2Si), 1.48 (s, 3 H, C*Me*$_2$), 1.58 (s, 3 H, C*Me*$_2$), 1.68 (m, 2 H, OCH$_2$CH_2), 4.16 (m, 2 H, (CO)OCH_2), 4.44 (s, 1 H, C*H*(CO)), 4.54 (s, 2 H, OCH_2CO), 5.56 (d, J_b = 4.1 Hz, 1 H, C*H*S), 5.70 (m, 3 H, NHC*H,* SiC*H*CH$_2$), 6.03

(m, 4 H, SiCHCH_2), 6.91 (d, J_c = 7.9 Hz, 2 H, CH_{Ar}), 7.01 (t, J_d = 7.4 Hz, 1 H, CH_{Ar}), 7.31 (m, 2 H, CH_{Ar}). $^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -5.9 (Si*Me*), 12.6 (*C*H_2Si), 20.1 (*C*H_2CH_2Si), 26.8 and 32.1 (SC*Me*$_2$), 31.9 (*C*H_2CH_2CH_2Si), 58.0 (NH*C*H), 64.7 (S*C*Me$_2$), 65.4 (COO*C*H_2), 67.1 (O*C*H_2CO), 67.8 (*C*HS), 70.5 (*C*HCOO), 114.7 (*C*H_{Ar}), 122.4 (*C*H_{Ar}), 129.8 (*C*H_{Ar}), 133.1 (SiCH*C*H_2), 136.6 (Si*C*HCH$_2$), 156.9 (*C*O$_{Ar}$), 167.6, 167.8 and 173.0 (*C*=O). MALDI: $[M+Na]^+$ = 525.19 uma (calcd. = 525.19 uma). Anal. Calcd. $C_{25}H_{34}N_2O_5SSi$ (502.70 g/mol): C, 59.73; H, 6.82; N, 5.57;Exp.: C, 60.22; H, 7.48; N, 6.16.

ClG_1(S-NMe_2·HCl)$_2$ (2). A mixture of ClG_1V_2 (0.200 g, 1.14 mmol), 2-(dimethylamino)ethanethiol hydrochloride (0.331 g, 2.34 mmol) and DMPA (0.054 g, 0.21 mmol) in THF/MeOH (2 mL/8 mL) were stirred under inert atmosphere and UV irradiated for 5 h. The amount of DMPA was added in two portions, one at the beginning of reaction and one after 2 h. Next, volatiles were removed under vacuum and the remaining solid was solved in the minimum amount of MeOH and precipitated with Et_2O (twice) to afford **2** as pale yellow solid (0.383 g, 76 %).

^{1}H-NMR (DMSO-d_6): δ -0.06 (s, 3 H, Si*Me*), 0.59 (m, 2 H, SiCH_2), 0.87 (t, J_a = 8.3 Hz, 4 H, SiCH_2CH$_2$S), 1.66 (m, 2 H, ClCH$_2$CH_2), 2.60 (t, J_a = 8.3 Hz, 4 H, SiCH$_2$CH_2S), 2.73 (s, 12 H, -N*Me*$_2$·HCl), 2.85 (t, J_b = 7.4 Hz, 4 H, SCH_2CH$_2$N$^+$), 3.20 (t, J_b = 7.4 Hz, 4 H, SCH$_2$CH_2N$^+$), 3.59 (t, J_c = 6.5 Hz, 2 H, ClCH_2). $^{13}C\{^1H\}$-NMR (DMSO-d_6): δ -5.71 (Si*Me*), 10.4 (ClCH$_2$CH$_2$*C*H$_2$), 13.5 (Si*C*H$_2$CH$_2$S), 24.2 (S*C*H$_2$CH$_2$N$^+$), 26.0 (SiCH$_2$*C*H$_2$S), 26.8 (ClCH$_2$*C*H$_2$), 41.4 (-N*Me*$_2$·HCl), 47.9 (Cl*C*H$_2$), 55.3 (*C*H$_2$N$^+$). ^{15}N-NMR (DMSO-d_6): -339.0 (-*N*Me$_2$H$^+$). ^{29}Si-NMR (DMSO-d_6): δ 2.2. ESI: q = 1 (421.17 $[M-Cl]^+$). Anal. Calc. $C_{16}H_{39}Cl_3N_2S_2Si$ (458.07 g/mol): C, 41.95; H, 8.58; N, 6.12; S, 14.00; Exp.: C, 41.94; H, 8.93; N, 5.49; S, 11.44.

ClG_1(S-NMe_2)$_2$ (3). This dendrimer was obtained mixing **2** (0.210 g, 0.41 mmol) and Na_2CO_3 (0.092 g, 0.87 mmol) in $CHCl_3/H_2O$, extracting the organic fraction and removing the solvent under vacuum. This procedure yielded **3** as a yellowish oil (0.174 g, 98 %).

^{1}H-NMR ($CDCl_3$): δ -0.06 (s, 3 H, *SiMe*), 0.58 (m, 2 H, ClCH$_2$CH$_2$CH_2Si), 0.88 (t, J_a = 8.7 Hz, 4 H, SiCH_2CH$_2$S), 1.70 (m, 2 H, ClCH$_2$CH_2), 2.24 (s, 12 H, -N*Me*$_2$), 2.47 (m, 4 H, SCH$_2$CH_2N), 2.52 (m, 4 H,

$SiCH_2CH_2S$), 2.59 (m, 4 H, SCH_2CH_2N), 3.49 (t, J_b = 6.8 Hz, 2 H, $ClCH_2$). $^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -5.3 (*Me*Si), 11.5 ($ClCH_2CH_2CH_2$), 14.6 ($SiCH_2CH_2S$), 27.7 ($SiCH_2CH_2S$), 29.9 ($SCH_2CH_2NMe_2$), 45.4 (NMe_2), 48.1 ($ClCH_2$), 59.3 ($SCH_2CH_2NMe_2$). ^{29}Si-NMR ($CDCl_3$): δ 2.1. MALDI: $[M+H]^+$ = 385.19 uma. Anal. Calc. $C_{16}H_{37}ClN_2S_2Si$ (385.15 g/mol): C, 49.90; H, 9.68; N, 7.27; S, 16.65; Exp.: C, 48.99; H, 10.38; N, 6.81; S, 16.84.

$ClG_1(S\text{-}NMe_3I)_2$ (4). A mixture of **3** (0.175 g, 0.45 mmol) and MeI (0.06 mL, 0.96 mmol) was stirred in THF for 16 h. Afterward, volatiles were removed under vacuum and the remainnig solid was washed with Et_2O (2 x 50 mL) to obtain **4** as a white solid (0.268 g, 89 %).

