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α,ω-Functionalized Poly(2-Oxazoline)s Bearing Hydroxyl and Amino Functions

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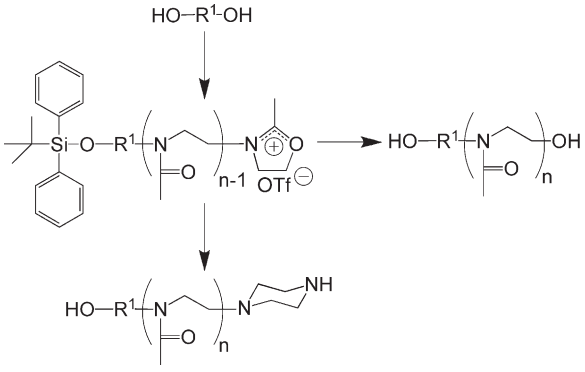
Novel α,ω-functionalized amphiphilic lipopolymers are prepared that are composed of a proximal lipid moiety and a hydrophilic poly(2-oxazoline)-based (POx) polymer chain. The synthesis begins from bifunctional lipoinitiators, which are asymmetrically protected as *tert*.butyldiphenylsilyl (TBDPS) ethers, followed by cationic living ring-opening polymerization of 2-oxazolines in a one-pot multistep reaction. This results in polymers with defined terminal end groups and narrow molar mass distributions. All protective groups involved can be readily cleaved in a single step reaction keeping the structure of the polymer intact, giving access to (lipo)polymers with a variety of defined identical or chemical orthogonal α,ω-functionalities. The synthetic strategy is a versatile tool for the preparation of defined polymer–drug or polymer–protein conjugates or asymmetric functionalized model lipid membranes for the quantitative study of membrane-associated phenomena such as transmembrane transport and cell adhesion/recognition.



Introduction

Cell membranes are crucial for the existence of all living matter. Biomembranes define cells and organelles and are an exceptional example of a self-organized system mainly based on the hydrophobic effect. Along with its premier function of compartmentalization, all active or passive transport of matter and information are membrane associated. However, as biological cell membranes are complex in their design and composition, direct studies of their interplay with the extra- and intracellular environment are difficult to be performed with natural membranes. To overcome this problem, several methods for the construction of artificial, ideally biomimetic membrane models such as black lipid membranes, liposomes or solid-supported membranes that mimic one more aspects of their natural counterparts have been investigated.[1–13] While solid-supported lipid bilayers allow integration of, e.g., ion channels and several membrane-spanning receptors, limitations are, e.g., their poor stability or sterical restrictions which makes it difficult to incorporate large transmembrane proteins.

To overcome the spatial and dynamic constrains, Sackmann[4] and Ringsdorf and co-workers[14] suggested to introduce soft hydrophilic polymeric layers to decouple the rigid substrate from the lipid bilayer.[4,15–17] The concept of such "polymer-supported" membranes can be realized by intermediate "polymer cushions"[15,18–21] or "polymer-tethered" membranes (PTM). In the latter, lipids with hydrophilic polymer head groups (lipopolymers) are incorporated into the lipid bilayer, acting as spacer to define the distance between membrane and substrate. A great

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number of compounds has been found suitable for this purpose, in particular polymers[17,22] and oligomers[23–26] of ethyleneoxide but also oligopeptides bearing thiol groups[27] and acrylates.[28–34] In a series of contributions we and others demonstrated that tailored poly(2-oxazoline) (**POx**) lipopolymers are a highly versatile system for the construction of PTMs.[35–44] **POx**-based PTMs have been successfully used to determine lateral mobility and functionality of reconstituted membrane proteins,[17,23,41,42,45] to modulate the interactions between substrate and membrane[46] but also the PTM structure.[47] **POx**-lipopolymers are prepared via living cationic ring-opening polymerization that provides a high structural definition of the polymer along with suitable functionalization methods of pendant and end-functions to tune the molecular dimensions as well as the amphiphilic contrast of the lipopolymer.

PTMs are most suitable for the incorporation of cell binding motifs as the intermediate flexible polymer tether not only decouples substrate and bilayer, but also directly connects the lipid moiety to a given lateral point by chemical grafting.[38,48] Three possible scenarios of lipopolymers equipped with ''extracellular'' (binding or signaling) motifs are outlined in Figure 1.

The easiest alternative is to introduce the binding or recognition site by incorporation of a functionalized membrane lipid (Figure 1a). This will allow control of the outer membrane composition (binding sites/unit area) and also allow free diffusion of the lipid within the outer membrane leaflet which is crucial for, e.g., the formation of focal adhesion sites. However, a free mobility of the lipid in the fluid membrane might be undesirable if one want to study adhesion/recognition at predetermined sites. Alternatively, the recognition site has to be fixed, relative to the underlying substrate which could be realized by the use of α,ω-functionalized transmembrane lipids, bearing one or two polymer spacers (Figure 1c).

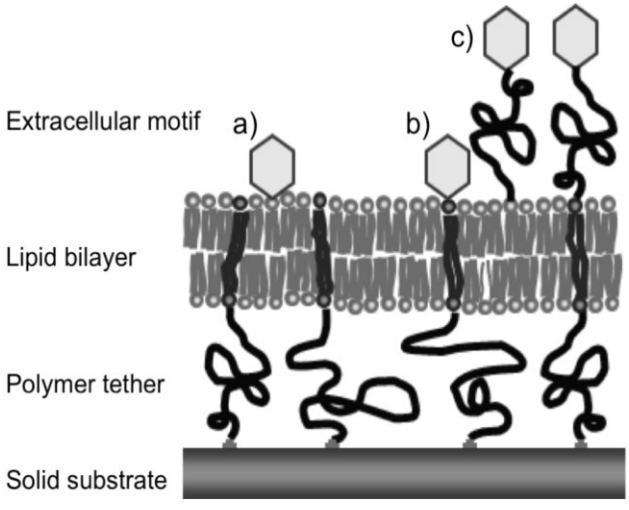


Figure 1. Three different scenarios of a polymer tethered membrane with an extracellular motif bound to the lipid bilayer. (a) Incorporation of binding sides by a functionalized lipid, (b) via a surface-tethered lipopolymer with a functionalized transmembrane lipid, (c) as (a) but with an additional polymer spacer to modulate the binding/recognition or finally analog to (b) but with an additional polymer spacer.

POx-based lipopolymers are prepared from lipid alcohols as precursor for lipoinitiators (triflates or tosylates) for the cationic polymerization. To prepare monofunctional lipopolymers from bifunctional lipid, the challenge is to identify a suitable protective group that is stable towards the reaction conditions used during sulfonation of the remaining hydroxyl-functionality. For the introduction of hydroxyl-bearing side chains several concepts have been reported.[49,50]

However, neither of these routes is straightforward applicable for initiator synthesis, but provides sufficient protections of the hydroxyl functions only during the comparably milder conditions applied during subsequent polymerization.

