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Carbosilane Dendrimeric Carbodiimides: Site Isolation as a Lactamization Tool

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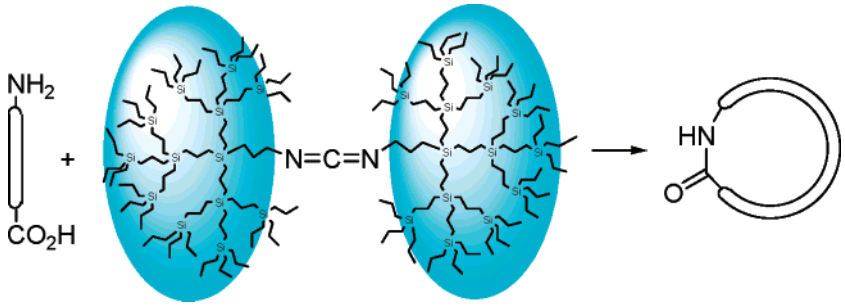

The convergent syntheses of three generations of carbosilane dendrimeric carbodiimides are described. The wedge-type building blocks were synthesized in a divergent way, starting from allyl chloride and a repetitive sequence of hydrosilylation with $HSiCl_3$ and a Grignard reaction with allylmagnesium bromide. Hydrogenation of the terminal double bonds led to inert and stable wedges. The chloride substitutent at the focal point was transformed into several functional groups that eventually led to dendrimeric structures with a carbodiimide core. The extent of the site isolation effect of the dendrimers was studied with dilution experiments monitored by FT-IR spectroscopy on the corresponding dendrimeric ureas. These studies showed that only the first generation self-aggregates via hydrogen bonding, while the second and the third do not, implying isolation of core-bound moieties. The dendrimeric carbodiimides mediated lactamization reactions to obtain homodiketopiperazines.

Introduction

Dendrimers are well-defined macromolecules with a regular and highly branched three-dimensional structure.[1] These macromolecules possess internal cavities that can exhibit site-isolation effects, as the branches shield the core to create a distinct nanoenvironment isolated from the bulk solution.[2] This peculiar feature of dendrimers has been explored in different research fields, especially homogeneous catalysis. Properties of dendrimers such as reactivity were, in some cases, different from those of the nondendrimeric analogues. For example, dendritic nickel catalysts used in the oligomerization of ethylene showed higher activity compared with their parent complex due to dendritic site isolation.[3] The ability of dendrimers to alter the local environments has seen application in other research fields, including material science and biology (drug delivery).[4]

Surprisingly, only a few applications of dendrimers are known in organic synthesis,[5] none of which utilize core-functionalized dendrimers. For example, Kim and co-workers[6] reported the

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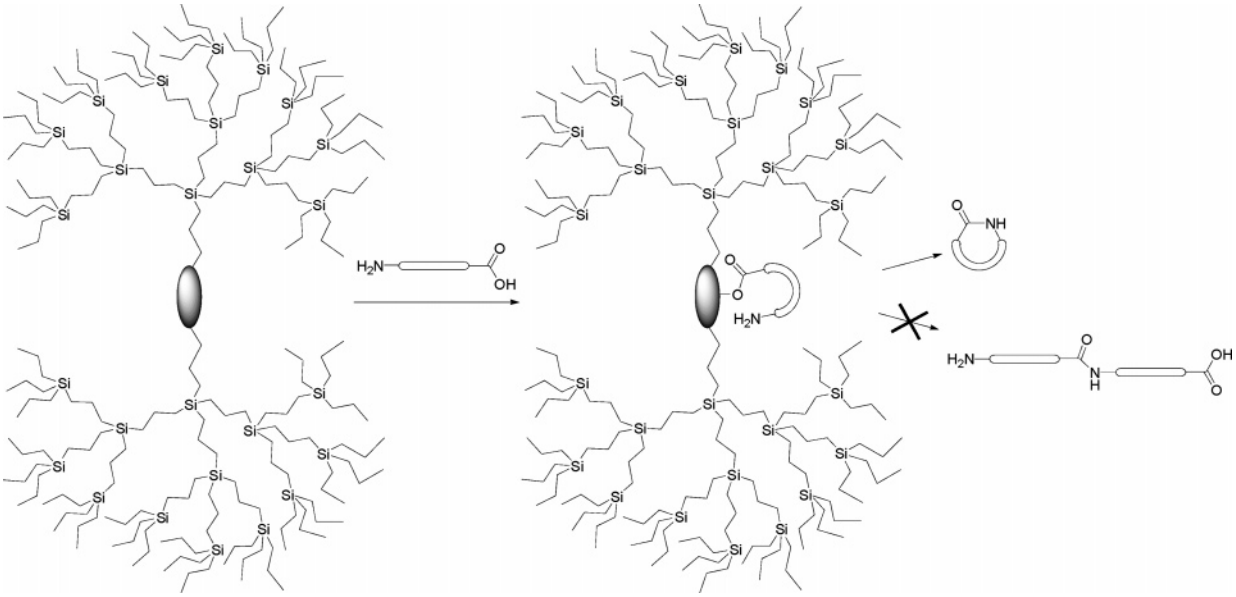
SCHEME 1. Encapsulation of the Linear Precursor Prevents Intermolecular Processes, Enabling the Intramolecular Reaction To Occur (Third Generation Carbosilane Dendrimer Is Shown)



use of periphery functionalized PAMAM dendrimers as a soluble support for the Fisher indole synthesis. Van Koten et al.[7] used the periphery of carbosilane dendrimers to synthesize a small library of β-lactams. Both groups demonstrated the value of dendrimers as soluble supports by the synthesis of a small set of compounds.[8]

Our group is interested in the development of new strategies toward the ring closure of medium-sized lactams. Head-to-tail cyclization of ω-amino acids and peptides suffers from competing intermolecular reactions yielding linear and cyclic oligomers.[9] Synthetic strategies toward macrolactams using classical peptide coupling reagents generally lead to poor results, unless high dilution conditions are employed. Even then, in many cases the cyclized product can only be obtained in poor yield.[10] Many approaches to perform head-to-tail lactamizations have been proposed and explored,[11] including cyclization on solid phase,[12] use of auxiliaries,[13] cyclization via the Staudinger ligation,[14] and chemoenzymatic cyclization.[15] However, we anticipated that dendrimeric site isolation could provide a tool to perform difficult cyclization reactions, which would be a novel application for dendrimer, as is depicted schematically in Scheme 1.

At the core of a diimide-containing dendrimer, a linear lactamization precursor is trapped via the *C*-terminus. The encapsulation of the activated ester generates a "pseudo-high-dilution" environment in the dendritic structure. Therefore, intermolecular processes (to give oligomers) are impaired, and the reaction can take place preferentially in an intramolecular fashion to give the desired monocyclic product.

Herein, we report the divergent synthesis of three different generations of carbosilane wedges having a primary chloride as focal point and the subsequent transformation into other functional groups. These wedges were employed to construct, in a convergent manner, dendrimers possessing a carbodiimide core. The (dendrimeric) peptide coupling reagents were investigated to mediate the ring-closure reaction providing seven-membered bis-lactams (homodiketopiperazines), which are difficult to access using traditional methods.

Results and Discussion

Carbosilane dendrimers possess excellent characteristics for our purposes: a straightforward synthesis, stability to a variety of conditions, and facile functionalization both at the periphery (to alter their physical properties) and in the core. Since the first report in 1992,[16] much work has been done to synthesize carbosilane dendrimers with modified structures and properties.[17] The flexibility of the route to construct these dendrimers in a convergent way from carbosilane wedges was demonstrated for

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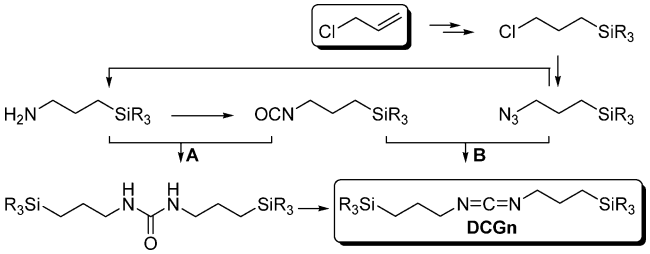
SCHEME 2. General Route to the Dendrimeric Carbodiimides

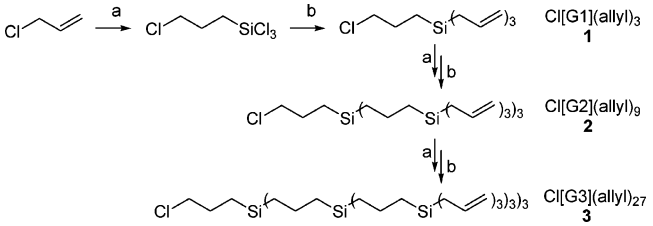


the first time in 1999 by van Leeuwen et al.[18] They used the divergent route consisting of sequential hydrosilylation and Grignard alkenylation to obtain carbosilane wedges up to the third generation possessing 3-bromopropyl at the focal point. The same synthetic strategy was employed to synthesize carbosilane wedges with an aryl bromide as the focal point group.[19]

With the aim of constructing dendrimers possessing a diimide moiety as the core, we focused on a synthesis starting from carbosilane wedges with the appropriate electrophilic and nucleophilic focal points. By connecting the single wedges via the mutually reactive focal point functional groups to a multivalent centerpiece, core-functionalized dendrimers are obtained in a convergent way.[20,21] This approach to synthesize dendrimers presents two noteworthy advantages: (i) access to a variety of core moieties and (ii) synthesis of dendrimers possessing a reactive core moiety (e.g., carbodiimide). The dendrimeric diimides have been prepared using two different strategies (Scheme 2). For both strategies, the key starting materials are carbosilane dendrimeric wedges with an azide as the focal point, allowing facile further transformation into an amine and isocyanate. Reaction of the amine and isocyanate wedges provides dendrimers with a urea in the core that subsequently can be dehydrated to give the final dendrimeric diimides (route A, Scheme 2). As an alternative, dendrimeric diimides were prepared in one step from the azide wedges by a Staudinger reaction with isocyanide-functionalized wedges (route B, Scheme 2).