^{1}H-NMR (DMSO-d_6): δ -0.06 (s, 3 H, Si*Me*), 0.56 (m, 2 H, $ClCH_2CH_2CH_2Si$), 0.85 (m, 4 H, $SiCH_2CH_2S$), 1.67 (m, 2 H, $ClCH_2CH_2CH_2Si$), 2.56 (m, 4 H, $SiCH_2CH_2S$), 2.88 (m, 4 H, $SCH_2CH_2N^+$), 3.07 (s, 18 H, $-NMe_3^+$), 3.49 (m, 4 H, $SCH_2CH_2N^+$), 3.57 (m, 2 H, $ClCH_2$). $^{13}C\{^1H\}$-NMR (DMSO-d_6): δ -5.7 (*Me*Si), 10.3 ($ClCH_2CH_2CH_2Si$), 13.5 ($SiCH_2CH_2S$), 23.1 ($SCH_2CH_2N^+$), 26.3 ($SiCH_2CH_2S$), 26.8 ($ClCH_2CH_2$), 47.9 ($ClCH_2$), 51.6 ($-NMe_3^+$), 63.9 (CH_2N^+). ^{15}N-NMR (DMSO-d_6): δ -330.1 ($-NMe_3^+$). ^{29}Si-NMR (DMSO-d_6): δ 2.5. ESI: q = 2 (213.12 $[M-2I]^{2+}$). Anal. Calc. $C_{18}H_{43}ClI_2N_2S_2Si$ (669.02 g/mol): C, 32.31; H, 6.48; N, 4.19; S, 9.59; Obt.: C, 31.69; H, 5.93; N, 3.96; S, 8.96.

$ClG_1(SiCl)_2$ (5). A teflon-valve ampoule containing a solution of ClG_1A_2 (1.000 g, 4.93 mmol) and Kardsted's catalyst (3 % mol) in hexane (2 mL) was cooled to 0º C and $HSiMe_2Cl$ (2.15 mL, 19.77 mmol) was slowly added. After 30 min stirring at this temperature, the solution was warmed until 60º C and stirred for 4 h. Afterwards, volatiles were removed under vacuum, hexane was added (20 mL) and the solution was filtered through active carbon. Removal of volatiles under vacuum gave **5** as colorless oil (1.914 g, 99 %). This product is moisture sensitive and has to be stored under inert atmosphere.

^{1}H-NMR ($CDCl_3$): δ -0.05 (s, 3 H, *Me*Si), 0.38 (s, 12 H, Me_2SiCl), 0.52 (m, 6 H, $SiCH_2$), 0.88 (m, 4 H, CH_2SiCl), 1.25 (m, 6 H, CH_2), 1.85 (m, 2 H, $ClCH_2CH_2$), 3.47 (t, J = 6.9 Hz, 2 H, $ClCH_2$). $^{13}C\{^1H\}$-NMR ($CDCl_3$): -5.2 (*Me*Si), 1.8 (Me_2Si), 11.4 ($ClCH_2CH_2CH_2$), 17.6 (CH_2), 17.8 (CH_2), 23.4 (CH_2SiCl), 27.6 ($ClCH_2CH_2$), 48.0 ($ClCH_2$). ^{29}Si-NMR ($CDCl_3$): 2.3 (Me*Si*), 31.1 (Me_2*Si*Cl).

$ClG_1(SiH)_2$ (6). An Et_2O solution (40 mL) of **5** (0.229 g, 0.58 mmol) was slowly added to an Et_2O solution (20 mL) of $LiAlH_4$ (0.33 mL, 0.66 mmol) at 0 ºC and stirred overnight at room temperature. Afterward, the mixture was added over a saturated water solution of NH_4Cl (50 mL) at 0 ºC, the organic phase was separated and the aqueous phase was extracted twice with Et_2O. After drying the organic phase over $MgSO_4$ and SiO_2, the solution was filtered and the volatiles were removed under vacuum, yielding **6** as colorless oil (0.145 g, 76 %).

^{1}H-NMR ($CDCl_3$): δ -0.06 (s, 3 H, *Me*Si), 0.04 (d, J = 3.8 Hz, 12 H, *Me*$_2$SiH), 0.60 (m, 10 H, SiC*H*$_2$), 1.36 (m, 4 H,SiCH$_2$C*H*$_2$CH$_2$Si), 1.72 (m, 2 H, ClCH$_2$C*H*$_2$), 3.48 (t, J = 6.9 Hz, 2 H, ClC*H*$_2$), 3.82 (m, 2 H, Si*H*); ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.2 (*Me*Si), -4.4 (*Me*$_2$SiH), 11.6 (ClCH$_2$CH$_2$*C*H$_2$), 17.8, 18.8 and 18.9 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 27.7 (ClCH$_2$*C*H$_2$), 48.1 (Cl*C*H$_2$). ^{29}Si-NMR ($CDCl_3$): δ -14.1 (Me$_2$*Si*H), 2.3 (Me*Si*). Anal. Calc. $C_{14}H_{35}ClSi_3$ (323.14 g/mol): C, 52.04; H, 10.92; Obt.: C, 52.45; H, 10.60.

$ClG_2(SiMeCl_2)_2$ (7). $HSiMeCl_2$ (5.1 mL, 49.46 mmol) was added to a cooled (0º C) teflon-valve ampoule containing a solution of ClG_1A_2 (2.506 g, 12.37 mmol) and Kardsted's catalyst (3 % mol) in hexane (3 mL) and the solution was stirred for 4 h at 60º C. Afterward, volatiles were removed under vacuum, hexane was added (10 mL) and the solution was filtered through active carbon. Removal of volatiles under vacuum gave **7** as colorless liquid (5.299 g, 99 %). This product is moisture sensitive and has to be stored under inert atmosphere.

^{1}H-NMR ($CDCl_3$): δ -0.01 (s, 6 H, Si*Me*), 0.05 (s, 3H, Si*Me*), 0.66 (m, 6 H, ClCH$_2$CH$_2$C*H*$_2$SiC*H*$_2$), 0.76 (s, 6 H, *Me*SiCl$_2$), 1.19 (m, 4 H, C*H*$_2$SiMeCl$_2$), 1.52 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.74 (m, 2 H, ClCH$_2$C*H*$_2$), 3.50 (t, J =7.0 Hz, 2 H, ClC*H*$_2$); ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.3 (Si*Me*), 5.4 (*Me*SiCl$_2$), 11.2 (ClCH$_2$CH$_2$*C*H$_2$), 17.2 (Si*C*H$_2$), 17.2 (SiCH$_2$*C*H$_2$), 25.8 (*C*H$_2$SiCl$_2$), 27.5 (ClCH$_2$*C*H$_2$), 47.9 (Cl*C*H$_2$).; ^{29}Si-NMR ($CDCl_3$): δ 2.3 (Me*Si*), 32.2 (Me*Si*Cl$_2$).