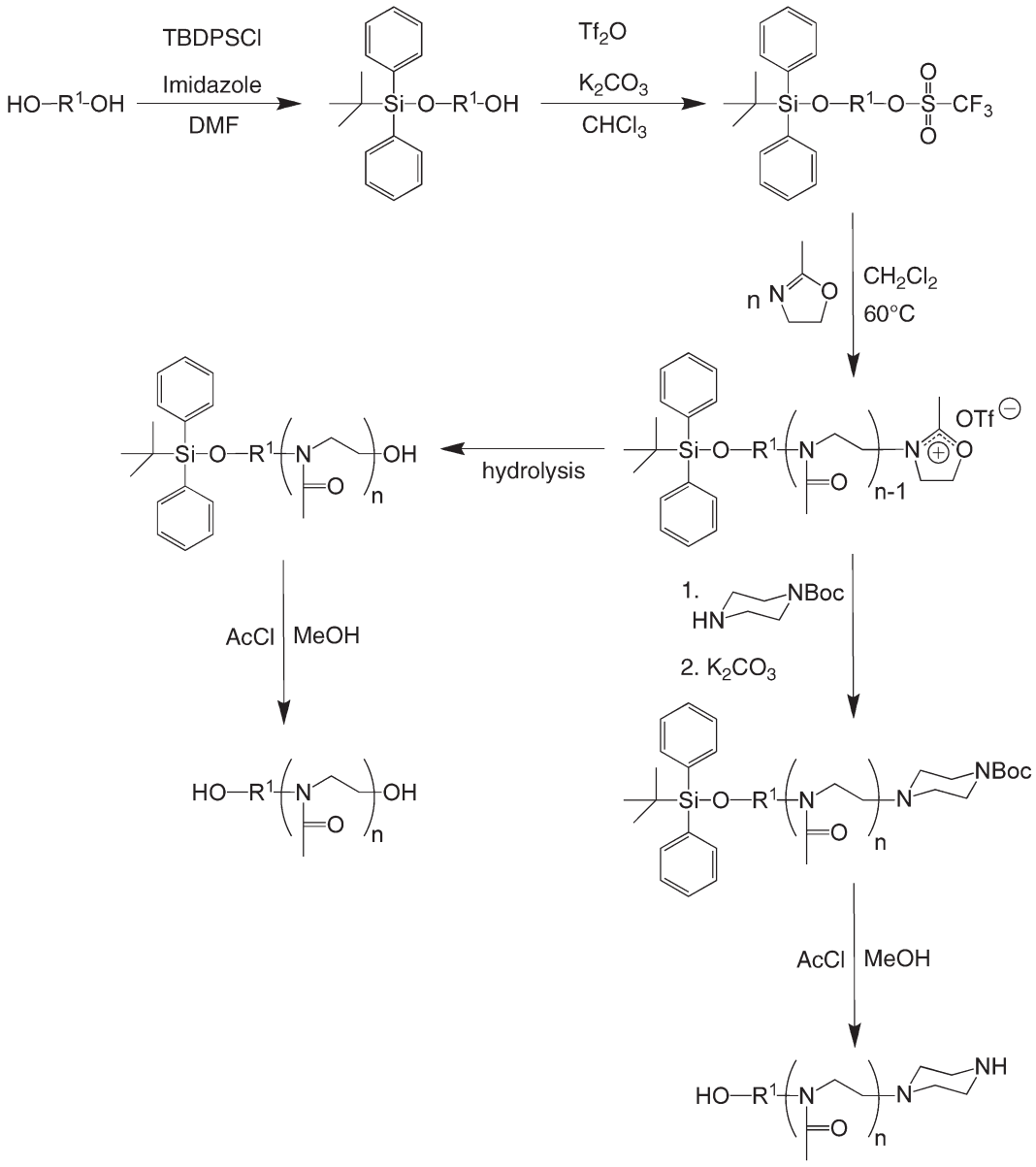
In this work, we demonstrate the synthesis of initiators for the living cationic ring-opening polymerization of 2-oxazolines derived from asymmetrically protected lipophilic diols for the polymerization of, e.g., 2-methyl-2-oxazoline (**MeOx**) leading to polymers with a proximal hydroxyl function and a distal amino-/or hydroxyl functionality after successful removal of all protective groups in a single step. This synthetic strategy may be useful for the defined preparation of novel α,ω-polymer-drug conjugates, and as shown here synthesis of lipopolymers for next generation polymer-tethered membrane models.

Results and Discussion

General

The synthesis of a α,ω - hydroxyl-/amino-functionalized **POx** was performed as outlined in Scheme 1, initially starting from a monoprotected hydrophobic diol, followed by sulfonation, polymerization, subsequent termination, and deprotection with a suitable reagent to yield α,ω-functional (lipo)polymers.

To ensure fast initiation of the living cationic ring-opening polymerization (LCROP) and thus, lower dispersities of the polymer products, triflates are used as initiators. Consequently, we identified a suitable protective group which proofed to be inert towards both, cationic conditions applied during polymerization and towards the even harsher conditions of the triflatization. Moreover, synthesis of the protected initiator should provide the same quantitative yields to facilitate a reliable adjustment of the degree of polymerization and to avoid side-products that



Scheme 1. Reaction scheme for the synthesis of α,ω-poly(2-oxazoline) lipopolymers equipped with two terminal hydroxyl or alternatively, an hydroxyl and amino function for further orthogonal functionalization. Alternatively, the oxazolinium chain end can be terminated with an excess of piperidine for monohydroxyl endfunctionalized POx. Termination reaction with an excess of unprotected piperazine yield directly an amino endfunctionalized polymer.

might interfere with the polymerization of 2-oxazolines. After preparation of the polymer, it is desirable to quantitatively remove the protective group(s) and to separate the polymer product from all residual small molecules. Given the fact that most hydroxyl protective groups are cleaved under more or less acidic conditions by Brønstedt or Lewis acids, these are quite challenging synthetic demands.[51]

Several hydroxyl-protective groups have been reported to be stable towards conditions of the LCROP of 2-oxazolines while attached to the monomer side chain.[49,50] Furthermore, **POx** from initiators with a protected aldehyde-functionality is described.[52,53] However, neither of these examples will yield a defined distal-terminal functionalization of POx with triflate initiators.

Initiator Synthesis

All initiator syntheses were performed from symmetric diol compounds as models for a transmembrane lipid such as

1,12-dodecanediol and 10,12-docosadiyne-1,22-diol, which was originally described by Bader and Ringsdorf[54] as an example for a synthetic transmembrane lipid.