Divergent Synthesis of 3-Chloropropyl Wedge Building Blocks. The 3-chloropropyl wedges were synthesized analogously to the 3-bromopropyl wedges.[18] Allyl chloride was used as the starting material for the platinum-catalyzed hydrosilylation with trichlorosilane (Scheme 3).[22] Excess of trichlorosilane was required to drive the reaction to completion. Hydrosilylation with tetrabutylammonium hexachloroplatinate (Lukevics' catalyst) gave clean product formation,[23] while other platinum catalysts used in previous work gave substantial amounts of side products (such as the branched adduct).[24] After an induction period of 30 min to 6 h, the reaction became exothermic, which was crucial for a successful outcome of the reaction. Reaction progress was assessed by ^{1}H NMR, and after typically 16 h disappearance of the allylic signals indicated complete conversion for the first generation, while longer reaction times were necessary for the higher generations (e.g., 5 days for multigram scale synthesis of the third generation). From ^{1}H NMR analysis, traces of a side product resulting from dechlorination during the hydrosilylation step were observed for all generations. For the first generation, the side product (*n*-propyltrichlorosilane) could be removed via distillation, however, only at the expense of product yield, unfortunately. Allylmagnesium bromide was used to substitute the chloride atoms of the trichlorosilane end groups for allylic groups. The reaction mixture was stirred for 5−24 h, depending on the generation. Higher generation dendritic wedges were synthesized, in a multigram scale, by repeating the hydrosilylation and Grignard alkylation steps. Wedges **2** and **3** were obtained in high yields (90 and 83%, respectively) after purification by flash column chromatography.

SCHEME 3. Synthesis of the Dendritic Carbosilane Wedges 1−3[a]



[a] Reaction conditions: (a) $HSiCl_3$, $(Bu_4N)_2PtCl_6$ (10^{-4} mol catalyst per mol of allyl end group), CH_2Cl_2/Et_2O, room temperature; (b) (allyl)MgBr, Et_2O, room temperature, 5−16 h.

The structure of the third generation wedge Cl[G3](allyl)$_{27}$ **3** was confirmed by MALDI-TOF mass spectrometry. The dominant peak (2121.92 *m*/*z*) results from the addition of silver ions (silver nitrate was used for the ionization of the molecules) and the loss of one allyl end group of the formed wedge **3**.

While allylic end groups present at the periphery of the wedges can be used to modify the surface of the dendrimers,[25] the stability of allylsilane containing dendrimers is reduced due to their reactivity toward acids and acetone and their sensitivity to light. We expected that the hydrogenation of the allylic groups would provide us with inert wedges suitable for the application described herein. Catalytic hydrogenation of Cl[G1](allyl)$_3$ **1** and Cl[G2](allyl)$_9$ **2** was achieved using a Pd(C) in a hydrogen atmosphere. Cl[G3](allyl)$_{27}$ **3**, having 27 terminal double bonds, required the use of the more active PtO_2 catalyst and prolonged reaction times (Scheme 4). The saturated wedges **4**−**6** were all obtained in excellent yields.

Indeed, the saturated wedges showed no decomposition upon storage over prolonged periods or exposure to light and moisture. Furthermore, they showed a remarkable stability toward a variety of reaction conditions (vide infra).

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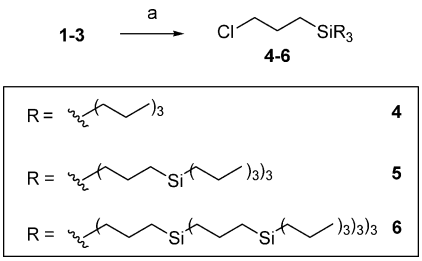
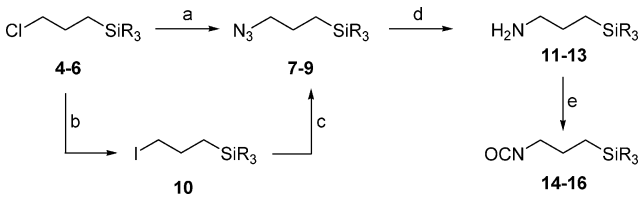
SCHEME 4. Synthesis of the Saturated Wedges[a]



[a] Reaction conditions: (a) H_2 balloon, 10% Pd/C, EtOAc/MeOH (3:1), 16 h for **1** (81%) and **2** (93%); PtO_2, EtOAc/MeOH (10:1), 48 h for **3** (81%).

SCHEME 5. Focal Point Modification Starting from the Saturated Chloro Wedges[a]



[a] Reagents and conditions: (a) NaN_3 (10 equiv), THF, 90 °C, 6 h, for **4**; THF/DMF (3:1), 90 °C, 16 h for 5; THF/DMA (3:1), 115 °C, 3 days, for **6**; quantitative; (b) Only for **6**: NaI (10 equiv) THF/DMA (3:1), 110 °C, 16 h, 95%; (c) NaN_3 (10 equiv), THF/DMA (3:1), 110 °C, 16 h, 95%. (d) For **7**−**9**: H_2 balloon, 10% Pd(C), EtOAc/MeOH (10:1), 56−71%. For **9**: (a) PPh_3 (1 equiv), THF, 70 °C, 16 h; (b) H_2O, 60 °C, 2 h, 95%; (e) phosgene/toluene (1.57 M, 2 equiv), toluene/ $NaHCO_3$ (aq), 0 °C, 2 h, 85−97%.

Focal Point Modification. Wedges with a 3-aminopropyl focal point group and allylic end groups have been previously synthesized by van Leeuwen and co-workers.[18] In their approach, the amino wedges were obtained by reaction of the 3-bromopropyl-functionalized wedges with a large excess of liquid ammonia at 70 °C under 15 bar of pressure in an autoclave. The formation of unwanted secondary amine-functionalized wedges could be avoided by using low concentrations. However, under these conditions it was hard to obtain large quantities of the wedges, making this approach not suitable for our purposes. As an alternative, a stepwise procedure by conversion of the bromine into a masked amino moiety such as an azide and subsequent transformation to the amine should enable the formation of large quantitites.

The 3-chloropropyl focal points of the saturated wedges **4** and **5** were converted into the desired azido wedges **7** and **8** in almost quantitative yields by reaction with an excess of sodium azide in DMF at 90 °C for 3−7 h (Scheme 5).

Unfortunately, employing the same conditions for **6** failed to provide any product, and only starting material was recovered. Increasing either temperature or reaction time led to the product, albeit in poor yields (a mixture of products and starting material was usually observed). Since the poor solubility of the third generation wedges in DMF likely slowed the reaction, the use of different solvent mixtures was explored. Mixtures of THF/DMF or THF/DMA (DMA = *N*,*N*-dimethylacetamide) in a ratio of 3:1 were the most suitable solvent combinations. These solvent systems probably induce a more open structure of the wedges, as has been observed for other dendrimers,[26] making the core more accessible to the nucleophile. In addition, sodium azide dissolves well in these mixtures, ensuring a high concentration of the nucleophile. When **6** was stirred with an excess (10 equiv) of NaN_3 and a stoichiometric amount of KI at 110 °C using THF as the solvent for 3 days in a sealed tube, the desired 3-azidopropyl wedge **9** was obtained in 90% yield (Scheme 5). A two-step route was also possible: substitution of the chloride in wedge **6** for iodide, followed by azide introduction. The first transformation is easily performed by reaction of the chloride wedge **6** with an excess of NaI using a mixture of THF/DMA (3:1) at 110 °C for 12 h. The resulting iodo wedge $I[G3](propyl)_{27}$ **10** could be converted into the desired azide $N_3[G3](propyl)_{27}$ **9** by reaction with NaN_3 in a mixture of THF/DMA (3:1) and stirring at 110 °C for 40 h. Both approaches resulted in an overall yield of 90%.