ClG_2A_4 (8). Br$Mg(C_3H_5)$ (59.4 mL, 59.40 mmol) was slowly added to a cooled Et_2O solution of $ClG_2(SiMeCl_2)_2$ (5.299 g, 12.40 mmol). The reaction mixture was refluxed for 3 hours and afterwards stirred overnight at room temperature. Next, a water solution of NH_4Cl was added (12%), the organic phase

was separated and the aqueous phase was extracted twice with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and SiO_2. The solution was filtered through active carbon and the volatiles were removed under vacuum, yielding **8** as colorless liquid (5.246 g, 94 %).

^{1}H-NMR ($CDCl_3$): δ -0.07 (s, 3 H, *Me*Si), -0.03 (s, 6 H, *Me*Si(C_3H_5)$_2$), 0.58 (m, 8 H, C*H*$_2$Si), 1.32 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.52 (d, J_b = 8.2 Hz, 8 H, SiC*H*$_2$CH), 1.72 (m, 2 H, ClCH$_2$C*H*$_2$), 3.47 (t, J_c = 6.9 Hz, 2 H, ClC*H*$_2$), 4.83 (m, 8 H, CH=C*H*$_2$), 5.75 (m, 4 H, C*H*=CH$_2$). ^{13}C{^{1}H}-NMR ($CDCl_3$): *δ* -5.8 (*Me*Si(C_3H_5)$_2$), -5.2 (*Me*Si), 11.5 (ClCH$_2$CH$_2$*C*H$_2$), 17.9, 18.1 and 18.5 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 21.3 (*C*H$_2$CH=CH$_2$), 27.7 (ClCH$_2$*C*H$_2$), 48.0 (Cl*C*H$_2$), 113.0 (CH=*C*H$_2$), 134.8 (*C*H=CH$_2$); ^{29}Si-NMR ($CDCl_3$): 2.0 (G_1-*Si*Me), 0.1 (G_2-*Si*Me). Anal. Calc. $C_{25}H_{49}ClSi_3$ (469.37 g/mol): C, 63.97; H, 10.52; Exp.: C, 65.60; H, 10.10.

ClG$_2$(SiCl)$_4$ (9). This product was synthesized following the synthetic procedure described for **5** from **8** (1.058 g, 2.33 mmol) and $HSiMe_2Cl$ (2.0 mL, 18.38 mmol), obtainen **9** as colorless oil (1.861 g, 96 %).

^{1}H-NMR ($CDCl_3$): δ -0.07 (s, 6 H, *Me*Si), 0.05 (s, 3 H, Si*Me*), 0.38 (s, 24 H, *Me*$_2$SiCl), 0.57 (m, 18 H, SiC*H*$_2$), 0.86 (m, 8 H, C*H*$_2$SiCl), 1.28 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.42 (m, 8 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.80 (m, 2 H, ClCH$_2$C*H*$_2$), 3.47 (t, J = 6.9 Hz, 2 H, ClC*H*$_2$). ^{13}C{^{1}H}-NMR ($CDCl_3$): -5.0 (*Me*Si), 1.8 (*Me*$_2$Si), 11.6 (ClCH$_2$CH$_2$*C*H$_2$), 17.7-18.7 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 23.5 (*C*H$_2$SiCl), 27.8 (ClCH$_2$*C*H$_2$), 48.1 (Cl*C*H$_2$); ^{29}Si-NMR ($CDCl_3$): 2.1 (Me*Si*), 31.1 (Me$_2$*Si*Cl).

ClG$_2$(SiH)$_4$ (10). This product was obtained following the synthetic procedure described for **6** from **9** (1.861 g, 2.24 mmol) and $LiAlH_4$ (2.60 mL, 5.20 mmol), obtaining **10** as colorless oil (1.158 g, 75 %).

^{1}H-NMR ($CDCl_3$): δ -0.09 and -0.06 (s, 9 H, *Me*Si), 0.04 (d, J = 3.9 Hz, 24 H, *Me*$_2$SiH), 0.59 (m, 26 H, SiC*H*$_2$), 1.36 (m, 6 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.72 (m, 2 H, ClCH$_2$C*H*$_2$), 3.48 (t, J = 7.0 Hz, 2 H, ClC*H*$_2$), 3.84 (m, 4 H, Si*H*). ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.0 (*Me*Si), -4.4 (*Me*$_2$SiH), 11.7 (ClCH$_2$CH$_2$*C*H$_2$), 18.1-19.0 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 27.8 (ClCH$_2$*C*H$_2$), 48.1 (Cl*C*H$_2$). ^{29}Si-NMR ($CDCl_3$): δ -14.1 (Me$_2$*Si*H), 1.1 (G_2-*Si*Me), 2.1 (G_1-*Si*Me). Anal. Calc. $C_{32}H_{79}ClSi_7$ (696.02 g/mol): C, 55.22; H, 11.44; Obt.: C, 56.45; H, 11.04.

$ClG_1(Si\text{-}NMe_2)_2$ (11). An excess of allyl-dimethylamine (0.21 mL, 1.76 mmol) and two drops of Karsted´s catalyst were added to a solution of **6** (0.145 g, 0.44 mmol) in THF (2 mL). The reaction mixture was heated at 80 ºC in a sealed ampoule under inert atmosphere for one night and then evaporated to dryness to remove the solvent and residual allyl-dimethylamine. Afterwards, hexane (10 mL) was added and the solution was filtered through active carbon and dried under vacuum to give **11** as pale yellow oil (0.194 g, 88 %).

^{1}H-NMR ($CDCl_3$): δ -0.06 (s, 12 H, Si*Me*$_2$), 0.04 (s, 3 H, Si*Me*), 0.44 (t, J_a = 8.4 Hz, 4 H, SiC*H*$_2$CH$_2$CH$_2$N), 0.57 (m, 10 H, SiC*H*$_2$CH$_2$C*H*$_2$Si and ClCH$_2$CH$_2$C*H*$_2$Si), 1.29 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.42 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$N), 1.72 (m, 2 H, ClCH$_2$C*H*$_2$), 2.19 (m, 16 H, C*H*$_2$NMe$_2$), 3.47 (t, J_b = 6.9 Hz, 2 H, ClC*H*$_2$). ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.2 (Si*Me*), -3.4 (Si*Me*$_2$), 11.6 (ClCH$_2$CH$_2$*C*H$_2$Si), 12.8 (Si*C*H$_2$CH$_2$CH$_2$N), 18.3, 18.5 and 20.0 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 22.1 (SiCH$_2$*C*H$_2$CH$_2$NMe$_2$), 27.7 (ClCH$_2$*C*H$_2$), 45.5 (-N*Me*$_2$), 48.1 (Cl*C*H$_2$), 63.4 (*C*H$_2$NMe$_2$). MS: $[M+H]^+$ = 493.4 uma (calcd. = 493.4 uma). Anal. Calc. $C_{24}H_{57}ClN_2Si_3$ (493.43 g/mol): C, 58.42; H, 11.64; N, 5.68; Exp.: C, 58.89; H, 11.57; N, 5.81.

