A New Soluble Polymer-Supported Sulfonyl Linker − Application to the Synthesis of Cyclic α-Amino Acids

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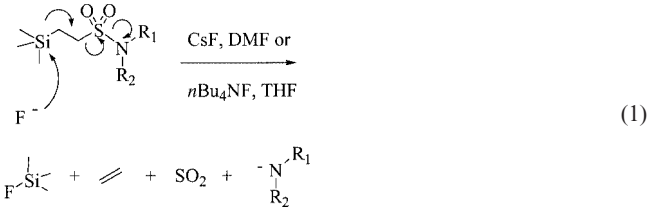
A new soluble poly(ethylene glycol)-supported protecting group of the SES (silylethylsulfonyl) type has been prepared and utilized in the synthesis of cyclic amino esters by ring-closing metathesis (RCM). Acidic cleavage from the support was performed to recover the fully deprotected amino acids. More conventional deprotection conditions with fluoride ions resulted in aromatization of the heterocycles in the case of the 6-membered ring and provided a new route to the synthesis of substituted pyridines.

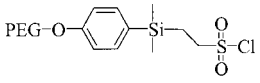
Introduction

The 2-(trimethylsilyl)ethylsulfonyl or SES group has proven to be a valuable protecting group in organic synthesis[1−3] [Equation (1)]. It is mainly used to protect a nitrogen atom as a sulfonamide. Removal of the SES group under mild conditions is usually performed in the presence of fluoride ions. Consequently, the SES group is also used as an activating group, increasing the acidity of the hydrogen borne by the protected nitrogen. Mitsunobu or base-activated alkylation may be then efficiently performed to construct a molecule or to functionalize it further.[4−10] These reactions are generally easily driven to completion, which is all the more important when the transformation takes place on a polymer support. Indeed, complete conversion is a requirement to avoid accumulation of undesired material during the synthesis.



(1)

We have recently been using sulfonamides in the synthesis of peptidomimetic[5,6] or amino acid[11] heterocyclic compounds. As part of our research into soluble polymer-supported synthesis,[6,11−14] we have been investigating a poly(ethylene glycol)-supported (PEG-supported) SES protecting and activating linker as shown in Figure 1. We report here the synthesis of a novel PEG-supported SES group[15−20] and its use in the synthesis of cyclic amino acids by ruthenium-catalyzed ring-closing metathesis (RCM).



PEG-OH = H-(O-CH_2-CH_2)$_n$-OH with an average MW = 3400

Figure 1. PEG-SES-Cl

Results and Discussion

Synthesis of the PEG-SES

We approached the synthesis of the PEG-SES group on the basis of the solution chemistry developed by Weinreb's group.[21] A phenyl ring was chosen to connect the oxygen of the polymer to the silicon atom. The synthesis (Scheme 1) was carried out as follows: 4-bromophenol (**1**) was transformed into the corresponding vinylsilyl derivative **2** by lithium−bromine exchange with 3 equivalents of *t*BuLi, followed by trapping with dimethyl vinylsilylchloride. Compound **2** was anchored to the polymer by etherification of the bifunctional mesylate PEG 3400 **4**.[22−29] Treatment of the water-soluble olefin **5** with Na_2SO_3/$NaHSO_3$ provided the corresponding sulfonate **6**.[30,31] The sulfonyl chloride **7** was obtained by the action of PCl_5.[21] Careful conditions had to be used in this reaction, since it seemed that a strongly acidic medium cleaved the bond between phenyl and silicon. At each step, the PEG-supported product was precipitated from Et_2O and filtered. ^{1}H NMR was routinely used to assess the reaction progress. Each product was characterized by ^{1}H and ^{13}C NMR, IR, and MS.[32−35]