^1H NMR analysis of $N_3[G3](propyl)_{27}$ **9** indicated, by the diagnostic signal shift of the CH_2 group flanking the focal point functional group, complete conversion of the chloride atoms into azides and no detectable structural defects. The high purity of **9** was also confirmed by the GPC trace.

The azido wedges $N_3[Gn](propyl)_3{}^n$ (n = 1, 2, 3) **7**−**9** were reduced into the corresponding amine wedges $NH_2[Gn](propyl)_3{}^n$ (n = 1, 2, 3) **11**−**13** by Pd(C)-catalyzed hydrogenation at atmospheric pressure in a mixture of EtOAc/MeOH (10:1) for 16 h. Purification was performed by simple filtration over Celite, yielding the amine wedges **11**−**13** in good yields (55−71%) (Scheme 5). In the case of the third generation wedge $N_3[G3](allyl)_{27}$ **9**, the catalytic reduction required very long reaction times and a higher catalyst loading.

Alternatively, reduction of $N_3[G3](allyl)_{27}$ **9** could be achieved by treatment with triphenylphoshine in THF at 70 °C for 16 h. Subsequent hydrolysis of the intermediate iminophosphorane by adding water provided $NH_2[G3](allyl)_{27}$ wedge **13** in 95% yield.[27,28] The reaction was monitored using IR spectrometry to observe the disappearance of the strong azide absorption at 2096 cm^{-1}. Taking advantage of the lipophilic character of the wedges, we accomplished purification of the amino wedge **13** by precipitation of triphenylphosphine oxide with hexanes or washing of the wedge with MeOH.

The amino group at the focal point of the wedges was converted into the corresponding isocyanate (Scheme 5) by reacting **11**−**13** with an excess of phosgene in a mixture of toluene and water for 2 h using $NaHCO_3$ as a base. The desired products $OCN[Gn](propyl)_3{}^n$ (n = 1, 2, 3) **14**−**16** were obtained in near quantitative yield, and no purification was necessary. The reaction was monitored by TLC for the first generation wedges, but for the higher generations, IR spectroscopy (appearance of the typical absorption band of isocyanate at 2266 cm^{-1}) and ^1H NMR in particular (variation of the protons adjacent to the focal point) provided more information.

All the wedges were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. FAB and MALDI-TOF analysis was only possible for the amine wedges that were ionizable under mild conditions.

Synthesis of Urea Core-Functionalized Carbosilane Dendrimers. The dendrimeric carbodiimides were obtained convergently from the wedges described above possessing a variety of focal points. The most common method to prepare diimides is via dehydration of ureas.[29] The urea wedges **17**−**19** were obtained in good yields (60−93%) by reacting the amino-

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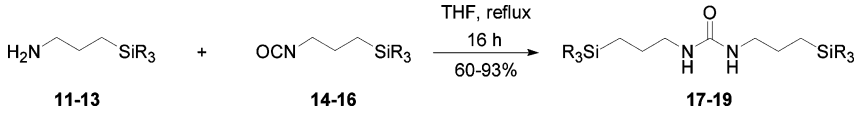
SCHEME 6. Dendrimeric Urea Synthesis



functionalized wedges **11**−**13** with an equimolar amount of the corresponding isocyanate **14**−**16** in refluxing THF (Scheme 6).

Simple filtration over a short silica pad furnished the pure compounds. The third generation urea **19** could also be purified using size exclusion chromatography. The integrity of **19** was confirmed by ^{1}H-, ^{13}C NMR, and MALDI-TOF analysis.

The first generation dendrimeric urea **17** is a solid (mp 66 °C) and dissolves in most organic solvents (toluene, $CHCl_3$, EtOAc, MeOH, etc.). The second generation dendrimeric urea **18** is an oil showing poor solubility in polar solvents such as MeOH. The third generation urea **19** is a viscous oil that phase separates in polar solvents (e.g., MeOH).

Dendrimeric Ureas: Aggregation Properties. We envisioned that the self-aggregation properties of a series of urea-functionalized dendrimers could provide information on the extent of the site-isolation effect, a relevant property for core-functionalized dendrimers. It is well-known that urea groups can form strong bifurcated hydrogen bonds to form linear chains as shown in Figure 1.[30] The strength (and the mode) of association of the aggregates is influenced by the electronic and steric properties of the substituents (R).

The hydrogen-bonding interactions of the three generations of dendrimeric urea were studied with FT-IR spectroscopy using toluene-d_8 as the solvent. FT-IR spectra of a solution of the first generation urea dendrimer **17** at low concentration (12 mM) showed two absorptions for the urea moiety: one at 3439 cm^{-1} (N−H) and another at 1691 cm^{-1} (amide I).[31] The same absorption bands were found when the concentration was increased to 22 mM. These bands are characteristic for non-hydrogen-bonded urea groups with a trans−trans conformation, pointing to self-aggregation as depicted in Figure 1. For a 60 mM solution, two N−H and two amide I bands are observed at 3433 and 1690 cm^{-1} corresponding to non-hydrogen-bonded urea moieties and signals at 3370 cm^{-1} (broad) and 1628 cm^{-1} corresponding to hydrogen-bonded urea moieties. Increasing the concentration to 120 mM solution gives two main bands at 3370 cm^{-1} (N−H) and at 1628 cm^{-1} (amide I), indicating that at high concentrations the first generation dendrimer **17** self-associates (Figure 2, only N−H shown).[32]

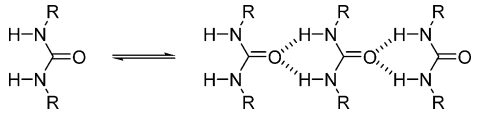


FIGURE 1. Association pattern of N,N′-disubstituted ureas.

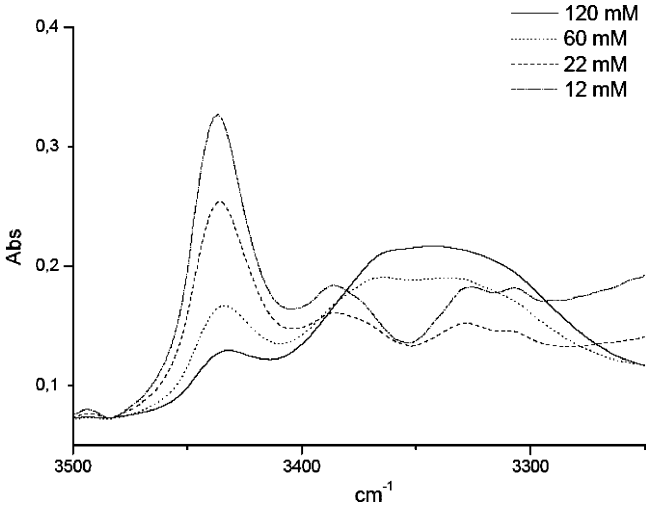


FIGURE 2. Normalized FT-IR spectra of the first generation urea **17** at different concentrations.

The FT-IR experiments for the second generation urea **18** were conducted at concentrations of 24, 60, and 90 mM (see Supporting Information). At these concentrations, only two stretching vibrations were observed, which are associated with the free N−H (3437 cm^{-1}) and C═O (1690 cm^{-1}) groups, and they indicate that the urea moieties have a trans−trans conformation. Thus, already in the second generation urea **18**, the wedges shield the core and inhibit the formation intermolecular hydrogen bonds.

The different aggregation properties of the first and second generation dendrimeric urea compounds **17** and **18** were confirmed by measuring their ^{1}H NMR spectra at different concentrations. It is known that upon aggregate formation the chemical shift of the NH varies with the concentration. In the ^{1}H NMR of **17** at low concentrations (i.e., solutions under 11 mM), the chemical shift of the NH does not change significantly (NH is at 3.75 ppm), but an increase in the concentration resulted in a clear upfield shift. This indicates that at low concentration **17** is mainly present as a monomer, whereas at higher concentrations the equilibrium is shifted in favor of aggregates.[33] The ^{1}H NMR spectrum of the second generation urea **18** shows little sensitivity to changes in concentration (see Supporting Information). The very small variation in chemical shift at different concentrations results from the steric bulk in the dendrimeric branches, which probably allows the formation of dimers, but not of higher oligomers.

As expected, the third generation urea **19** did not show any hydrogen bonding. At 50 and 100 mM, only non-hydrogen-bonded species were present, as indicated by the weak stretching vibrations at 3439 cm^{-1} for N−H and 1690 cm^{-1} for C═O (Figure 3, only N−H shown). In addition, ^{1}H NMR analysis at various concentrations of **19** in toluene-d_8 showed no change in the chemical shifts of the NH−CH_2 protons.