In order to find a suitable protective group chemistry, several protective groups reported in the literature have been studied.[51] All esters commonly used for protection are too labile towards acidolysis so that we exclusively examined protective groups attached to the hydroxyl functions via an ether bond and reported as most stable. In particular, we investigated the MEM-ether, silyl ethers such as TBDMS and TBDPS and benzyl ethers including derivates such as 2-nitrobenzyl ether and 4-methoxybenzyl ether.

Sulfonization can be generally performed either in pyridine using the chlorides of the corresponding sulfonic acids or directly from the anhydride. We considered the latter route since triflic anhydride can be easily removed by evaporation at reduced pressure. Moreover, potential downscaling of the reactions is facilitated which becomes important for the synthesis with transmembrane lipids.

First screening of suitable protective groups were performed by means of stability tests towards triflic anhydride, removal or subsequent triflatization of the remaining free hydroxyl group which would result in a mixture of mono- and bis-sulfonated initiators. We found that all of the investigated protective groups were not suitable, except for benzyl- and TBDPS-ethers. Both were found to be sufficient stability towards triflic anhydride. As benzyl ethers are cleaved reductively via hydrogenolysis, this alternative is unsuitable, as these conditions would also reduce the amide side groups of **POx**.

The ethers of TBDPS were found to be stable under adjusted reaction conditions for triflatization—-i.e., use of a deficit of triflic anhydride (0.97 equivalents) at rather high dilution. Additionally, a higher amount of the inorganic base (K_2CO_3) had to be added to neutralize all acid produced during the sulfonation. If the monoprotected initiator was applied directly for the subsequent polymerization after its preparation, we initially observed the formation of proton-initiated polymer as side product by MALDI-TOF mass spectrometry.

This could be solved successfully by evaporation of the organic solvent of the reaction mixture to dryness in the presence of the inorganic base at reduced pressure. Since TBDPS-protected triflates were chemically instable and tended to decompose during storage, it was not possible to isolate the same in pure state for further analytic characterization. Instead, TBDPS-monoprotected initiators were applied as solution in chloroform instantly after work-up for subsequent polymerization. This complies with an observation reported previously for compounds with TBDPS- and triflate-functions.[55] Following the adapted preparation protocol (Scheme 1), TBDPS-protected triflate initiators were obtained in quantitative yields.

Although a deficit of anhydride for initiator preparation was used, no termination reaction by hydroxyl functionalities during polymerization could be observed. A possible explanation is that after consumption of triflic anhydride during workup, all remaining free OH-groups reacted with the sulfonic esters forming ethers. However, these ethers did not interfere with the subsequent polymerization.

Living-Cationic Ring Opening Polymerization (LCROP)

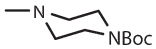
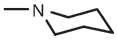
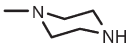
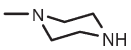
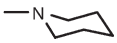
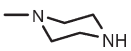
The living cationic ring opening polymerization (LCROP) was performed with TBDPS-protected initiators and 2-methyl-2-oxazoline (**MeOx**) as the monomer (Scheme 1). Termination of the LCROP was carried out with piperidine, 1-boc-piperazine[56] or water. Kobayashi et al.[57] reported a method for aqueous termination in acetonitrile as solvent. However, since we have to use chloroform to effectively dissolve the diol (i.e., long transmembrane lipid) to ensure uniform polymerization initiation, we used ternary mixtures of chloroform/methanol/water and chloroform/acetonitrile/water.

Both of the investigated initiators, from 1,12-dodecanediol and 10,12-docosadiyne-1,22-diol were found to be suitable for the LCROP of **MeOx**. The observed dispersities (Đ) were very low (1.01–1.03) and degrees of polymerization as determined by MALDI-TOF mass spectrometry and ^{1}H NMR spectroscopy (endgroup analysis) were found to be in excellent agreement with the initial $[M]_0/[I]_0$ ratio indicating a living ionic polymerization mechanism and a fast initiation reaction ($k_i \gg k_p$). However, it should be noted that the work-up by precipitation of lipopolymers is automatically associated with loss of material because of aggregate formation in any given solvent or solvent combination of the strongly amphiphilic polymer and intrinsic tendency to self-assemble. Thus, molar mass distribution of the crude polymer product might be slightly higher than after work-up. Furthermore, MALDI-TOF MS may discriminate either higher or lower molar mass fractions. As the molar mass distribution of the MALDI-TOF-MS as well as the GPC elugrams are very symmetrical the latter can be ruled out to some extend. However, the consistent data obtained by NMR endgroup analysis, MALDI-TOF-MS and GPC strongly indicate a living and stochiometric cationic polymerization. According to these data all of the TBDPS ether protecting groups remained fully intact after polymerization in chloroform at 60 °C. In Table 1, the different POx lipopolymer compositions (R^1 and R^2) are listed along with their analytical data and yields.

A typical ^{1}H NMR spectrum of (**7**) is given in Figure 2A. All signals could be unambiguously assigned. The signal integrals are in good agreement with the desired degrees of polymerization.

For all protected polymers, a monomodal mass distribution, very low dispersity values and excellent agreement of

Table 1. Composition and analytical data of protected lipopolymers of POx.

No.	R^1	R^2	Yield [%]	$\overline{M}_n$ [a)] [g·mol^{-1}]	Đ [b)]	$[M]_0/[I]_0$ [a)]	$\overline{DP}$ [b)]	$\overline{DP}$ [c)]
7	TBDPSO–$(CH_2)_{12}$–		74	3 586	1.01	35	35	37
8	TBDPSO–$(CH_2)_{12}$–		71	2 259	1.02	20	21	24
9	TBDPSO–$(CH_2)_{12}$–	–OH	71	5 021	1.01	50	54	50
10	TBDPSO–$(CH_2)_{12}$–		67	4 951	1.01	50	52	58
11	TBDPSO–$(CH_2)_9$–C≡C–C≡C–$(CH_2)_9$–		68	3 205	1.01	32	29	30
12	HO–$(CH_2)_{12}$–		79	3 122	1.02	35	33	36
13	HO–$(CH_2)_{12}$–		78	2 189	1.02	20	23	23
14	HO–$(CH_2)_{12}$–	–OH	85	4 728	1.01	50	53	52
15	HO–$(CH_2)_9$–C≡C–C≡C$(CH_2)_9$–		77	2 653	1.03	30	26	33

[a)]Assuming quantitative yields for initiator synthesis; [b)]Determined from MALDI-TOF mass spectrometry; [c)]Determined by endgroup analysis based on ^{1}H NMR spectroscopy.

the degree of polymerization with the targeted degrees of polymerization were found by MALDI-TOF mass spectrometry (example **7** shown in Figure 2B). All mass signals could be assigned to the same polymer population. In case of TBDPSO$(CH_2)_{12}$p(MeOx)$_{35}$boc-piperazine (**7**) the main mass distribution patterns could be assigned to either [TBDPSO$(CH_2)_{12}$p(MeOx)$_{35}$boc-piperazine + K^+] with a maximum at $m/z^{exp} = 3\,625.0$ corresponding to a $\overline{DP} = 35$ ($m/z^{calc} = 3\,626$). Mass differences between the signals calculated to $m/z = 85.1$, corresponding to the monomer unit mass of MeOx ($M = 85.05$ g·mol^{-1}). Moreover, no cleavage of the TBDPS group or uncontrolled termination took place and no termination by remaining alcohol groups is noticeable. This confirms our assumptions discussed above that all available hydroxyl functionalities were converted to triflates and the reactions occurs solely according to Scheme 1.