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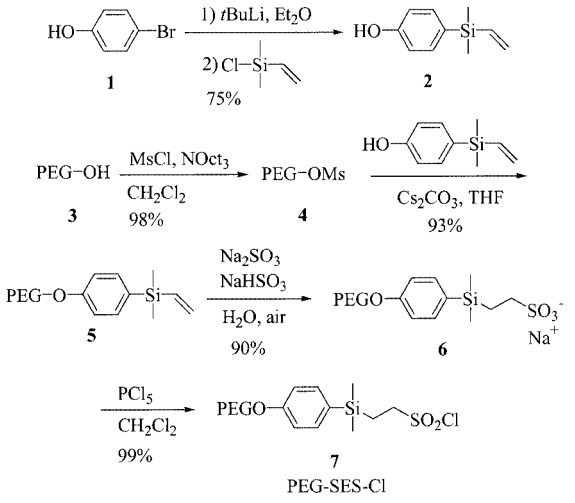
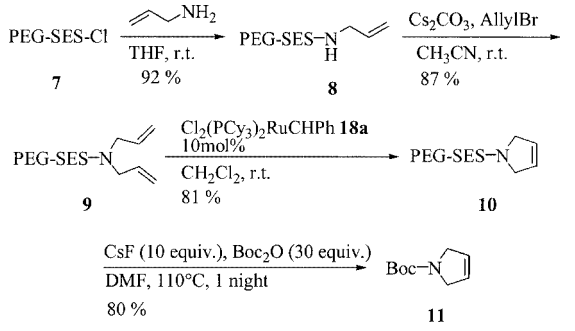


Scheme 1

Validation of the PEG-SES

We first wanted to confirm the feasibility of using the PEG-SES group in the following sequence of reactions: anchoring of an amine to the linker, base-activated *N*-allylation, ring-closing metathesis, and deprotection/cleavage of the product (Scheme 2).



Scheme 2

Ring-closing metathesis has proven to be a powerful tool in organic synthesis for the generation of cyclic structures through C−C bond formation.[36−44] We had already shown that a soluble polymer such as PEG was compatible with the conditions of the ring-closing metathesis reaction.[11]

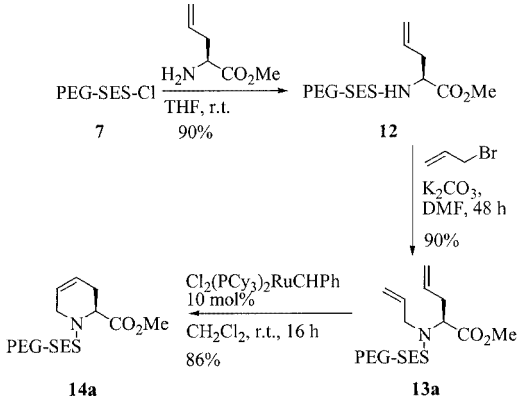
PEG-SES-Cl **7** was treated with allylamine, and the resulting supported sulfonamide **8** was alkylated with allyl bromide to provide **9**. RCM with Grubbs' catalyst **18a** was performed to give the cyclic compound **10**. Deprotection in the presence of CsF, with in situ trapping of the otherwise too volatile pyrroline with Boc_2O,[45] yielded **11** in good yield.

We then decided to apply the PEG-SES group to the synthesis of *N*-heterocyclic α-amino acids.[46−61]

Synthesis of Cyclic Amino Acids by Ring-Closing Metathesis

We had previously shown that enantiomerically pure cyclic amino acids could easily be synthesized by use of PEG-supported RCM of various *N*-alkylated allylglycines anchored through ester bonds.[11] The new PEG-SES enabled the linear precursor to be anchored on the nitrogen atom of the amino ester.

The synthesis of a didehydropipecolic derivative **14a** was considered first (Scheme 3). The synthesis of the linear precursor **13a** was carried out as previously, by treatment of enantiomerically pure L-allylglycine methyl ester with PEG-SES-Cl to give **12**. Alkylation with allyl bromide, followed by RCM under classical conditions (10 mol % of Grubbs' catalyst **18a**) yielded compound **14a**.