The absence of any concentration dependence in the IR and ^{1}H NMR spectra of **19** indicates the lack of hydrogen-bonding interactions and therefore of core−core interactions. These results suggest that shielding of the core unit occurs also for the dendrimeric carbodiimides. In accordance with the hydrogen-

(29) Review: Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233−284.

(30) (a) Mohmeyer, N.; Schmidt, H−W. *Chem.*−*Eur. J.* **2005**, *11*, 863−873. (b) Lortie, F.; Boileau, S.; Boutellier, L. *Chem.*−*Eur. J.* **2003**, *9*, 3008−3014.

(31) Dobrowolski, J. Cz.; Jamroz, M. H.; Mazurek, A. P. *Vib. Spectrosc.* **1994**, *8*, 53−60.

(32) (a) Hanasuba, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949−1951. (b) Schoonbeck, F. S.; de Loos, M.; Kooijman, H.; Kellogg, R. M.; Feringa, B. L. *Chem.*−*Eur. J.* **1999**, *5*, 937−950.

(33) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891−8896.

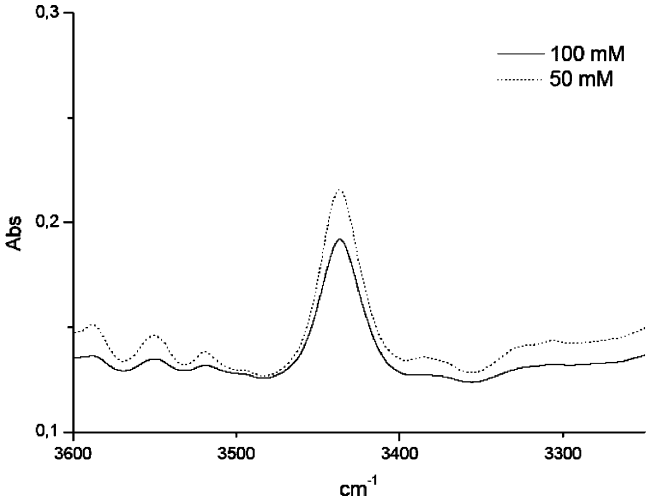


FIGURE 3. Normalized FT-IR spectra of the third generation urea **19** at different concentrations.

TABLE 1. Dehydrating Reagents Evaluated on 17[a]

dehydrating agent	base	carbodiimide
$COCl_2$	DBU or NH_3	none
$Cl_3CCOCCl_3$	pyridine or DiPEA	none
$SOCl_2$	Et_3N	none
TosCl	K_2CO_3 or pyridine	low
PPh_3Br_2	Et_3N	yes

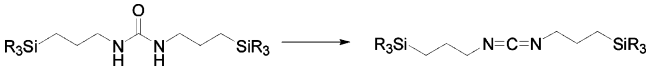
[a] DiPEA = *N*,*N*-diisopropylethylamine.

bonding studies performed on the dendrimeric ureas, the CPK models (Figure 4) of the three generation dendrimeric carbodiimides **DCG1**, **DCG2**, and **DCG3** also show that core encapsulation becomes more efficient as generations increase.

Synthesis of Diimide Core-Functionalized Carbosilane Dendrimers. To achieve dehydration of the urea to furnish a carbodiimide, the first generation urea **17** was subjected to various conditions (i.e., dehydrating reagents in combination with different bases).[29] Reaction of **17** with phosgene, trisphosgene, thionyl chloride, or tosyl chloride either failed to furnish the desired product or provided only trace amounts. Gratifyingly, triphenylphosphine dibromide proved to be an efficient dehydrating agent (Table 1).

Reaction of the dendrimeric ureas **17** and **18** with a stoichiometric amount of triphenylphosphine dibromide (prepared in situ) in the presence of triethylamine as the base gave the desired carbodiimides **DCG1** and **DCG2** in good yields (Scheme 7).

SCHEME 7. Synthesis of the First and Second Generation Dendrimeric Carbodiimides[a]



17,18 **DCG1, DCG2**

[a] Reagents and conditions: PPh_3 (1.1 equiv), Br_2 (1.1 equiv), Et_3N (2.5 equiv), CH_2Cl_2, from 0 °C to room temperature, 16 h; **DCG1** 63% and **DCG2** 74%.

These carbodiimides proved to be stable under basic conditions, allowing purification via filtration over a short basic alumina pad to give the pure products **DCG1** and **DCG2**.

Surprisingly, application of the same conditions to the dehydration of **19** gave, according to ^1H NMR of the reaction mixture, some **DCG3**, despite longer reaction times. Although urea and carbodiimide functionalities typically have considerably different properties, this large difference in physical properties was not observed for urea **19** and carbodiimide **DCG3**. In this case, the carbosilane dendritic bulk determines the physical properties (e.g., polarity). As a result, purification of **DCG3** by column chromatography was troublesome. Moreover, the similar molecular weights of urea **19** and carbodiimide **DCG3** preclude the use of size exclusion chromatography as a means of purification. As a result, the separation of the third generation dendrimeric carbodimiide **DCG3** and its urea **19** congener was only partially successful, making this route unappealing. We therefore turned to the Staudinger reaction, which has been reported to be useful in the synthesis of carbodiimides.[34] The highly nucleophilic iminophosphorane species ($R-N_3 + PPh_3 \rightarrow R-N{=}PPh_3 + N_2$) can be "trapped" by isocyanates to yield a carbodiimide and triphenylphosphine oxide. We anticipated that use of the third generation azidopropyl wedge could be the key intermediate in our synthetic strategy.

N_3[G3](propyl)$_{27}$ **9** was reacted at 65 °C in THF with 1 equiv of triphenylphosphine for 6 h to ensure quantitative formation of the iminophosphorane. Gratifyingly, subsequent addition of an equimolar amount of OCN[G3](propyl)$_{27}$ **16** followed by refluxing in THF for 16 h afforded the desired dendrimeric carbodiimide **DCG3** in a yield of 72% (Scheme 8).

Clearly, the advantage of this route is that no urea is involved. The byproducts, unreacted wedges and triphenylphosphine oxide, can be separated easily from the product **DCG3** by size exclusion chromatography or column chromatography on basic alumina. Further, this convergent approach to obtain **DCG3** also opens up the possibility for a straightforward synthesis of asymmetric dendrimeric carbodiimides.

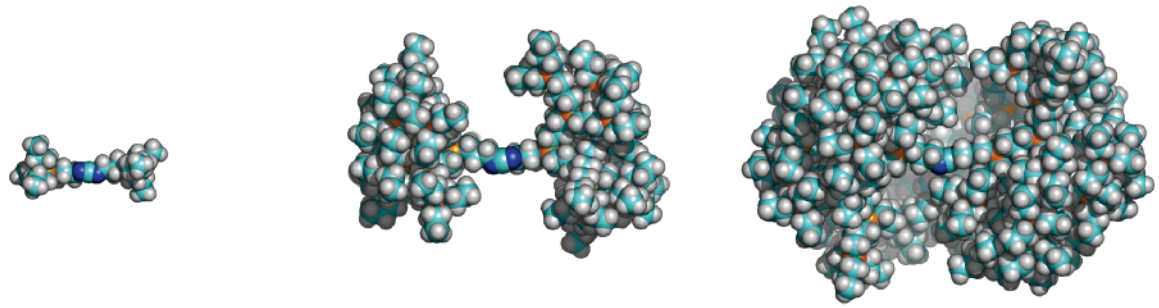
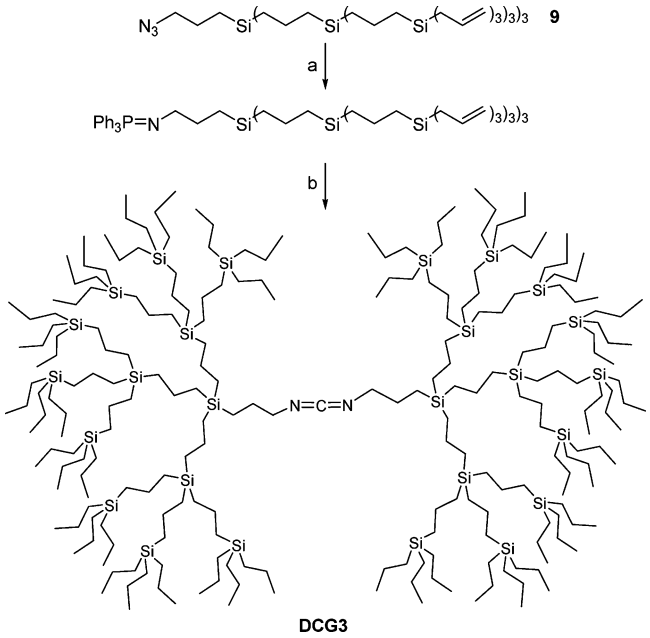


FIGURE 4.

SCHEME 8. Two-Step One-Pot Convergent Synthesis of Dendrimeric Carbodiimide DCG3[a]



[a] Reagents and conditions: (a) PPh_3 (1 equiv), THF, 65 °C, 6 h; (b) OCN[G3](propyl)$_{27}$ **16** (1 equiv), reflux, 16 h, 72%.