$ClG_2(Si\text{-}NMe_2)_4$ (12). This product was synthesized following the synthetic procedure described for **11** from $ClG_2(SiH)_4$ (0.512 g, 0.74 mmol) and $C_3H_5NMe_2$ (0.70 mL, 5.91 mmol), giving **12** as yellowish oil (0.763 g, 99 %).

^{1}H-NMR ($CDCl_3$): δ -0.07 (s, 24 H, Si*Me*$_2$), 0.03 (s, 9 H, Si*Me*), 0.45 (m, 8 H, SiC*H*$_2$CH$_2$CH$_2$N), 0.56 (m, 26 H, SiC*H*$_2$CH$_2$C*H*$_2$Si and ClCH$_2$CH$_2$C*H*$_2$Si, overlapped), 1.30 (m, 8 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.41 (m, 8 H, SiCH$_2$C*H*$_2$CH$_2$N), 1.73 (m, 2 H, ClCH$_2$C*H*$_2$), 2.18 (m, 32 H, -N*Me*$_2$ and C*H*$_2$NMe$_2$), 3.46 (t, J_b = 6.8 Hz, 2 H, ClC*H*$_2$). ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.1 and -5.0 (Si*C*H$_3$), -3.3 (Si*Me*$_2$), 11.6 (ClCH$_2$CH$_2$*C*H$_2$Si), 12.9 (Si*C*H$_2$CH$_2$CH$_2$N), 18.4-20.1 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 22.1 (SiCH$_2$*C*H$_2$CH$_2$NMe$_2$), 27.8 (ClCH$_2$*C*H$_2$), 45.5 (-N*Me*$_2$), 48.1 (Cl*C*H$_2$), 63.4 (*C*H$_2$NMe$_2$). ^{29}Si-NMR ($CDCl_3$): δ 2.1 (G_1 *Si*Me), 0.9 (G_2–*Si*Me), 1.9 (G_2–*Si*Me$_2$). MS: $[M+H]^+$ = 1035.8 uma (calcd. = 1035.8 uma).Anal. Calc. $C_{52}H_{123}ClN_4Si_7$ (1036.61 g/mol): C, 60.25; H, 11.96; N, 5.40; Exp.: C, 58.53; H, 11.10; N, 4.62.

$ClG_1(Si\text{-}NMe_3I)_2$ (13). A mixture of **11** (0.220 g, 0.44 mmol) and MeI (0.11 mL, 1.76 mmol) in THF (50 mL) were stirred for 16 h. Afterwards, volatiles were removed under vacuum and the remaining solid was washed with Et_2O (50 mL), obtaining **13** as a white solid (0.300 g, 87 %).

^{1}H-NMR (DMSO-d_6): δ -0.07 (s, 3 H, Si*Me*), 0.00 (s, 12 H, Si*Me*$_2$), 0.38 and 0.56 (m, 14 H, SiC*H*$_2$), 1.31 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.62 (m, 6 H, *CH*$_2$CH$_2$N$^+$ and ClCH$_2$C*H*$_2$), 3.05 (s, 18 H, -N*Me*$_3^+$), 3.25 (t, J_a = 7.8 Hz, 4 H, C*H*$_2$N$^+$), 2.58 (t, J_b = 6.5 Hz, ClC*H*$_2$). ^{13}C{^{1}H}-NMR (DMSO-d_6): δ -5.6 (Si*Me*), -3.9 (Si*Me*$_2$), 10.6 (Si*C*H$_2$CH$_2$CH$_2$N$^+$), 16.4-17.4 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 18.6 (*C*H$_2$CH$_2$N$^+$), 26.7 (ClCH$_2$*C*H$_2$), 47.8 (Cl*C*H$_2$), 51.6 (-N*Me*$_3^+$), 67.4 (SiCH$_2$CH$_2$*C*H$_2$NMe$_3^+$). ^{29}Si-NMR (DMSO-d_6): δ 2.1 (*Si*Me), 2.4 (*Si*Me$_2$). ESI: (776.21 g/mol) q=1 (649.31 [M-I]$^+$). Anal. Calc. $C_{26}H_{63}ClI_2N_2Si_3$ (777.31 g/mol): C, 40.17; H, 8.17; N, 3.60; Exp.: C, 40.78; H, 8.39; N, 3.93.

$ClG_2(Si\text{-}NMe_3I)_4$ (14). This product was synthesized following the synthetic procedure described for **13** from **12** (0.638 g, 0.62 mmol) and MeI (0.16 mL, 2.59 mmol), which led to **14**as white solid (0.805 g, 81 %).

^{1}H-NMR (DMSO-d_6): δ -0.09 (s, 9 H, Si*Me*), -0.01 (s, 24 H, Si*Me*$_2$), 0.37 and 0.57 (m, 34 H, SiC*H*$_2$, overlapped), 1.30 (m, 12 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.61 (m, 10 H, *CH*$_2$CH$_2$N$^+$ and ClCH$_2$C*H*$_2$), 3.03 (s, 36 H, -N*Me*$_3^+$), 3.23 (t, J_a = 8.3 Hz, 8 H, C*H*$_2$N$^+$), 3.57 (t, J_b = 6.4 Hz, 2 H, ClC*H*$_2$). ^{13}C{^{1}H}-NMR (DMSO-d_6): δ -5.3 (Si*Me*), -3.9 (Si*Me*$_2$), 10.7 (Si*C*H$_2$CH$_2$CH$_2$N$^+$), 16.4–17.7 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 18.8 (*C*H$_2$CH$_2$N$^+$), 26.7 (ClCH$_2$*C*H$_2$), 47.8 (Cl*C*H$_2$), 51.6 (N*Me*$_3^+$), 67.4 (SiCH$_2$CH$_2$*C*H$_2$NMe$_3^+$). ^{29}Si-NMR ($CDCl_3$): δ 2.2 (G_1–*Si*), 1.1 (G_2–*Si*Me), 2.4 (G_2–*Si*Me$_2$). ESI: q=2 (674.35; [M-2I]$^{2+}$), q=3 (407.28; [M-3I]$^{3+}$) and q=4 (273.7; [M-4I]$^{4+}$). Anal. Calc. $C_{56}H_{135}ClI_4N_4Si_7$ (1604.37 g/mol): C, 41.92; H, 8.48; N, 3.49; Exp.: C, 42.22; H, 8.27; N, 3.46.

(PenV)$G_1(Si\text{-}NMe_3I)_2$ (15). To a solution of **13** (0.050 g, 0.06 mmol) in dry DMF, PenVK (0.027 g, 0.07 mmol) was added in the presence of 18C6 (0.002 g, 0.01 mmol) and a catalytic amount of NaI. The mixture was heated at 80 ºC in a sealed ampoule under argon atmosphere for 2 nights after which volatiles

were removed. After washing the residues with water, dendron **15** was obtained as a very hygroscopic white solid (0.062 g, 89 %).