It can be concluded that the conversion of MeOx with the TBDPS protected lipidinitiators follow strictly a living cationic polymerization mechanism.

Additionally, all polymers were analyzed by gel permeation chromatography (GPC) using poly(styrene) standards with *N*,*N*-dimethylacetamide as eluent. Due to these standards, the average masses of the polymers are generally overestimated, under the given conditions. Dispersities as determined by GPC were generally higher as compared to MALDI-TOF-MS data, because of polymer-stationary phase interaction and/or formation of aggregates of the amphiphilic lipopolymers. This effect was especially noticeable for polymers containing deprotected lipid moieties such as (**13**). However, in agreement with previously recorded MALDI mass spectra, no bimodal mass distributions were found in the corresponding GPC elugrams.

In case of compound (**11**) a minor loss of the protective group was observed by ^{1}H NMR spectroscopy, which could be further confirmed by mass spectrometry. Since MALDI-TOF-MS or GPC indicated neither a multimodal mass distribution nor the presence of other side-products could be detected, it can be concluded that deprotection did occur during the work-up procedure of the reaction products and not during LCROP. This assumption is corroborated by the analytical data of (**15**) subsequently, the deprotected pendant of (**11**) at which all analytical data were found to be in good agreement with the expected values.

Polymer Deprotection

Several deprotection routes as reported in the literature have been investigated for their suitability to quantitatively remove the TBDPS groups from the polymers. All attempts following the conventionally applied route via, e.g., TBAF failed since it was found to be impossible to quantitatively remove remaining deprotection reagent and cleaved protective group from the polymer at overall acceptable yields.[31,51] However, an alternative route by treatment with aqueous hydrochloric acid followed by subsequent neutralization and a final extraction step with chloroform did lead to quantitative deprotection of all involved protective groups and facile work-up of the polymer products.

Another mild deprotection route was employed following a procedure reported in the literature which involves acetyl chloride in dry methanol generating methanolic HCl

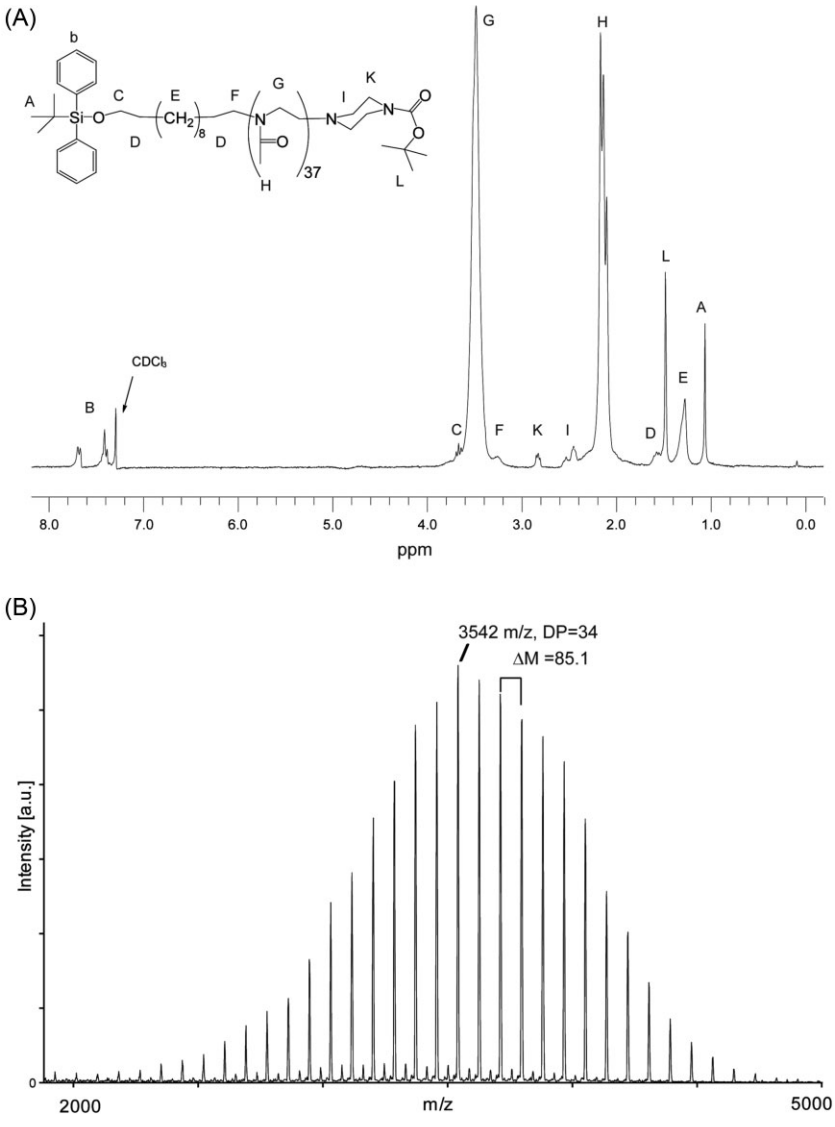


Figure 2. (A) ^{1}H NMR spectroscopy and (B) MALDI-TOF mass spectrometry of doubly protected lipopolymer (7).

in situ, allowing faster reaction rates and quantitative deprotection.[58]

Following either of these routes, all signals of the deprotected polymers could be unambiguously assigned in the corresponding ^{1}H NMR spectra as demonstrated in Figure 3A for polymer (**12**). MALDI-TOF spectrometry gave a clean spectrum with only minimal subdistributions slightly above the detection limit that might be assignable to [polymer-OAc]-like species (Figure 3B). However, since neither acidic proton initiation or loss of polymer side-groups was observed in the corresponding ^{1}H NMR spectra, we argued that these signals could only represent very minor traces of side products.

Interestingly, substituting acetyl chloride with equimolar amounts of methanolic HCl, we noticed substantial deacetylation of the polymer by ^{1}H NMR and MALDI-TOF-MS. From these observations, we concluded that deamidation might as well take place with acetyl chloride. However, methanolized acid chloride might lead to a "healing" of the damaged polymer backbone by re-acetylation.

In summary, we consider both deprotection routes to be useful for the quantitative cleavage of TBDPS- and, simultaneously, Boc-protective groups from **POx** in a single step, whereas the latter described method is advantageous in terms of its reaction rates.