Lactamization Reactions. The dendrimeric analogue of the classical carbodiimides (e.g., dicyclohexylcarbodiimide) was explored in the ring closure of homodiketopiperazines (seven-membered cyclodipeptides). These compounds can be obtained via lactamization of their linear dipeptide precursors, but this is known to be very difficult using traditional solution carboxylic acid activating agents. Dipeptides H-βAla-(*N*Bn)Phe-OH **20** and H-Phe-(*N*Bn)βAla-OH **21**, consisting of an α- and a β- amino acid[35] and possessing a tertiary amide bond in the backbone, were used in our lactamization studies (Figure 5).[36] Substitution at the amide promotes the population of the cisoid amide bond conformation and thus facilitates ring closure. Dipeptides **20** and **21** were chosen to study the influence of steric congestions at the *C*- or *N*-terminus, respectively, on the cyclization efficiency.

As a control experiment, the head-to-tail ring closure of the N-substituted dipeptide **20** was also performed using the common dicyclohexylcarbodiimide (DCC) peptide coupling reagent. Compound **20** was reacted with DCC in 0.01 M THF in the presence of 1 equiv of DiPEA (to liberate the trifluoroacetic acid salt). Under these conditions, the cyclized product was obtained in a maximum of 12% yield. Next, the linear precursor **20** was reacted under the same conditions employing **DCG1**, **DCG2**, and **DCG3** as dendrimeric carbodiimides (Table 2).

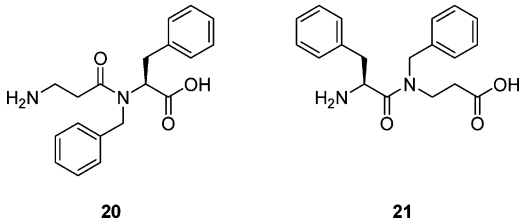


FIGURE 5. Dipeptides utilized as cyclization precursors.

Because ^{1}H NMR or HPLC proved inapplicable to monitor the reactions for all generations, the yield of the desired monocyclic product was determined after purification by column chromatography. In addition to the desired cyclo[-βAla-(*N*Bn)-Phe-] **22**, a side product was formed during cyclization mediated by **DCG1**, insoluble in solvents such as $CHCl_3$ and MeOH and most likely emerging from oligomerization. In the crude reaction mixture of the **DCG2**-mediated cyclization, the cyclic dimer (616 *m*/*e*, LC−MS) was observed. Interestingly, reaction with the first generation dendrimer generated a higher yield than DCC. This result is an accordance with literature precendent describing that a good solubility of the ureas formed may improve the coupling yield.[37,38] The second generation showed a yield comparable to the first generation, while the yield of the **DCG3**-mediated reaction was slightly lower (20%) than that of **DCG2**. Neither changing the solvent (CH_2Cl_2, mixture of DMF/THF) nor heating the reaction mixture improved the results. In apolar solvents such as hexanes, only starting material (**DCG3**) was recovered. We attribute the low yield obtained with the highest generation dendrimeric diimide **DCG3** to steric hindrance of the *C*-terminus of **20** hampering the activation step leading to the intermediate *O*-acylurea species. As a result of this steric interference, the concentration of the *O*-acylurea is low compared to that of free dipeptide, leading to side product formation via unwanted intermolecular pathways.

Consequently, the less hindered dipeptide **21** with respect to the *C*-terminus should give rise to a faster activation and thus higher cyclization yield. Initially, a blank experiment was conducted by reacting **21** with DCC using the standard cyclization conditions (THF, 0.01 M). The cyclized product **23** was obtained in 30% yield (vs 12% obtained with **20**), suggesting that a substrate with a less hindered *C*-terminus indeed results in fewer side reactions (oligomer formation). Dipeptide **21** was then subjected to cyclization mediated by the **DCG1**, **DCG2**, and **DCG3** dendrimeric carbodiimides (see Table 2).[39] Ring closure of **21** mediated by **DCG1** afforded the desired cyclo[-Phe-(*N*Bn)βAla-] **23** in yields almost twice as high as that found for the dipeptide **20**. Again, LC−MS analysis of the crude reaction mixtures of all dendrimer generations indicated the presence of linear (635 *m*/*e*) and ring-closed (617 *m*/*e*) dimers. However, a small but significant positive trend toward the formation of lactam **23** was observed going from **DCC** to **DCG3**. In fact, once the *O*-acylurea species is formed, the dendritic wedges can, especially for **DCG3**, hamper the side reactions.

A further advantage of employing dendrimeric carbodiimides is the ease of product purification. Whereas using DCC as the coupling reagent leads to a very tedious separation of the urea

(34) (a) Katritzky, A. R.; Jiang, J.; Urogdi, L. *Synthesis* **1990**, 565−567. (b) Ding, M.-W.; Tu, H.-Y.; Liu, Z.-J. *Synth. Commun.* **1997**, *27*, 3657−3662. (c) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron* **2001**, *57*, 4371−4388.

(35) Synthesized according to: Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Biomol. Chem.* **2003**, *1*, 1830−1832.

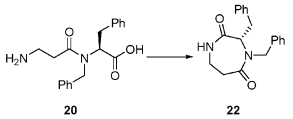
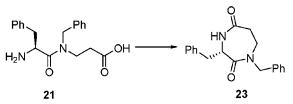
(36) Initially, it was our intention to cyclize unfunctionalized ω-amino acids, leading to 7-, 9-, 11-, and 13-membered lactams. These linear precursors can be excellent substrates since they present no conformational bias, and therefore the dendrimeric effect could be maximized. Unfortunately, they could not be used since they are not soluble in any of the solvents screened (THF, CH_2Cl_2, $CHCl_3$, MeOH) due to their dominating zwitterionic nature.

(37) Izdebski, J.; Kunce, D. *J. Pept. Sci.* **1997**, *3*, 141−144.

(38) Tartar, A.; Gesquiere, J. C. *J. Org. Chem.* **1979**, *44*, 5000−5001.

(39) It was noticed that the cyclization experiments required the addition of DiPEA prior to the addition of the carbodiimide to obtain reproducible results.

TABLE 2. Yields of the Lactamization Reactions[a]

	DCC	DCG1	DCG2	DCG3
 20 22	12%	24%	27%	20%
 21 23	30%	48%	50%	56%
Recovered Dendrimer		95%[b]	99%	99%

[a] Reaction conditions: DiPEA (1 equiv), THF (0.01 M), rt, 16 h. Isolated yields after column chromatography. [b] Recovered via column chromatography.

byproduct from the product, with dendrimeric carbodiimides such a process proved much easier and the dendrimers were recovered quantitatively (Table 2). In fact, the lipophilic properties of the ureas **18** and **19** permit facile separation of the dendrimers from the bulk solution by stirring with MeOH, which dissolves the peptide-based compounds but not the dendrimeric products. Additionally, the urea byproducts derived from **DCG1** and **DCG2** can be converted to the active carbodiimide easily and can therefore be reused.

Conclusions

In conclusion, the divergent synthesis of carbosilane wedges up to the third generation on a multigram scale having a versatile primary chloride as focal point moiety and allylic end groups was reported. Hydrogenation of the terminal allylic groups led to saturated dendrimers that were much more stable and inert. Efficient synthetic strategies were developed to convert the focal point into several reactive groups, both having electrophilic and nucleophilic properties ultimately leading to dendrimers containing a carbodiimide in the core in a convergent way. The Staudinger reaction proved to be a highly efficient route to obtain the third generation dendritic diimide **DCG3**. Such dendritic carbodiimides are stable and highly soluble in many organic solvents. Further, dendrimeric ureas **17**−**19** were analyzed for their tendency to aggregate via hydrogen bonding. FT-IR measurements showed that intermolecular hydrogen bonding occurs for the first generation dendrimer, but not for higher generations. This indicates that core-bound moieties are isolated from the bulk solution in higher generation carbosilane dendrimers. We exploited this shielding effect to enforce intramolecular reactions and thus explored the application of the dendrimeric carbodiimides to lactamization reactions. **DCG1**, **DCG2**, and **DCG3** successfully mediated cyclization of dipeptides that are difficult to ring-close with traditional methods. Although a positive dendritic effect was observed, the formation of side products could not be completely suppressed. Overall, it can be concluded that core-functionalized dendrimers have considerable potential in facilitating difficult cyclization reactions. We are currently developing a recyclable dendrimeric carboxylic acid-activating reagent with a more controllable mechanism to broaden the scope and utility of this new concept.

Experimental Section

All manipulations involving air- or water-sensitive compounds were performed using standard Schlenk techniques under a nitrogen atmosphere. Tetrahydrofuran and diethyl ether were freshly distilled from sodium with benzophenone as indicator. Dry DMF and CH_2Cl_2 were distilled from CaH_2. Triethylamine was dried and distilled from KOH pellets. All commercially available reagents were used as received, unless indicated otherwise.