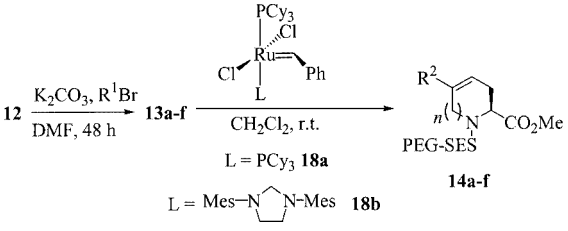
Scheme 3

In our previous study[11] we had noted that a ring-closing metathesis performed on a PEG-supported substrate anchored through an ester bond required a larger amount of catalyst than usual and a longer reaction time to complete the reaction. We hypothesized about the possible formation of unproductive chelates.[62] When a similar linear diene was supported on PEG-SES (compound **13a**), the amount of catalyst needed dropped to 10 mol %. Probably the presence of the SES linker on the diene moves the reacting center further away from the PEG than when an ester bond is present. Nevertheless, the reaction rate decreased when the required amount of catalyst was lower, indicating that the presence of the polymer was still slowing down the reaction.

Various alkylating agents were chosen in order to synthesize cyclic amino acids of different ring sizes, such as the seven- and eight-membered rings **14b** and **14c** (Scheme 4, Table 1). Olefin substitution or enyne RCM produced 5-substituted didehydro pipecolic acid derivatives **14d−f**. RCM of the methallyl derivative provided 5-methyldidehydropipecolic methyl ester **14e**. As observed previously,[63,64] enyne metathesis required a slightly larger amount of catalyst to provide **14d**. It should be noted that the methyl ester-substituted olefin did not cyclize with catalyst **18a**, and so the more reactive catalyst **18b**[65] was required to provide the novel aminodiester derivative **14f**, in excellent yield.

Table 1. Synthesis of cyclic amino esters

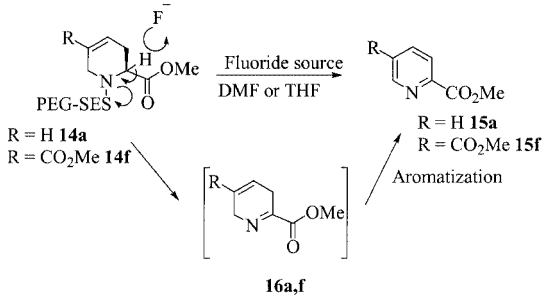
Entry	R^1	**13**	Catalyst	*n*	R^2	Yield of **14** (%)
1	allyl	**a**	**18a**	1	H	86
2	$H_2C=CH(CH_2)_2-$	**b**	**18a**	2	H	91
3	$H_2C=CH(CH_2)_3-$	**c**	**18a**	3	H	96
4	propargyl	**d**	**18a**	1	$CH=CH_2$	83
5	$H_2C=C(CH_3)-CH_2-$	**e**	**18a**	1	CH_3	94
6	$H_2C=C(CO_2Me)-CH_2-$	**f**	**18b**	1	CO_2Me	93



Scheme 4

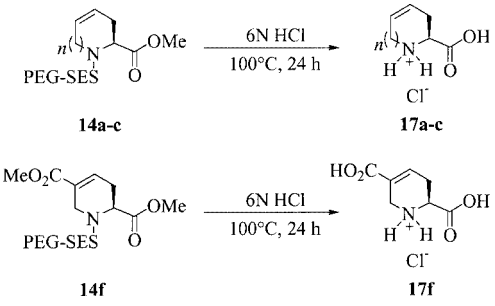
Only a few examples of ruthenium-catalyzed cyclization of ester-substituted dienes such as **13f** have been reported in the literature.[66,67]

We then used the deprotection/cleavage conditions described for the pyrroline synthesis. Surprisingly, when **14a** was treated with TBAF in THF in the presence of Boc_2O, only 20% of the expected product was obtained. The major product from this reaction was 2-methoxycarbonyl pyridine **15a** (Scheme 5). In the absence of Boc_2O, **15a** was obtained as the sole product. Our hypothesis is that the fluoride anion normally responsible for the deprotection of the SES group by β-elimination was responsible for the abstraction of the acidic proton of the amino ester **14a**, which presumably yielded **16a** after elimination of the PEG-SES sulfinic acid. Further aromatization provided the substituted pyridine **15a**. This phenomenon has been described in the literature in the case of *N*-sulfonyl(didehydro)pipecolic derivatives.[68–74] Product **14f** yielded the corresponding substituted pyridine **15f**, while **14b** and **14c** – intended to provide the seven- and the eight-membered rings, respectively – gave complicated mixtures from which no major compound could be isolated. Many fluoride sources[21,75,76] were used, but in each case the aromatized product was the major compound.