^{1}H-NMR ($CDCl_3$): δ 0.00 (s, 12 H, Si*Me*$_2$), 0.04 (s, 3 H, Si*Me*), 0.57 (m, 14 H, SiC*H*$_2$), 1.29 (m, 4 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.48 (s, 3 H, C*Me*$_2$), 1.58 (s, 3 H, C*Me*$_2$), 1.70 (m, 6 H, *CH*$_2$CH$_2$N$^+$ and OCH$_2$C*H*$_2$), 3.41 (s, 18 H, -N*Me*$_3^+$), 3.63 (m, 4 H, C*H*$_2$N$^+$), 4.08 (t, J_a = 8.4 Hz, 2 H, (CO)OC*H*$_2$), 4.43 (s, 1 H, C*H*(CMe$_2$)), 4.53 (s, 2 H, OC*H*$_2$CO), 5.56 (d, J_b = 4.3 Hz, 1 H, C*H*S), 5.70 (m, 1 H, NHC*H*), 6.90 (d, J_c = 7.6 Hz, 2 H, C*H*$_{Ar}$), 7.01 (t, J_d = 7.4 Hz, 1 H, C*H*$_{Ar}$), 7.30 (m, 2 H, C*H*$_{Ar}$). ^{13}C{^{1}H}-NMR ($CDCl_3$): δ -5.0 (Si*C*H$_3$), -3.2 (Si*Me*$_2$), 9.9 (*C*H$_2$Si), 11.4 (Si*C*H$_2$CH$_2$CH$_2$N$^+$), 17.9, 18.0 and 18.3 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 19.8 (*C*H$_2$CH$_2$N$^+$), 23.2 (OCH$_2$*C*H$_2$), 26.8 and 32.0 (SC*Me*$_2$), 53.7 (-N*Me*$_3^+$), 58.0 (NH*C*H), 64.7 (S*C*Me$_2$), 67.1 (*C*H$_2$N$^+$), 67.7 (O*C*H$_2$CO), 68.4 (COO*C*H$_2$), 69.5 (*C*HS), 70.5 (*C*HCOO), 114.7 (*C*H$_{Ar}$), 122.4 (*C*H$_{Ar}$), 129.8 (*C*H$_{Ar}$), 156.8 (*C*O$_{Ar}$), 167.6, 167.8 and 173.0 (*C*=O). ESI: (1090.32 g/mol) q = 1 (963.42 [M-I]$^+$), q = 2 (418.26 [M-2I]$^{2+}$). Anal. Calc. $C_{42}H_{80}I_2N_4O_5SSi_3$ (1091.24 g/mol): C, 46.23; H, 7.39; N, 5.13; Exp.: C, 45.94; H, 7.07; N, 4.43.

(PenV)G$_2$(Si-NMe$_3$I)$_4$ (16). This product was synthesized following the synthetic procedure described for **15** from **14** (0.120 g, 0.07 mmol), PenCO$_2$K (0.030 g, 0.08 mmol) and 18C6 (0.002 g, 0.01 mmol) but heating at 100º C, obtaining **16** as a highly hygroscopic white solid (0.136 g, 95 %). In this case purification was performed using dyalysis with a membrane of MWCO of 500.

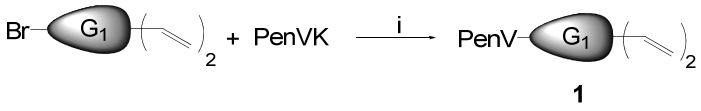
^{1}H-NMR (DMSO-d$_6$): δ -0.13 (s, 9 H, Si*Me*), 0.00 (s, 24 H, Si*Me*$_2$), 0.41and 0.57 (m, 34 H, SiC*H*$_2$), 1.27 (m, 12 H, SiCH$_2$C*H*$_2$CH$_2$Si), 1.61 (m, 16 H, C*Me*$_2$, *CH*$_2$CH$_2$N$^+$ and OCH$_2$C*H*$_2$), 3.07 (s, 36 H, -N*Me*$_3^+$), 3.21 (m, 8 H, C*H*$_2$N$^+$), 4.07 (m, 2 H, (CO)OC*H*$_2$), 4.41 (s, 1 H, C*H*(CO)), 4.58 (s, 2 H, OC*H*$_2$CO), 5.57 (m, 1 H, C*H*S), 5.61 (m, 1 H, NHC*H*), 6.97 (m, 3 H, C*H*$_{Ar}$), 7.31 (m, 2 H, C*H*$_{Ar}$). ^{13}C{^{1}H}-NMR (DMSO-d$_6$): δ -5.6 and -5.4 (Si*Me*), -3.9 (Si*Me*$_2$), 8.9 (OCH$_2$CH$_2$*C*H$_2$Si), 10.6 (Si*C*H$_2$CH$_2$CH$_2$N$^+$), 16.4-17.7 (Si*C*H$_2$*C*H$_2$*C*H$_2$Si), 18.7 (*C*H$_2$CH$_2$N$^+$), 22.1 (OCH$_2$*C*H$_2$ and SC(*Me*)$_2$), 51.6 (-N*Me*$_3^+$), 57.9 (NH*C*H), 63.5 (S*C*Me$_2$), 65.6 (O*C*H$_2$CO), 66.9 (O*C*H$_2$), 67.4 (*C*H$_2$N$^+$), 69.4 (*C*HCOO), 113.9 (*C*H$_{Ar}$), 120.7 (*C*H$_{Ar}$), 129.0 (*C*H$_{Ar}$), 157.0 (*C*O$_{Ar}$), 167.2, 167.3, and 172.5 (*C*=O). ^{29}Si-NMR (DMSO-d$_6$): δ 1.1 (G$_2$–*Si*Me) 2.2

(G_1–*Si*Me), 2.4 (G_2–*Si*Me_2). ESI: q=2 (831.4; $[M-2I]^{2+}$), q=3 (512.0; $[M-3I]^{3+}$) and q=4 (352.2; $[M-4I]^{4+}$). Anal. Calc. $C_{72}H_{152}I_4N_6O_5SSi_7$ (1918.29 g/mol): C, 45.08; H, 7.99; N, 4.38; Exp.: C, 42.50; H, 8.58; N, 4.97.