Conclusion

The synthesis of α,ω-functional **POx**-based lipopolymers with defined end groups, derived from TBDPS-monoprotected diol compounds is presented. Exclusively monomodal, narrow mass distributions were observed for all polymers synthesized in MALDI-TOF-MS and size exclusion chromatography, indicating full stability of the TBDPS group during both, initiator synthesis and subsequent living cationic ring-opening polymerization (LCROP). All involved protective groups could be cleaved in a single step. The polymer structure was found to be fully intact and no formation of undesired side-products could be detected.

Following this route allows the introduction of distal functionalities such as hydroxyls that are normally incompatible with the LCROP. Termination with an adequate reagent leads to polymers that may bear identical or, if desired, chemically orthogonal terminal functional groups allowing access to selective subsequent polymer-analog modifications.

Lipopolymers obtained following this route are promising candidates to construct next-generation model cell membranes (polymer-tethered membranes) and are well-suited for the synthesis of polymer-drug or polymer-protein conjugates.[59,60] Respective experiments are currently ongoing in our laboratories.

Experimental Section

Materials and General Methods

All solvents, *tert.*butyldiphenylsilyl chloride (98%), imidazole (99%), triflic anhydride (98%), 2-methyl-2-oxazoline (99%), piperazine

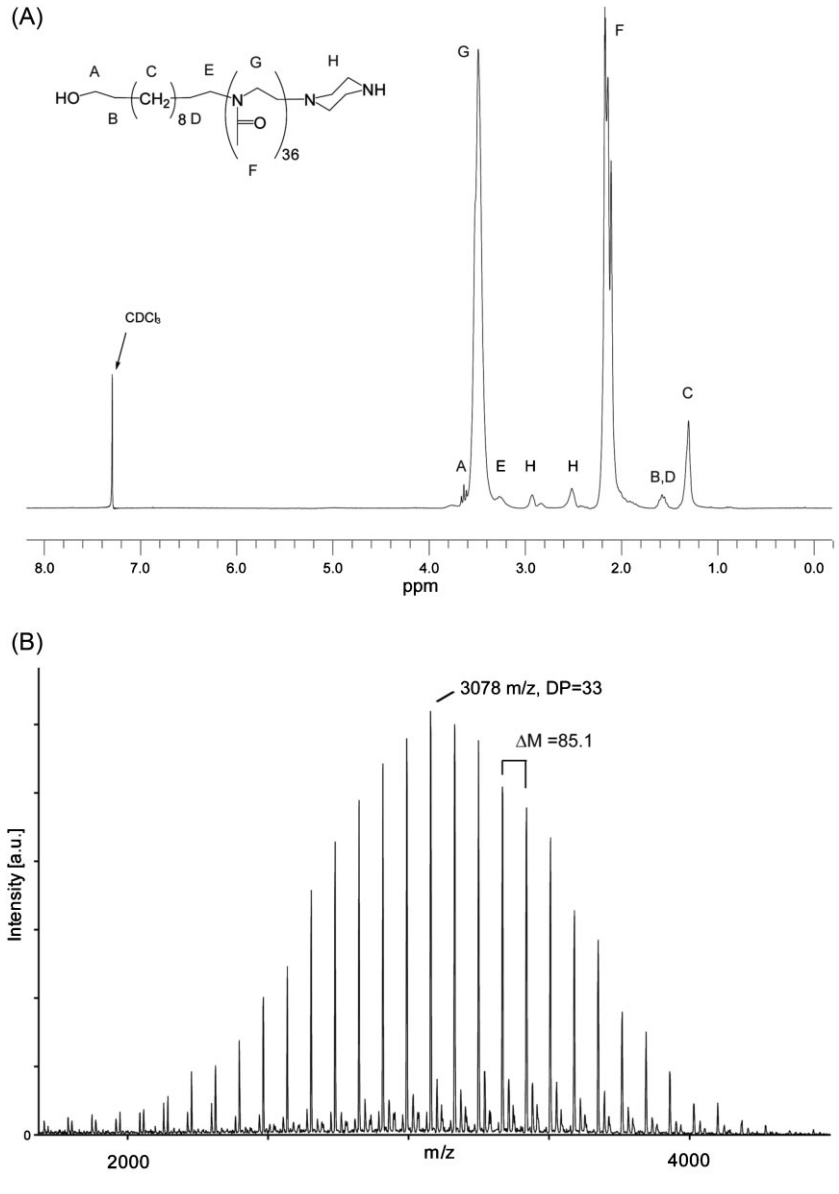


Figure 3. (A) ^{1}H NMR spectroscopy and (B) MALDI-TOF spectrometry of the deprotected α,ω-functionalized POx (**12**) bearing a terminal hydroxyl and amino group.

(99%), potassium carbonate (99%), sodium hydrogencarbonate (99.5%), copper (I) chloride (95%), and copper (II) acetate (98%) were purchased from Acros Organics (Belgium), 1,12-dodecandiol (99%) and 1-boc-piperazine (97%) from Sigma-Aldrich (Steinheim, Germany) and 10-undecyn-1-ol (97%) from ABCR (Karlsruhe, Germany).

All solvents used in triflatization and polymerization reactions were distilled and dried by distillation over calcium hydride prior use. Other chemicals used for polymerization were distilled over calcium hydride or freeze-dried using dry benzene.

NMR spectra were recorded on a Bruker ARX 300 (^{1}H: 300.13 MHz, ^{13}C: 75.48 MHz) and a Bruker AC 250 (^{1}H: 250.13 MHz) at $T = 300$ K in $CDCl_3$.

MALDI-TOF mass spectra were obtained on a Bruker Biflex III mass spectrometer. The measurements were performed by mixing chloroform solutions of the polymer and dithranol as the matrix (10 mg · mL^{-1}) in a ratio of 1:1 (v/v).

Electron impact mass spectrometry (EI-MS) was performed on a Finigann MAT 8200 at an electron energy of 70 eV.

Gel permeation chromatography (GPC) were recorded on a Waters gel-permeation chromatograph with a Waters 717 autosampler, two columns PLgel 5 μm MIXED-C 300 × and two columns PLgel 3 μm MIXED-E 300 × 7.5 mm of Polymer Laboratories, a Waters 410 RI detector and Cirrus software. HPLC-grade *N,N*-dimethylacetamide was used as eluent at a flow of 1 mL · min^{-1}, the injection volume of the sample was 100 μL.