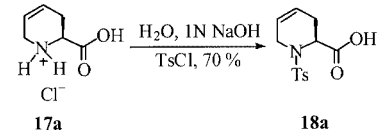
Scheme 5

To circumvent this problem, we decided to perform acid hydrolysis.[11] Trifluoroacetic acid (30%) in CH_2Cl_2 did not cleave the cyclic compounds. Eventually, the PEG-supported amino esters were treated in refluxing 6 N HCl for 24 h to provide the corresponding fully deprotected amino acids **17a–c** and **17f** after separation from the PEG by precipitation in cold *i*PrOH (Scheme 6). In the case of **14f**, both esters were deprotected, to yield the diacid **17f** in good yield.



Scheme 6

In order to investigate possible racemization during the cleavage process, amino acid **17a** was reprotected with a tosyl group (Scheme 7). Compound **18a** was analyzed by chiral HPLC and the spectrum of **18a** was compared to the spectrum obtained with the corresponding racemic structure. Only one isomer could be detected, confirming that no racemization had occurred.



Scheme 7

Conclusion

We have developed a novel PEG-supported protecting-activating group of the SES type. This group was validated in the case of the synthesis of pyrroline. It also provided a practical tool for the synthesis of cyclic amino acids by RCM. Whereas the usual deprotection step in the presence of fluoride ions instead provided a novel route to substi-

tuted pyridines, the expected cyclic amino acids were obtained in good yields by acid hydrolysis.

The use of the SES linker could be also extended to solid-phase synthesis, since phenol **2** could easily be anchored to a Merrifield resin in the presence of base, similarly to the synthesis of Wang resin.[77]

Experimental Section

General Remarks: All reagents including poly(ethylene glycol) 3400 were obtained from Aldrich Chemical Co. and used without purification. ^{1}H and ^{13}C NMR analyses were performed with 200 MHz and 400 MHz NMR spectrometers, respectively. Infrared spectra were recorded by diffuse reflectance or by transmittance as a micro cup of KBr or by transmittance in KBr plates. Mass spectra (electrospray ionization mode, ESIMS) were recorded on a Platform II (Micromass, Manchester, U.K.) quadrupole mass spectrometer fitted with an electrospray interface. We report the mass spectrometry for bifunctional PEG 3400. The mass spectrometer was calibrated in the positive and negative ion ESI modes. The samples were dissolved in H_2O/CH_3CN (50:50 in vol.). Multiprotonated and multicationized ions were recovered in the positive and negative modes. PEG 3400-supported molecules appeared as distributions corresponding to charge states ranging from +2 to +5, and oligomers between $n = 74$ to $n = 88$ were detected. Only two significant peaks were reported, and we used the mass increment between the product and the PEG 3400 to confirm the spectrum. Correlations between the calculated and measured values were observed in both of the states considered. Optical rotations were recorded on a polarimeter at 589 nm and reported as α_D values (concentration in grams/100 mL of solvent). The chiral HPLC analyses were carried out at a wavelength of 230 nm, with a Chiracel OD column, (5 μm, 250 × 4.6 mm) and a flow rate of 1 mL/min eluent: hexane/2-propanol/TFA, 92:8/0.4.