CAUTION: Hydrosilylation reactions are highly exothermic, and good care should be taken. As a precaution, a dry ice/acetone bath should be kept at hand when adding the trichlorosilane.

First Generation Carbosilane Wedges Cl[G1](allyl)$_3$ (1).[40] Freshly distilled allyl chloride (60 mL, 0.74 mol) was divided into two portions and transferred in two dry Schlenk vessels under a nitrogen atmosphere; to each of them the cosolvents CH_2Cl_2 (1.5 mL for 1 g of allyl chloride) and Et_2O (1.0 mL for 1 g of allyl chloride) were added. A freshly prepared solution of $[Bu_4N]_2[PtCl_6]$[23] in dichloromethane was added (10^{-4} mol catalyst per mol of allyl end group). After the solution was stirred for 10 min, $HSiCl_3$ was added (1.5 equiv based on the amount of allyl end groups). Subsequently, a $CaCl_2$ tube was placed on the flask, and the nitrogen inlet was removed. The reactions were followed by ^{1}H NMR spectroscopy. If no more progress was observed, fresh catalyst was added. When conversion was complete (disappearance of allyl groups, usually observed after 16 h) the solvents were evaporated in vacuo. Distillations: membrane pump 110 °C product ^{1}H NMR ($CDCl_3$): 3.60 (t, 2H), 2.09−2.02 (m, 2H), 1.57 (t, 2H). (Side product not isolated.) The hydrosilylation product of the two reactions were combined and diluted with Et_2O (40 mL) and added dropwise to a cooled 2 M allylmagnesium bromide solution in Et_2O (1.1 equiv per chlorine end group). The reaction mixture was stirred for 5 h at room temperature. Excess allylmagnesium bromide was quenched by the addition of 10% $NH_4Cl_{(aq)}$ at 0 °C. The aqueous layer was extracted with diethyl ether (3×), and the combined organic layers were washed with water (1×) and brine (1×), dried over $MgSO_4$, and concentrated in vacuo. The crude product was filtered over a short silica column (pentane/Et_2O 10:1) to afford the product **1** (90 g, 52%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 5.83−5.73 (m, 3*H*), 4.91−4.85 (m, 6*H*), 3.36 (t, J = 6.9 Hz, 2*H*), 1.88−1.85 (m, 2*H*), 1.58 (d, 6*H*), 0.72−0.66 (m, 2*H*). ^{13}C NMR ($CDCl_3$): 133.6, 113.7, 47.3, 27.0, 19.4, 9.0. FAB-MS for $C_{12}H_{21}ClSi$: 186.9 [M − allyl], 144.9 [M − 2allyl].

Second Generation Carbosilane Wedges Cl[G2](allyl)$_9$ (2). The first generation carbosilane wedge Cl[G1](allyl)$_3$ **1** (20 g, 0.087 mol) was transferred in a dry Schlenk vessel under a nitrogen atmosphere; the cosolvents CH_2Cl_2 (30 mL) and Et_2O (20 mL) were added. A freshly prepared solution of $[Bu_4N]_2[PtCl_6]$[23] in dichloromethane was added (10^{-4} mol catalyst per mol of allyl end group). After the solution was stirred for 10 min, $HSiCl_3$ was added (39.5 mL, 0.39 mol). Subsequently, a $CaCl_2$ tube was placed on the flask,

(40) This method has been developed by Van Leeuwen/Van der Made at Shell (Amsterdam).

and the nitrogen inlet was removed. The reaction was followed by ^{1}H NMR spectroscopy. If no more progress was observed, fresh catalyst was added. When conversion was complete (disappearance of allyl groups, usually observed after 2 or 3 days), the solvents were evaporated in vacuo. The hydrosilylation product was diluted with Et_2O and was added dropwise to a cooled 2.2 M allylmagnesium bromide solution in Et_2O (1.1 equiv per chlorine end group). The reaction mixture was stirred for 6 h at room temperature. Excess allylmagnesium bromide was quenched by the addition of 10% $NH_4Cl_{(aq)}$ at 0 °C. The aqueous layer was extracted with diethyl ether (3×), and the combined organic layers were washed with water (1×) and brine (1×), dried over $MgSO_4$, and concentrated in vacuo. The crude product was filtered over a short silica column (pentane/Et_2O 95:5) to afford the pure product **2** as a colorless oil (54 g, 90%). ^{1}H NMR ($CDCl_3$): 5.83−5.73 (m, 9*H*), 4.91−4.85 (m, 18*H*), 3.49 (t, J = 6.9 Hz, 2*H*), 1.75−1.60 (m, 2*H*), 1.58 (d, 18*H*), 1.37−1.31 (m, 6*H*), 0.68−0.56 (m, 14*H*). ^{13}C NMR ($CDCl_3$): 134.1, 113.4, 47.6, 27.6, 19.7, 17.3, 17.2, 16.4, 9.9. MALDI-TOF MS calcd for $C_{39}H_{69}ClSi_4$, 684.42. Found, 643.3 [M − allyl]$^+$.

Third Generation Carbosilane Wedges Cl[G3](allyl)$_{27}$ (3). This compound was prepared according to the procedure described for the second generation starting from **2** (38 g, 55 mmol), stirring the hydrosilylation reaction for 5 days, and yielding after column chromatography (pentane) **3** as a colorless oil (94 g, 83%). ^{1}H NMR ($CDCl_3$): 5.83−5.73 (m, 27*H*), 4.90−4.85 (m, 54*H*), 3.49 (t, J = 6.9 Hz, 2*H*), 1.76−1.72 (m, 2*H*), 1.58 (d, 54*H*), 1.36−1.26 (m, 24*H*), 0.68−0.54 (m, 50*H*). ^{13}C NMR ($CDCl_3$) δ 134.3, 113.4, 47.9, 27.8, 19.6, 18.2, 17.4, 16.5. MALDI-TOF MS: calcd for $C_{120}H_{213}ClSi_{13}Ag$, 2124.3. Found, 2121.9 [M − allyl + Ag]$^+$.

Cl[G1](propyl)$_3$ (4). To a solution of Cl[G1](allyl)$_3$ **1** (3.47 g, 10 mmol) in EtOAc/MeOH (60 mL, 3:1 v/v) 10% Pd/C (0.3 g) was added. The resulting mixture was stirred under hydrogen pressure (1 atm, balloon) for 16 h. The reaction was filtered over Celite, and the solvents were evaporated under reduced pressure to afford the product **4** (1.9 g, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.49 (t, J = 6.9 Hz, 2H), 1.82−1.65 (m, 2H), 1.40−1.20 (m, 6H), 0.90 (t, J = 7.2 Hz, 9H), 0.50−0.40 (m, 6H). ^{13}C NMR ($CDCl_3$): 48.1, 27.8, 18.6, 17.4, 15.7, 10.4.

Cl[G2](propyl)$_9$ (5). This compound was prepared according to the procedure described for the first generation starting from **2** (1.94 g, 2.8 mmol) and yielding **5** (1.8 g, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.44 (t, J = 6.8 Hz, 2H), 1.78−1.74 (m, 2H), 1.41−1.32 (m, 24H), 1.01−0.97 (t, J = 7.2 Hz, 27H), 0.65−0.53 (m, 32H). ^{13}C NMR ($CDCl_3$): 43.1, 29.5, 18.5, 17.8, 17.6, 17.3, 15.5, 9.3.

Cl[G3](propyl)$_{27}$ (6). To a solution of Cl[G3](allyl)$_{27}$ **3** (4 g, 1.9 mmol) in EtOAc/MeOH (50 mL, 10:1 v/v) 10% PtO_2 (0.4 g) was added. The resulting mixture was stirred under hydrogen pressure (1 atm, balloon) for 2 days. The reaction was filtered over Celite, and the solvents were evaporated under reduced pressure to afford the product **6** (4.14 g, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 3.47 (t, J = 6.7 Hz, 2H), 1.77−1.75 (m, 2H), 1.35−1.28 (m, 78H), 0.97−0.93 (t, J = 7.2 Hz, 81H), 0.57−0.47 (m, 104H). ^{13}C NMR ($CDCl_3$, 500 MHz): 43.1, 29.5, 18.4, 17.6, 17.3, 15.2. Anal. calcd for $C_{120}H_{267}ClSi_{13}$: C, 68.28; H, 12.75; Si, 17.30. Found: C, 68.14; H, 12.70; Si, 17.24.