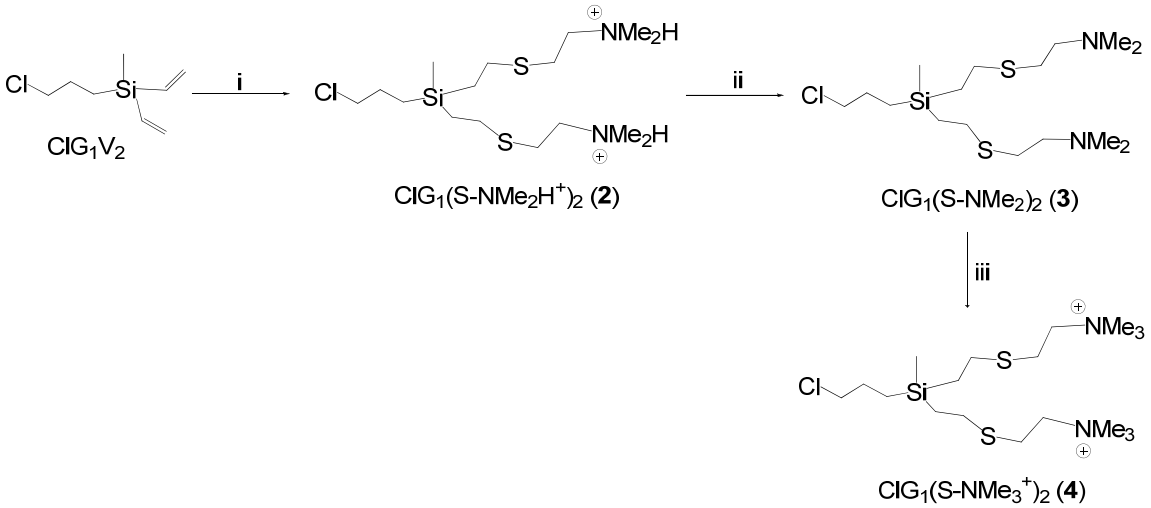
S.2. References

1. Fuentes-Paniagua, E.; Peña-González, C. E.; Galán, M.; Gómez, R.; de la Mata, F. J.; Sánchez-Nieves, J. *Organometallics* **2013,** 32, 1789−1796.
2. Fuentes-Paniagua, E.; Sánchez-Nieves, J.; Fernández-Ezequiel, A.; Hernández-Ros, J. M.; Soliveri, J.; Copa-Patiño, J. L.; Gómez, R.; de la Mata, F. J. *RSC Adv.* **2016,** 6, 7022–7033.
3. Downing, C. M.; Missaghi, M. N.; Kung, M. C.; Kung, H. H. *Tetrahedron* **2011,** 67, 7502-7509.
4. Wolf, C.; Pirkle, W. H. *J. Chromatogr. A* **1998,** 799, 177–184.
5. *Reference Methods for the testing the "in vitro" activity of antimicrobial agents against bacteria involved in infectious diseases* **2006**, ISO 20776-1.

S.3 Reaction schemes and NMR spectra.



Scheme S1. Synthesis of dendron (PenV)G_1V_2 (**1**). i) DMF, 90 ºC, ether crown 18-C-6.



Scheme S2. Synthesis of dendron $ClG_1(S\text{-}NMe_3^+)$ (**4**).♯) $HS(CH_2)_2NMe_2 \cdot HCl$, DMPA, hυ; ii) Na_2CO_3; iii) MeI.

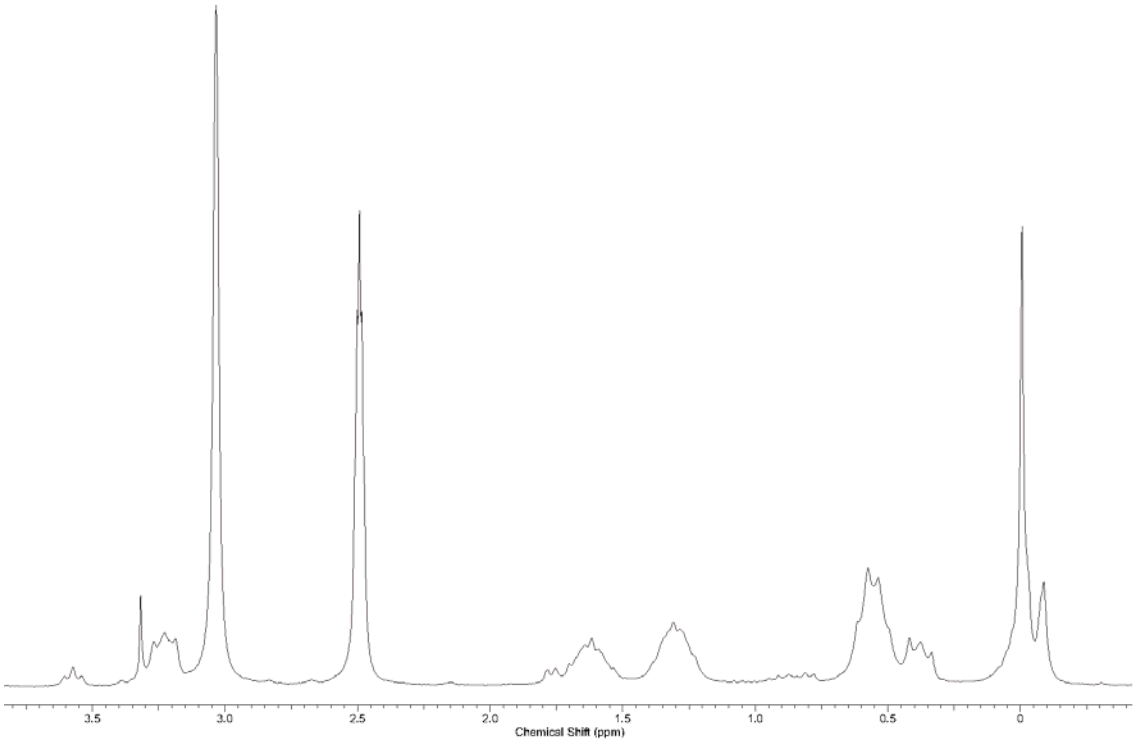


Figure S1. ^{1}H-NMR (DMSO-d_6) spectra of compound $ClG_2(Si\text{-}NMe_3^+)_4$ (**14**).