4-(Dimethylvinylsilanyl)phenol (2): A solution of *t*BuLi in pentane (100 mL, 170.0 mmol) was added dropwise at −70 °C to a solution of *p*-bromophenol (9.8 g, 57.0 mmol) in 100 mL of ether. The mixture was stirred at room temperature for 1 h. Chlorovinyldimethylsilane (7.8 mL, 57.0 mmol) was added dropwise at −50 °C, and the mixture was heated under reflux overnight. The organic layer was washed with a saturated NaCl aqueous solution (3 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 8:2) to yield 7.1 g (70%) of the title compound: IR: $\tilde{\nu}$ = 3368 (s), 2958 (s), 1895 (w), 1706 (s), 1258(s) cm^{-1}. ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 0.35 (s, 6 H), 4.85 (s, 1 H), 5.75 (dd, J_1 = 4.2 Hz, J_2 = 19.8 Hz, 1 H), 6.05 (dd, J_1 = 4.2 Hz, J_3 = 14.6 Hz, 1 H), 6.30 (dd, J_2 = 19.8 Hz, J_3 = 14.6 Hz, 1 H), 6.85 (d, J_4 = 6.5 Hz, 2 H), 7.45 (d, J_4 = 6.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = 0.0, 117.7, 132.2, 135.4, 138.3, 141.0, 159.1 ppm. HRMS: calcd. for $C_{10}H_{14}OSi$ [M$^+$] 178.0814; found 178.0809.

Poly(ethylene Glycol)-3400 Bis(methanesulfonate) (4): Trifluoromethanesulfonyl chloride[29] (4.0 g, 35.0 mmol) was added dropwise at −20 °C to a solution of PEG-OH (10.0 g, 2.94 mmol) and trioctylamine (12.4 g, 35.0 mmol) in 40 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature overnight. The product was precipitated from ether, and then filtered and dried in vacuo to yield 10.3 g (98%) of the title compound: IR: $\tilde{\nu}$ = 2871 (s), 1968 (m), 1466 (s), 1114 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 3.10 (s, 6 H), 3.55−3.70 (bs, ≈ 310 H), 3.70−3.75 (m, 4 H), 4.35−4.40 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = 38.1, 69.4, 69.7, 70.9 ppm. MS (Electrospray): *m*/*z*: *n* = 72: 1673.5 (2 +, 2 H$^+$); *n* = 78: 1211.6 (3 +, 2 H$^+$/Na$^+$).

Poly(ethylene Glycol)-3400 Bis[*p*-(dimethylvinylsilyl)phenyl] Ether (5): A solution of **2** (3.0 g, 17.1 mmol) in 20 mL of THF was added to a solution of PEG-OMs (24.3 g, 6.83 mmol) and Cs_2CO_3 (11.1 g, 34.16 mmol) in 80 mL of THF. The mixture was heated under reflux overnight. The solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 and filtered through Celite. The product was precipitated from ether, filtered, and dried in vacuo to yield 23.8 g (93%) of the title compound: IR: $\tilde{\nu}$ = 3055 (m), 1964 (w), 1643 (m), 1594 (s), 1110 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 0.35 (s, 12 H), 3.55-3.75 (bs, ≈ 310 H), 3.85 (t, J_1 = 5.3 Hz, 4 H), 4.15 (t, J_1 = 5.3 Hz, 4 H), 5.70 (dd, J_2 = 4.2 Hz, J_3 = 19.8 Hz, 2 H), 6.05 (dd, J_2 = 4.2 Hz, J_4 = 14.6 Hz, 2 H), 6.30 (dd, J_3 = 19.8 Hz, J_4 = 14.6 Hz, 2 H), 6.95 (d, J_5 = 8.6 Hz, 4 H), 7.45 (d, J_5= 8.6 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.3, 67.5, 70.1, 70.9, 71.2, 114.6, 129.7, 132.9, 135.6, 138.7, 160.0 ppm. MS (Electrospray): *m*/*z*: *n* = 80: 1295.8 (3 +, 2 H$^+$/ Na$^+$); *n* = 82: 988.7 (4 +, 4 H$^+$).