N$_3$[G1](propyl)$_3$ (7). To a solution of Cl[G1](propyl)$_3$ **4** (0.7 g, 3 mmol) in DMF (15 mL) was added NaN_3 (1 g, 15 mmol). The resulting mixture was warmed to 90 °C and stirred for 6 h. Then, most of the solvents were evaporated; the remaining mixture was diluted with water (15 mL) and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with water (1 × 10 mL) and aqueous saturated NaCl (10 mL), dried over $MgSO_4$, and concentrated in vacuo to afford N$_3$[G1](propyl)$_3$ **7** (0.62 g, 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$): 3.22 (t, J = 6.8 Hz, 2*H*), 1.61−1.54 (m, 2H), 1.35−1.28 (m, 6H), 0.95 (t, J = 7.2 Hz, 9H), 0.56−0.49 (m, 8H). ^{13}C NMR ($CDCl_3$): 54.5, 23.6, 18.4, 17.2, 14.9, 9.6. IR (NaCl): ν 2955 to 2869 (CH_2, CH_3 stretch), 2094, 1464 (CH_2 deformation).

N$_3$[G2](propyl)$_9$ (8). This compound was prepared according to the procedure described for the first generation starting from **5** (1 g, 1.4 mmol), stirring at 90 °C for 16 h, and yielding **8** (1 g, 99%) as a colorless oil. ^{1}H NMR: 3.22 (t, J = 6.9 Hz, 2H), 1.60−1.53 (m, 2H), 1.21−1.17 (m, 24H), 0.83 (t, J = 7.2 Hz, 27H), 0.50−0.35 (m, 32H). ^{13}C NMR ($CDCl_3$): 54.7, 23.9, 18.6, 17.9, 17.7, 17.6, 15.4, 9.9. IR (NaCl): ν 2955 to 2869 (CH_2, CH_3 stretch), 2096, 1461 (CH_2 deformation).

I[G3](propyl)$_{27}$ (10). To a solution of Cl[G3](propyl)$_{27}$ **6** (2 g, 0.95 mmol) in THF/DMF (80 mL, 3:1 v/v) was added NaI (1.42 g, 9.5 mol). The resulting mixture was warmed to 110 °C and stirred for 16 h. Then, most of the solvents were evaporated; the remaining mixture was diluted with water (50 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with water (1 × 20 mL) and aqueous saturated NaCl (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford I[G3](propyl)$_{27}$ **5c** (2 g, 95%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 3.17 (t, J = 7.1 Hz, 2H), 1.82−1.78 (m, 2H), 1.35−1.29 (m, 78H), 0.95 (t, J = 7.2 Hz, 81H), 0.58−0.47 (m, 104H). ^{13}C NMR (500 MHz, $CDCl_3$): 29.3, 19.0, 18.9, 18.1, 18.0, 17.8, 15.7.

N$_3$[G3](propyl)$_{27}$ (9). To a solution of I[G3](propyl)$_{27}$ **10** (2 g, 0.90 mmol) in THF/DMF (20 mL, 3:1 v/v) was added NaN_3 (0.6 g, 9 mmol). The resulting mixture was warmed to 110 °C and stirred for 2 days. Then, most of the solvents were evaporated; the remaining mixture was diluted with water (30 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (1 × 20 mL) and aqueous saturated NaCl (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford N$_3$[G3](propyl)$_{27}$ **9** (1.74 g, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 3.14 (t, J = 6.8 Hz 2H), 1.60−1.57 (m, 2H), 1.28−1.22 (m, 78H), 0.88 (t, J = 7.2 Hz, 81H), 0.51−0.40 (m, 104H). ^{13}C NMR (500 MHz, $CDCl_3$): 54.7, 23.9, 18.7, 18.6, 17.8, 17.7, 17.5, 15.4, 1.0. IR (NaCl): ν 2955 to 2795 (CH_2, CH_3 stretch), 2095, 1455 (CH_2 deformation). Anal. calcd for $C_{120}H_{267}N_3Si_{13}$: C, 68.06; H, 12.71; N, 1.98. Found: C, 68.21; H, 12.75; N, 2.02.

One-Pot Procedure for the Synthesis of N$_3$[G3](propyl)$_{27}$ Starting from Cl[G3](propyl)$_{27}$. To a solution of Cl[G3](propyl)$_{27}$ **6** (2 g, 0.95 mmol) in THF/DMF (20 mL, 3:1 v/v) in a sealed tube were added KI (0.16 g, 0.9 mmol) and NaN_3 (0.6 g, 9 mmol). The resulting mixture was warmed to 110 °C and stirred for 3 days. Then, most of the solvents were evaporated; the remaining mixture was diluted with water (30 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (1 × 20 mL) and aqueous saturated NaCl (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford N$_3$[G3](propyl)$_{27}$ **9** (1.8 g, 90%) as a yellow oil.

NH$_2$[G1](propyl)$_3$ (11). To a solution of N$_3$[G1](propyl)$_3$ **7** (0.5 g, 2.1 mmol) in EtOAc/MeOH (25 mL, 10:1 v/v) 10% Pd/C (0.05 g) was added. The resulting mixture was stirred under hydrogen pressure (1 atm, balloon) for 16 h. The reaction was filtered over Celite, and the solvents were evaporated under reduced pressure to afford the product **11** (0.32 g, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.94−2.90 (m, 2H), 1.74−1.70 (m, 2H), 1.30−1.26 (m, 6H), 0.95 (t, J = 7.2 Hz, 9H), 0.57−0.49 (m, 8H). ^{13}C NMR ($CDCl_3$): 43.4, 22.2, 18.6, 17.2, 14.8, 9.5. IR (NaCl): ν 3167 (N−H stretch), 2728 (CH_2, CH_3 stretch), 1459 (CH_2 deformation). HRMS (FAB$^+$) *m*/*e* found 216.2145 (MH$^+$ $C_{12}H_{30}NSi$ requires 216.2148).

NH$_2$[G2](propyl)$_9$ (12). To a solution of N$_3$[G2](propyl)$_9$ **8** (0.5 g, mmol) in EtOAc/MeOH (30 mL, 10:1 v/v) 10% Pd/C (0.05 g) was added. The resulting mixture was stirred under hydrogen pressure (1 atm, balloon) for 16 h. The reaction was filtered over Celite, and the solvents were evaporated under reduced pressure to afford the product **12** (0.42 g, 56%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.91 (t, J = 6.9 Hz, 2H), 1.68−1.65 (m, 2H), 1.35−1.26 (m, 24H), 0.94 (t, J = 7.2 Hz, 24H), 0.59−0.46 (m, 32H). ^{13}C NMR ($CDCl_3$): 42.5, 22.0, 18.5, 17.5, 16.9, 15.0, 8.0. IR (NaCl): ν 2956 to 2870 (CH_2, CH_3 stretch), 1454 (CH_2 deformation).

NH$_2$[G3](propyl)$_{27}$ (13). Method A (Catalytic Hydrogenation). To a solution of N$_3$[G3](propyl)$_{27}$ **9** (1 g, 0.47 mmol) in EtOAc/

MeOH (50 mL, 10:1 v/v) 10% Pd/C (0.1 to 0.4 g) was added. The resulting mixture was stirred under hydrogen pressure (1 atm, balloon) for 16 h. The reaction was filtered over Celite, and the solvents were evaporated under reduced pressure to afford the product **13** (0.7 g, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.67 (t, J = 6.9 Hz, 2H), 1.53−1.27 (m, 80H), 0.97−0.94 (t, J = 7.2 Hz, 81H), 0.58−0.48 (m, 104H). ^{13}C NMR ($CDCl_3$): 46.0, 29.0, 19.0, 18.9, 18.8, 14.4, 8.8. MALDI-TOF MS: calcd for $C_{120}H_{269}NSi_{13}$, 2089.811. Found, 2091.889 $[M + H]^+$.

Method B (Staudinger Reduction). To a solution of N_3[G3](propyl)$_{27}$ **9** (1 g, 0.47 mmol) in THF (10 mL) PPh_3 (0.13 g, 0.47 mmol) was added. The resulting mixture was stirred at 70 °C overnight. After this time, a few drops of water were added and stirring was continued for 2 h. The solvent was removed under reduced pressure, and the resulting slurry was diluted with pentane (10 mL). The solid (PPh_3O) was filtered off and washed with additional pentane. The organic layer was evaporated to afford the product **13** (0.93 g, 95%) as a colorless oil.

OCN[G1](propyl)$_3$ (14). To a stirred solution of $NaHCO_3$ (2.3 g, 27 mmol) in water (18 mL), H_2N[G1](propyl)$_3$ **11** (1.5 g, 7 mmol) in toluene (18 mL) was added. The resulting mixture was cooled at 0 °C, and phosgene (14 mL, 27 mmol) was added in once. The white solution was stirred for 2 h. The layers were separated, and the aqueous layer was extracted with Et_2O (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford OCN[G1](propyl)$_3$ **14** (1.57 g, 93%) as a colorless oil, which was used without further purification. ^{1}H NMR: 3.22 (t, J = 6.8 Hz, 2H), 1.61−1.56 (m, 2H), 1.34−1.27 (m, 6H), 0.95 (t, J = 7.2 Hz, 9H), 0.55−0.46 (m, 8H). ^{13}C NMR ($CDCl_3$): 122.0, 45.9, 26.1, 18.2, 17.2, 14.9, 9.4. IR (NaCl): ν 2922 (CH_2, CH_3 stretch), 2268 (O═C═N stretch).