Synthesis

1-(*tert*.Butyldiphenylsilyl)oxy-dodecan-12-ol **(1)**

In a Schlenk flask, 1,12-dodecandiol (7.96 g, 39.4 mmol, 1 eq) was dissolved in 40 mL of dry DMF under a dry nitrogen atmosphere. Imidazole (2.63 g, 38.6 mmol, 1 eq) and *tert*.butylchlorodiphenylsilane (10.84 g, 39.4 mmol, 1 eq) were added and the reaction mixture was heated to 45 °C. After stirring for 48 h, the reaction was quenched with 300 mL of distilled water. The aqueous phase was extracted four times with diethyl ether (three times 100 mL), the organic phases were collected and washed with 2N HCl (twice 100 mL), once with saturated $NaHCO_3$ (200 mL), saturated NaCl (200 mL) and dried over Na_2SO_4. Column chromatography (silica gel) using 10/1 hexane/ethyl acetate as eluent yielded 7.98 g (46%) of the desired product as slightly yellowish oil.

^{1}H NMR (300.13 MHz): $\delta = 1.05$ ppm (s, 9H, *tert*.butyl), 1.26 (br, 16H, $-O-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.58 (m, 4H, $-O-CH_2-C\underline{H}_2-$), 3.65 (m, 4H, $-O-C\underline{H}_2-$), 7.40 (m, 6H, phenyl), 7.69 (m, 4H, phenyl). ^{13}C NMR (75.48 MHz): $\delta = 19.2$ ppm, 25.7, 25.8, 25.9, 29.3, 29.4, 29.58, 29.6, 32.6, 32.8, 63.1, 64.0, 127.5, 129.4, 134.1, and 135.6.

12-(*tert*.Butyldiphenylsilyl)oxy-dodecyl-1-trifluoromethanesulfonate **(2)**

A Schlenk flask was loaded with anhydrous K_2CO_3 (320 mg, 23.4 mmol, 10 eq) under a dry argon atmosphere, followed by **(1)** (103 mg, 2.34 mmol, 1 eq). A solution of trifluoromethanesulfonic anhydride in 3.2 mL of dry chloroform was added subsequently and the suspension was vigorously stirred. After 16 h the solvent was evaporated under reduced pressure, followed by the addition of 3 mL of dry chloroform. Filtration through a PTFE syringe filter under protective atmosphere, followed by evaporation of the solvent yielded (**2**) 134 mg (100%) as a colorless liquid.

^{1}H NMR (250.13 MHz): $\delta = 1.05$ ppm (s, 9H, *tert*.butyl), 1.26 (br, 16H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.56 (m, 2H, $-Si-O-CH_2-\underline{CH_2}-$), 1.83 (m, 2H, $F_3C-SO_2-O-CH_2-\underline{CH_2}-$), 3.66 (t, 2H, $^3J = 5$Hz, $-Si-O-\underline{CH_2}-$), 4.53 (t, 2H, $^3J = 6.5$ Hz, $F_3C-SO_2-O-\underline{CH_2}-$), 7.40 (m, 6H, phenyl), 7.69 (m, 4H, phenyl).

10,12-Docosadiyne-1,22-diol **(3)**

10,12-Docosadiyne-1,22-diol was synthesized according to a procedure reported by Bader and Ringsdorf[54] starting from 10.3 g 10-undecyn-1-ol (61.2 mmol). The reaction yielded 9.5 g (28.4 mmol, 93%) of the desired product.

^{1}H NMR (250.13 MHz): $\delta = 1.26$ ppm (br, 20H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.54 (m, 8H, $-O-CH_2-\underline{CH_2}-$ and $-C\equiv C-CH_2-\underline{CH_2}-$), 2.24 (t, 4H, $^3J = 6.8$ Hz, $-C\equiv C-\underline{CH_2}-$), 3.64 (t, $^3J = 6.7$ Hz, $HO-\underline{CH_2}-$). ^{13}C NMR (75.48 MHz): $\delta = 25.69$ ppm, 25.72, 26.9, 28.30, 28.34, 28.8, 29.00, 29.04, 29.30, 29.34, 29.4, 32.5, 32.8, 63.1, 64.0, 127.5, 129.5, 134.1, and 135.6.

1-(*tert*.Butyldiphenylsilyl)oxy-10,12-docosadiyne-22-ol **(4)**

1-(*tert*.Butyldiphenylsilyl)oxy-10,12-docosadiyne-22-ol was synthesized following the same procedure as for (**1**) and obtained in comparable yields using 9.40 g of (**3**) (28.1 mmol) as diol component. 6.50 g of 1-(*tert*.butyldiphenylsilyl)oxy-10,12-docosadiyne-22-ol (11.1 mmol, 40%).

^{1}H NMR (250.13 MHz): $\delta = 1.05$ ppm (s, 9H, *tert*.butyl), 1.26 (br, 20H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.53 (m, 8H, $-O-CH_2-\underline{CH_2}-$ and $-C\equiv C-CH_2-\underline{CH_2}-$), 2.24 (t, 4H, $^3J = 6.8$ Hz, $-C\equiv C-\underline{CH_2}-$), 3.64 (t, 2H, $^3J = 6.5$ Hz, $-Si-O-\underline{CH_2}-$), 3.65 (t, 2H, $^3J = 6.5$ Hz, $HO-\underline{CH_2}-$), 7.40 (m, 6H, phenyl), 7.69 (m, 4H, phenyl).

22-(*tert*.Butyldiphenylsilyl)oxy-10,12-docosadiyne-1-trifluoromethanesulfonate (**5**)

22-(*tert*.Butyldiphenylsilyl)oxy-10,12-docosadiyne-1-trifluoromethanesulfonate was synthesized analog to **(2)** in quantitative yield.

^{1}H NMR: $\delta = 1.05$ ppm (s, 9H, *tert*.butyl), 1.30 (br, 20H, $-O-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.54 (br, 8H, $-O-CH_2-\underline{CH_2}-$, $-C\equiv C-CH_2-\underline{CH_2}-$), 2.24 (m, 2H, $CF_3SO_2-O-CH_2-\underline{CH_2}-$), 3.65 (t, 2H, $^3J = 7$ Hz, $-C\equiv C-\underline{CH_2}-$), 4.53, (t, 2H, $^3J = 7$ Hz, $F_3C-SO_2-O-\underline{CH_2}-$), 7.40 (m, 6H, phenyl), 7.68 (m, 4H, phenyl).

EI-MS: $m/z = 646.9$ [M – *tert*.butyl]$^+$, 496.9 [M – *tert*.butyl, $-OSO_2CF_3$]$^+$

General Procedure for Polymerization

Under a dry argon atmosphere, 0.2 3 mmol (1 eq) of a ω-TBDPS protected triflate was dissolved in 6 mL of dry chloroform in a Schlenk flask. 2-Methyl-2-oxazoline (587 mg, 6.91 mmol, 30 eq) was added, the reaction mixture was heated to 60 °C and stirred. After 24 h, 212 mg *tert*.butyl piperazine-1-carboxylate (1.14 mmol, 5 eq) was added and the mixture was stirred for 5 h, followed by the addition of approximately 300 mg K_2CO_3 and stirred over night. After cooling to room temperature, the polymer was precipitated by a ten-fold excess of ice-cold distilled diethyl ether and centrifuged for 15 min at 4 000 rpm. After decantation of the liquid phase, the solid phase was dried under a gentle flow of air and dissolved in distilled water. Lyophilization gave the desired polymer.