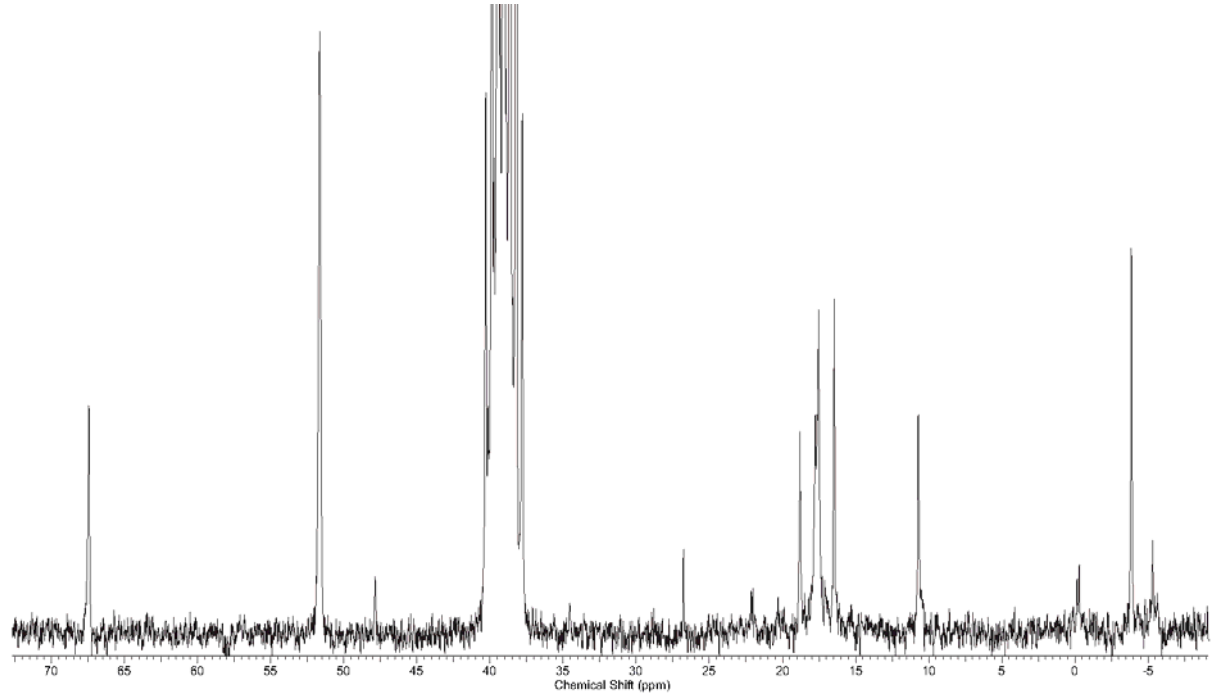


Figure S2. ^{13}C NMR (DMSO-d_6) spectra of compound $ClG_2(Si\text{-}NMe_3^+)_4$ (**14**).

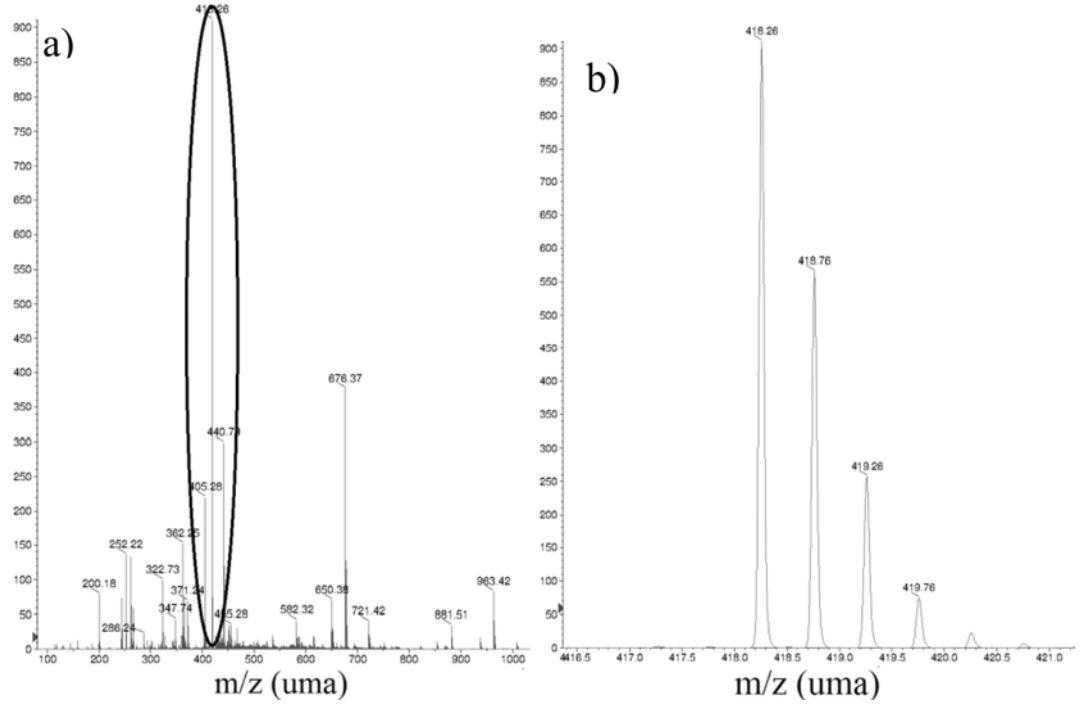


Figure S3. MS spectrum of [(PenV)G_2(Si-NMe_3)$_4$(I)$_4$] (**16**) (a), observing the presence of the fragment [M-2I]$^{2+}$ (b).

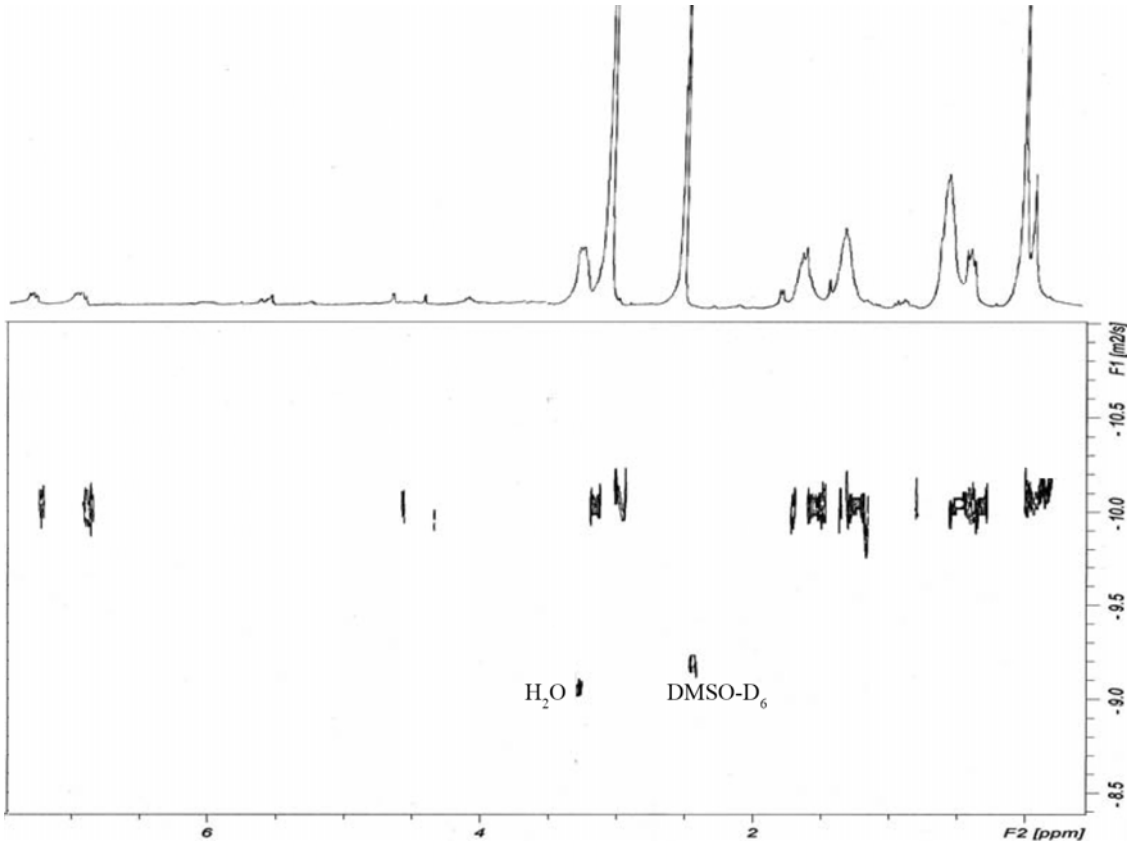


Figure S4. ^{1}H-NMR and DOSY-2D (DMSO-d_6) spectra of compound (PenV)G_2(Si-NMe_3^+)$_4$ (**16**).