OCN[G2](propyl)$_9$ (15). This compound was prepared according to the procedure described for the first generation starting from H_2N[G2](propyl)$_9$ **12** (2 g, 2.9 mmol) and yielding **15** (2.1 g, 97%) as a colorless oil. ^{1}H NMR($CDCl_3$): 3.24 (t, J = 6.9 Hz, 2H), 1.55−1.50 (m, 2H), 1.37−1.29 (m, 24H), 0.96 (t, J = 7.2 Hz, 27H), 0.60−48.00 (m, 32H). ^{13}C NMR ($CDCl_3$): 121.0, 45.0, 26.0, 18.4, 18.2, 17.0, 16.5, 15.6, 11.1.

OCN[G3](propyl)$_{27}$ (16). This compound was prepared according to the procedure described for the first generation starting from **13** (0.6 g, 0.29 mmol) and yielding **16** (0.52 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.21 (t, J = 6.9 Hz, 2H), 1.55−1.52 (m, 2H), 1.37−1.30 (m, 78H), 0.96 (t, J = 7.2 Hz, 81H), 0.59−0.48 (m, 104H). ^{13}C NMR ($CDCl_3$): 120.0, 45.0, 27.0, 19.0, 18.0, 17.0, 15.0, 7.0. IR (NaCl): ν 2953 to 2868 (CH_2, CH_3 stretch), 2266 (O═C═N stretch), 1455 (CH_2 deformation).

First Generation Urea (17). A solution of OCN[G1](propyl)$_3$ **14** (440 mg, 1.8 mmol) and H_2N[G1](propyl)$_3$ **10** (340 mg, 1.6 mmol) in dry toluene (5 mL) was stirred at 90 °C for 16 h. The solution was then concentrated in vacuo, and the crude product was purified by flash column chromatography (PE/EtOAc 1:1) to afford urea **17** (900 mg, 89%) as a white solid (mp 66 °C). ^{1}H NMR ($CDCl_3$): 4.20 (bs, NH), 3.13−3.10 (m, 4H), 1.48−1.44 (m, 4H), 1.35−1.25 (m, 12H), 0.93 (t, J = 7.2 Hz, 18H), 0.51−0.46 (m, 16H). ^{13}C NMR ($CDCl_3$): 157.9, 43.9, 24.7, 18.4, 17.2, 15.0, 9.6. IR (NaCl): ν 3366 (NH stretch), 2954 to 2867 (CH_2, CH_3 stretch), 1630, 1578 (CO stretch). HRMS (FAB$^+$) *m*/*e*: found 439.3907 (MH^+ $C_{25}H_{55}N_2Si_2$ requires 439.3904).

Second Generation Urea (18). This compound was prepared according to the procedure described for the first generation starting from **11** (420 mg, 0.6 mmol) and **15** (468 mg, 0.7 mmol) and yielding **18** (770 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 4.20 (bs, NH), 3.13−3.11 (m, 4H), 1.47−1.44 (m, 4H), 1.34−1.25 (m, 48H), 0.94 (t, J = 7.2 Hz, 54H), 0.58−0.47 (m, 64H). ^{13}C NMR ($CDCl_3$): 157.8, 44.0, 29.2, 18.4, 17.7, 17.5, 15.3, 9.9. IR (NaCl): ν 3326 (NH stretch), 2954 to 2867 (CH_2, CH_3 stretch), 1640, 1566 (CO stretch), 1464 (CH_2 deformation). HRMS (FAB$^+$) *m*/*e* found 1394.2010 (MH^+ $C_{79}H_{177}N_2OSi_8$ requires 1394.2015).

Third Generation Urea (19). This compound was prepared according to the procedure described for the first generation starting from **12** (200 mg, 0.1 mmol) and **16** (200 mg, 0.1 mmol) and yielding **19** (239 mg, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$): @NH 3.12 (m, 4H), 1.50−1.41 (m, 4H), 1.38−1.26 (m, 156H), 0.96 (t, J = 7.2 Hz, 162H), 0.55−0.49 (m, 208H). ^{13}C NMR ($CDCl_3$): 157.0, 44.1, 24.7, 18.5, 18.4, 17.7, 17.5, 17.3, 15.2. IR (neat NaCl): ν 2957 to 2725 (CH_2, CH_3 stretch), 1698, 1518 (CO stretch), 1458 (CH_2 deformation). MALDI-TOF MS: calcd for $C_{241}H_{536}N_2OSi_{26}$, 4207.6. Found, 4231.0 $[M + Na]^+$.

First Generation Carbodiimide (DCG1). A solution of PPh_3 (500 mg, 1.9 mmol) in dry CH_2Cl_2 (10 mL) was cooled at 0 °C. Bromine (99 μL, 1.9 mmol) was added dropwise followed by the addition of Et_3N (0.61 mL, 4.2 mmol) in one portion. After the solution was stirred for 10 min, **17** (800 mg, 1.7 mmol) was added to the yellow suspension. The mixture was allowed to warm to room temperature and stirred for 16 h. The resulting red slurry was concentrated in vacuo before dilution with dry pentane (5 mL). The solids were filtered off and washed with additional pentane. The organic layer was evaporated, and the crude product was purified by flash column chromatography (basic alumina, 5% Et_3N in pentane) to afford the carbodiimide **DCG1** (470 mg, 63%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.15 (t, J = 6.9 Hz, 4H), 1.56−1.52 (m, 4H), 1.34−1.28 (m, 12H), 0.95 (t, J = 7.1 Hz, 18H), 0.55−0.48 (m, 16H). ^{13}C NMR ($CDCl_3$): 141.0, 50.0, 25.9, 18.4, 17.2, 15.0, 9.7. IR (NaCl): ν 2955 (CH_2, CH_3 stretch), 2120 (N═C═N stretch), 1461 (CH_2 deformation). Anal. calcd for $C_{25}H_{54}N_2Si_2$: C, 68.42; H, 12.40; N, 6.38. Found: C, 68.33; H, 12.29; N, 6.31.

Second Generation Carbodiimide (DCG2). This compound was prepared according to the procedure described for the first generation starting from **18** (610 mg, 0.4 mmol) and yielding **DCG2** (450 mg, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.17 (t, J = 7.0 Hz, 4H), 1.56−1.54 (m, 4H), 1.36−1.29 (m, 48H), 0.95 (t, J = 7.2 Hz 54H), 0.58−0.47 (m, 64H). ^{13}C NMR ($CDCl_3$): 140.5, 50.5, 26.4, 18.9, 18.8, 10.1, 17.9, 17.8, 15.7, 10.2. IR (NaCl): ν 2955 to 2868 (CH_2, CH_3 stretch), 2130 (N═C═N stretch), 1411 (CH_2 deformation). HRMS (FAB$^+$) *m*/*e* found 1376.1912 (MH^+ $C_{79}H_{175}N_2Si_8$ requires 1376.1910). Anal. calcd for $C_{78}H_{170}N_2Si_8$: C, 68.84; H, 12.59; N, 2.06. Found: C, 69.03; H, 12.75; N, 2.01.

Third Generation Carbodiimide (DCG3). To a solution of N_3[G3](propyl)$_{27}$ **9** (850 mg, 0.40 mmol) in THF (12 mL) was added PPh_3 (105 mg, 0.40 mmol). The resulting mixture was stirred at 65 °C for 6 h. After this time OCN[G3](propyl)$_{27}$ **16** (930 mg, 0.44 mmol) was added, and stirring was continued under reflux for 16 h. Then, the solvent was evaporated. The crude product was purified using column chromatography (basic alumina, hexanes) to afford the carbodiimide **DCG3** (1.2 gr, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$): 3.18 (t, J = 7.0 Hz, 4H), 1.54−1.52 (m, 4H), 1.37−1.28 (m, 156H), 0.98 (t, J = 7.2 Hz, 162H), 0.58−0.48 (m, 208H). ^{13}C NMR (500 MHz, $CDCl_3$): 139.6, 50.3, 26.3, 18.7, 17.9, 17.8, 17.7, 15.7. IR (NaCl): ν 2954 to 2866 (CH_2, CH_3 stretch), 2130 (N═C═N stretch), 1411 (CH_2 deformation). Anal. calcd for $C_{241}H_{534}N_2Si_{26}$: C, 69.07; H, 12.84; N, 0.67. Found: C, 69.15; H, 12.76; N, 0.69.

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Supporting Information Available: Analytical equipment used and procedures of the lactamization experiments toward **22** and **23** (part I). Copies of the spectral data of compounds **1**−**23** (**1**−**9**, part I; **10**−**16**, part II; **17**−**23**, part III). This material is available free of charge via the Internet at http://pubs.acs.org.

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