TBDPSOC$_{12}$MeOx$_{37}$PiperazineBoc (**7**)

The polymer was synthesized from (**2**) (125 mg, 0.22 mmol, 1 eq) and 2-methyl-2-oxazoline (650 mg, 7.65 mmol, 35 eq). After 24h cationic polymerization was terminated by addition of *tert*.butyl piperazine-1-carboxylate (406 mg, 2.18 mmol, 10 eq). Yield: 644 mg (77%).

^{1}H NMR: $\delta = 1.02$ ppm (s, 9H, $-Si-C(\underline{CH_3})_3$), 1.24 (br, 16H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.44 (br, 16H, $-CO-O-(\underline{CH_3})_3$, $-O-CH_2-\underline{CH_2}-$, $-N-CH_2-\underline{CH_2}-CH_2-$), 2.10 (m, br, 109H, $-N-CO-\underline{CH_3}$), 2.36–2.55 (m, br, 5H, $H^{piperazine}$), 2.79 (br, 2H, $-CH_2-\underline{CH_2}-CH_2-N(CO-CH_3)-$), 3.12–3.68 (m, br, 151H, $-N-\underline{CH_2}-\underline{CH_2}-N-$, $-Si-O-\underline{CH_2}-$), 7.33–7.73 (m, 8H, H^{phenyl}). MALDI-TOF-MS: $\overline{M}_n = 3\,586$ g · mol^{-1}, Đ = 1.01. GPC (DMAc): $\overline{M}_n = 5\,626$ g · mol^{-1}, Đ = 1.27.

TBDPSOC$_{12}$MeOx$_{24}$Piperidine (**8**)

The polymer was synthesized from (**2**) (1.09 g, 1.90 mmol, 1 eq) and 2-methyl-2-oxazoline (3.15 g, 37.0 mmol, 20 eq). Polymerization was terminated after 26 h by addition of piperidine (0.85 g, 10.0 mmol, 5.3 eq). Yield: 3.16 g (63%).

^{1}H NMR: $\delta = 1.03$ ppm (s, 9H, $-Si-C(\underline{CH_3})_3$), 1.24 (br, 17H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.54 (br, 10H, $-O-CH_2-\underline{CH_2}-$, $-N-CH_2-\underline{CH_2}-CH_2-$, $H^{piperidine}$), 2.13 (m, br, 72H, $-N-CO-\underline{CH_3}$), 2.43 (br, 5H, $H^{piperidine}$), 3.12–3.73 (br, 100H, $-N-\underline{CH_2}-\underline{CH_2}-N-$, $-Si-O-\underline{CH_2}-$), 7.32–7.77 (m, 9H, H^{phenyl}). MALDI-TOF-MS: $\overline{M}_n = 2\,259$ g · mol^{-1}, Đ = 1.02. GPC (DMAc): $\overline{M}_n = 4\,463$ g · mol^{-1}, Đ = 1.18.

TBDPSOC$_{12}$MeOx$_{50}$OH (**9**)

The polymer was synthesized from (**2**) (89 mg, 0.17 mmol, 1 eq) and 2-methyl-2-oxazoline (736 mg, 8.65 mmol, 53 eq) in 4.5 mL of chloroform and terminated by addition of 433 mg (5.15 mmol, 30 eq) sodium hydrogencarbonate dissolved in a mixture of 4.5 mL water and 9.4 mL methanol. This mixture was heated to 60 °C and stirred over night. The solvent was evaporated and the solid residue was extracted with chloroform (6 mL). Injection into a ten-fold excess of diethyl ether via a PTFE syringe filter and subsequent freeze-drying using water gave 586 mg (73%) of the polymer (method A).

Instead of terminating with the methanol/chloroform/water mixture, polymerization can also be terminated following two additional pathways by addition of a solution of 549 mg (3.97 mmol) of potassium carbonate in 3.3 mL water and 20.4 mL acetonitrile. After heating at 60 °C a ternary mixture was formed and stirred over night. After evaporation of the solvent it was proceeded as described above (method B).

Alternatively, hydroxyl termination was achieved by evaporating the reaction mixture to dryness at reduced pressure and dissolving the solid residue in water (method C).

^{1}H NMR: $\delta = 1.03$ ppm (s, 9H, $-Si-C(\underline{CH_3})_3$), 1.24 (br, 16H, $-CH_2-CH_2-\underline{CH_2}-CH_2-CH_2-$), 1.54 (br, 4H, $-O-CH_2-\underline{CH_2}-$, $-N-CH_2-\underline{CH_2}-CH_2-$), 2.10 (m, br, 151H, $-N-CO-\underline{CH_3}$), 3.45 (br, 201H, $-N-\underline{CH_2}-\underline{CH_2}-N-$, $HO-\underline{CH_2}-$, $-Si-O-\underline{CH_2}-$), 7.29–7.72 (m, 9H, H^{phenyl}). MALDI-TOF-MS: $\overline{M}_n = 5\,022$ g · mol^{-1}, Đ = 1.01. GPC (DMAc): $\overline{M}_n = 7\,286$ g · mol^{-1}, Đ = 1.08.

TBDPSOC$_{12}$MeOx$_{58}$Piperazine (**10**)

The polymer was synthesized from (**2**) (89 mg, 0.17 mmol, 1 eq) and 2-methyl-2-oxazoline (720 mg, 8.46 mmol, 50 eq) in 4.5 mL of

chloroform and terminated by injection of a solution of 450 mg piperazine (5.23 mmol, 20 eq) in 4.5 mL of chloroform at 60 °C. Purification by subsequent dialysis yielded 551 mg (67%) of the product.

^{1}H NMR: $\delta = 1.03$ ppm (s, 8H, $-Si-C(C\underline{H}_3)_3$), 1.24 (br, 16H, $-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.54 (br, 3H, $-O-CH_2-C\underline{H}_2-$), 2.14 (br, 173H, $-N-CO-C\underline{H}_3$), 3.45 (br, 234H, $-N-C\underline{H}_2-C\underline{H}_2-N-$, $-Si-O-C\underline{H}_2-$), 7.31–7.75 (m, 9H, H^{phenyl}). MALDI-TOF-MS: $\overline{M}_n = 4\,961$ g·mol^{-1}, Đ = 1.01. GPC (DMAc): $\overline{M}_n = 8\,144$ g·mol^{-1}, Đ = 1.24.