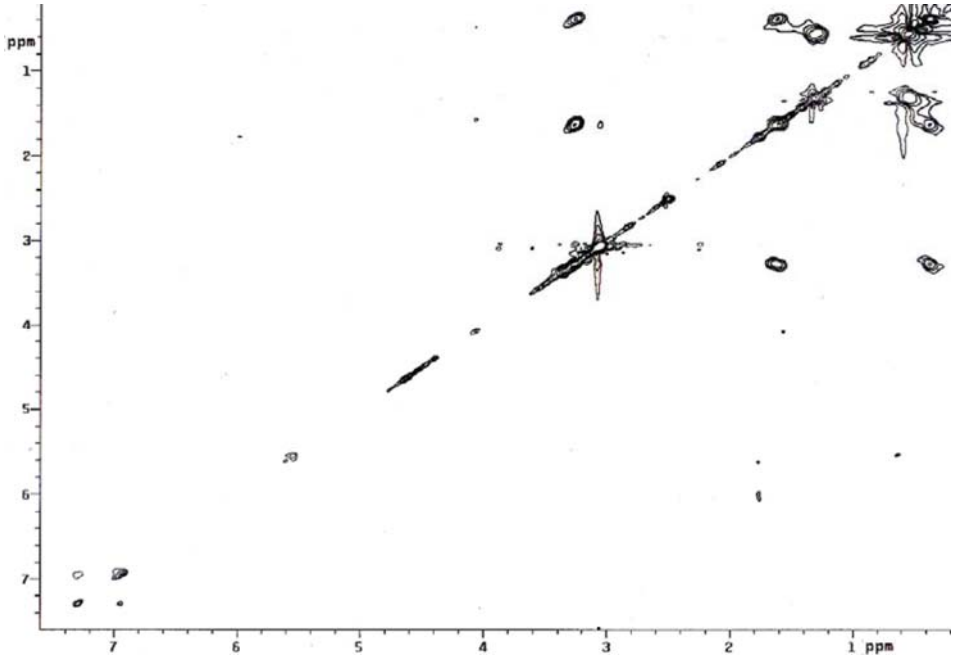


Figure S5. TOCSY (DMSO-d_6) spectra of compound (PenV)G_2(Si-NMe_3^+)$_4$ (**16**).

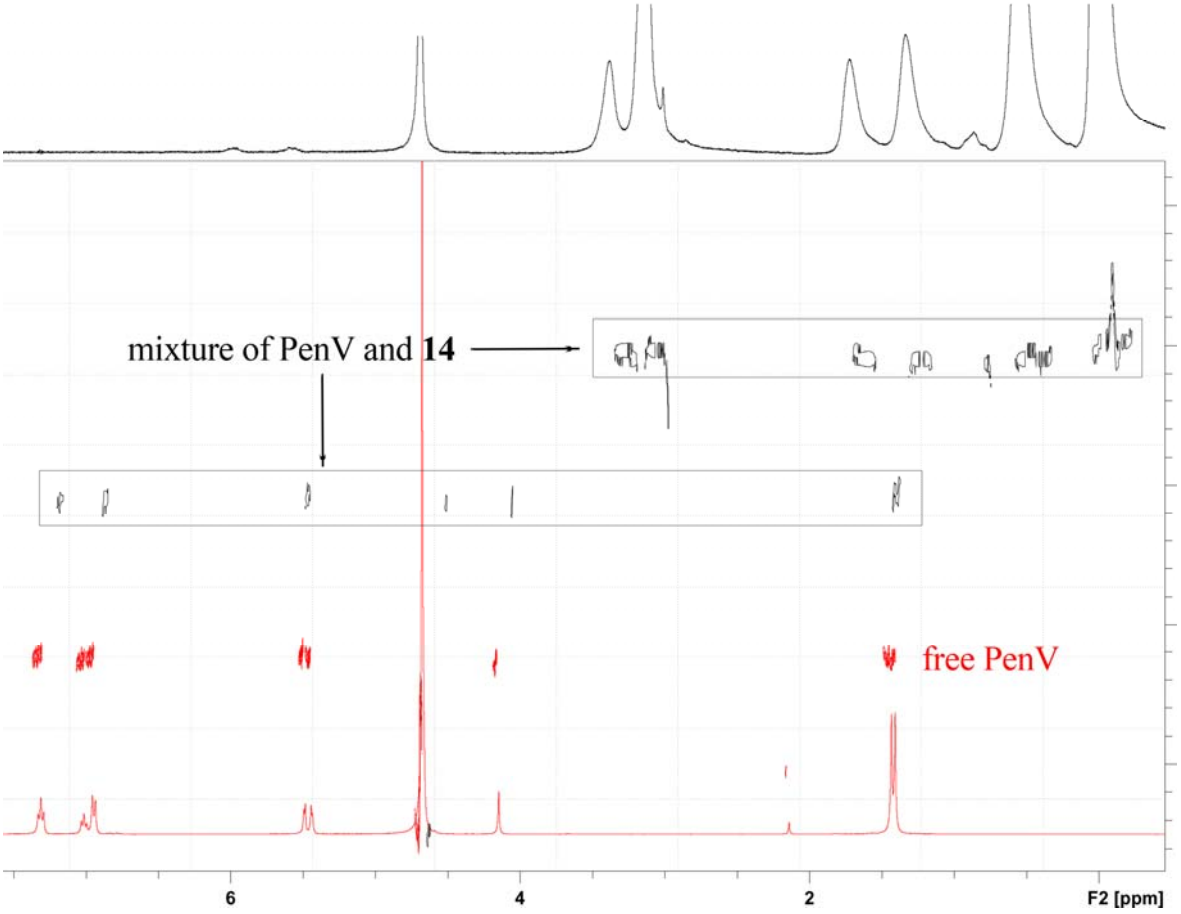


Figure S6. ^{1}H NMR and DOSY 2D spectra (D_2O) of free PenV (red) and ^{1}H NMR and DOSY 2D spectra (D_2O) of an equimolecular mixture of PenVK and dendron $[ClG_2(Si\text{-}NMe_3)_4]^{4+}$ (**14**) (black).