TBDPSODocoMeOx$_{30}$PiperazineBoc (**11**)

The polymer was synthesized from (**5**) (203 mg, 0.29 mmol, 1 eq) and 2-methyl-2-oxazoline (788 mg, 9.26 mmol, 32 eq) in 6 mL of chloroform and terminated with *tert*.butyl piperazine-1-carboxylate (374 mg, 2.02 mmol, 7 eq). Yield: 699 mg (74%).

^{1}H NMR: $\delta = 1.03$ ppm (s, 6H, $-Si-C(C\underline{H}_3)_3$), 1.19–1.39 (m, br, 20H, $-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.44–1.60 (m, br, 17H, $-N-CO-O-(C\underline{H}_3)_3$, $-O-CH_2-C\underline{H}_2-$, $-N-CH_2-C\underline{H}_2-$, $-C{=}C-CH_2-C\underline{H}_2-$), 2.13 (m, br, 87H, $-N-CO-C\underline{H}_3$), 2.23 (t, 3H, $^3J = 6.75$ Hz, $-C{\equiv}C-C\underline{H}_2-$), 2.36–2.54 (m, br, 5H, $H^{piperazine}$), 3.00 (m, 5H), 3.14–3.59 (m, br, 125H, $-N-C\underline{H}_2-C\underline{H}_2-N-$), 3.63 (t, 2H, $^3J = 6.5$ Hz, $-Si-O-C\underline{H}_2-$), 3.70 (t, 2H, $^3J = 5$ Hz, $HO-C\underline{H}_2-$), 7.29–7.73 (m, 7H, H^{phenyl}). MALDI-TOF-MS: $\overline{M}_n = 3\,205$g·mol^{-1}, Đ = 1.01. GPC (DMAc): $\overline{M}_n = 6\,170$ g·mol^{-1}, Đ = 1.23.

Deprotection

Method A

The *tert*.butyldiphenylsilyl- and/or *tert*.butylcarboxylate-protected POx was dissolved in 2 N aqueous hydrochloric acid (3 mL per 100 mg polymer) and stirred. After 24 h the resulting suspension was neutralized with of $NaHCO_3$, filtrated through cellulose and freeze-dried. The solid residue was extracted with chloroform (3 mL per 100 mg polymer) for 3 h. The polymer was precipitated by a ten-fold excess of diethyl ether at room temperature. Decantation of the ether phase and subsequent freeze-drying of the solid phase using water gave the desired polymer.

Method B

The *tert*.butyldiphenylsilyl- and/or *tert*.butylcarboxylate-protected POx was dissolved in dry methanol (1 mL per 40 mg polymer) under a dry argon atmosphere followed by addition of 10 mg (0.32 mmol) of acetyl chloride per mL solvent. The reaction mixture was stirred vigorously. After 48 h the reaction was quenched by addition of 2.5 mL of a saturated aqueous solution of $NaHCO_3$. The solvent was removed in vacuum and the solid residue was freeze-dried using water. The residual solid was extracted with chloroform (1 mL per 40 mg polymer) and the polymer was precipitated in ice-cold diethyl ether. Subsequent freeze-drying (water) gave the desired product.

HOC$_{12}$MeOx$_{36}$Piperazine (**12**)

The deprotection of (**7**) (50 mg, 13.0 μmol) according to method A yielded 36 mg (10.3 μmol, 79%) of (**12**).

^{1}H NMR: $\delta = 1.26$ ppm (m, br, 16H, $-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.54 (m, 4H, $-O-CH_2-C\underline{H}_2-$), 2.14 (m, br, 114H, $-N-CO-C\underline{H}_3$), 2.49 (br, 5H, $H^{piperazine}$), 3.44 (br, 141H, $-N-C\underline{H}_2-C\underline{H}_2-N-$). MALDI-TOF: $\overline{M}_n = 3\,122$ g·mol^{-1}, Đ = 1.02. GPC (DMAc): $\overline{M}_n = 7\,646$ g·mol^{-1}, Đ = 1.30.

HOC$_{12}$MeOx$_{23}$Piperidine (**13**)

The deprotection of (**8**) (250 mg, 11.0 mmol) according to *method A* yielded 201 mg (78%) of (**13**).

^{1}H NMR (250 MHz): $\delta = 1.25$ ppm (br, 16H, $-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.36–1.62 (m, br, 8H, $-O-CH_2-C\underline{H}_2-$, $-N-CH_2-C\underline{H}_2-$, $H^{piperidine}$), 2.12 (m, br, 71H, $-N-CO-C\underline{H}_3$), 2.39 (m, br, $H^{piperidine}$), 3.12–3.67 (m, br, 95H, $-N-C\underline{H}_2-C\underline{H}_2-N-$, $HO-C\underline{H}_2-$). MALDI-TOF: $\overline{M}_n = 2\,189$ g·mol^{-1}, Đ = 1.02. GPC (DMAc): $\overline{M}_n = 4\,730$ g·mol^{-1}, Đ = 1.18.

HOC$_{12}$MeOx$_{52}$OH (**14**)

Deprotection of (**9**) (356 mg, 75.9 μmol) according to *method A* yielded 270 mg of (**14**) (57 μmol, 76%).

^{1}H NMR: $\delta = {}^1$H NMR: $\delta = 1.26$ ppm (br, 16H, $-CH_2-CH_2-C\underline{H}_2-CH_2-CH_2-$), 1.52 (m, 4H, $-O-CH_2-C\underline{H}_2-$, $-N-CH_2-C\underline{H}_2-$), 2.13 (m, br, 162H, $-N-CO-C\underline{H}_3$), 3.44 (m, br, 202H, $-N-C\underline{H}_2-C\underline{H}_2-N-$, $-O-C\underline{H}_2-$). MALDI-TOF: $\overline{M}_n = 4\,728$ g·mol^{-1}, Đ = 1.01. GPC (DMAc): $\overline{M}_n = 9\,590$ g·mol^{-1}, Đ = 1.20.

HODocoMeOx$_{33}$Piperazine (**15**)

Deprotection of (**11**) (217 mg, 67.7 μmol) according to method B yielded 149 mg (77%) of (**15**).

^{1}H NMR (300 MHz): $\delta = 1.13$–1.61 ppm (m, br, 28H, $-CH_2-C\underline{H}_2-CH_2-$), 2.13 (m, br, 101H, $-N-CO-C\underline{H}_3$), 2.23 (t, 3H $^3J = 5.75$ Hz, $-C{\equiv}C-C\underline{H}_2-$), 3.14–3.63 (m, br, 133H, $-N-C\underline{H}_2-C\underline{H}_2-N-$, $HO-C\underline{H}_2-$). MALDI-TOF: $\overline{M}_n = 5\,313$ g·mol^{-1}, Đ = 1.03. GPC (DMAc): $\overline{M}_n = 6\,165$ g·mol^{-1}, Đ = 1.16.

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