Poly(ethylene Glycol)-3400 Bis{*p*-[dimethyl(2-sulfonatoethyl)-silyl]phenyl} Ether, Disodium Salt (6): Na_2SO_3 (0.814 g, 6.46 mmol) and $NaHSO_3$ (6.7 g, 64.5 mmol) were added to a solution of **5** (12.0 g, 3.23 mmol) in 100 mL of H_2O. The mixture was stirred at room temperature overnight. H_2O was evaporated in vacuo, and the residue was coevaporated several times with MeOH. It was then dissolved in CH_2Cl_2, and the product was precipitated from ether, filtered, and dried in vacuo to yield 11.6 g (90%) of the title compound: IR: $\tilde{\nu}$ = 3456 (s), 1954 (w), 1646 (m), 1470 (m), 1108 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 0.20 (s, 12 H), 1.20−1.35 (m, 4 H), 2.65−2.80 (m, 4 H), 3.50−3.75 (bs, ≈ 310 H), 3.85 (t, J_1 = 5.5 Hz, 4 H), 4.10 (t, J_1 = 5.5 Hz, 4 H), 6.85 (d, J_2 = 8.5 Hz, 4 H), 7.40 (d, J_2 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.9, 11.9, 47.2, 67.6, 70.0, 70.8, 71.2, 114.6, 130.0, 135.4, 159.9 ppm. MS (Electrospray): *m*/*z*: *n* = 71: 1813.4 (2 −); *n* = 76: 1923.9 (2 −).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-(chlorosulfonyl)dimethylethyl]-silyl}phenyl) Ether (7): A solution of PCl_5 (1.3 g, 6.28 mmol) in 10 mL of CH_2Cl_2 was added at −20 °C to a solution of **6** (5.0 g, 1.26 mmol) in 90 mL of CH_2Cl_2. The mixture was stirred at −20 °C for 30 min and then precipitated from ether. The product was filtered off and dried in vacuo to yield 4.9 g (99%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 0.35 (s, 12 H), 1.45−1.55 (m, 4 H), 3.45−3.55 (m, 4 H), 3.55−3.80 (bs, ≈ 310 H), 3.85 (t, J_1 = 5.0 Hz, 4 H), 4.15 (t, J_1 = 5.0 Hz, 4 H), 6.95 (d, J_2 = 8.5 Hz, 4 H), 7.40 (d, J_2 = 8.5 Hz, 4 H) ppm.

Poly(ethylene Glycol)-3400 Bis[*p*-({2-[(allylamino)sulfonyl]ethyl}-dimethylsilyl)phenyl] Ether (8): Allylamine (0.055 g, 0.97 mmol) and pyridine (0.174 g, 2.2 mmol) were added at room temperature to a solution of **7** (1.73 g, 0.44 mmol) in 40 mL of THF. The mixture was stirred at room temperature overnight, THF was evaporated, and the residue was precipitated from *i*PrOH, redissolved in CH_2Cl_2 and precipitated from *i*PrOH. The product was dissolved in CH_2Cl_2, precipitated from ether, filtered, and dried in vacuo to yield 1.6 g (92%) of the title compound: IR: $\tilde{\nu}$ = 2876 (s), 1965 (w), 1644 (m), 1469 (s), 1112 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, Me_4Si): δ = 0.40 (s, 12 H), 1.20−1.30 (m, 4 H), 2.35−2.45(m, 4 H), 3.50−3.80 (bs, ≈ 310 H), 3.90 (t, J_1 = 5.5 Hz, 4 H), 4.15 (t, J_1 = 5.5 Hz, 4 H), 4.25 (m, 2 H), 5.15−5.35 (m, 4 H), 5.70−5.90 (m, 4 H), 6.95 (d, J_2 = 8.5 Hz, 4 H), 7.40 (d, J_2 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.5, 46.0, 49.6, 67.5, 70.0, 70.9, 114.9, 117.8, 128.1, 135.3, 160.4 ppm. MS (Electrospray): *m*/*z*: *n* = 75: 1943.2 (2 +, 2 H$^+$); *n* = 76: 1310.5 (3 +, 3 H$^+$).

Poly(ethylene Glycol)-3400 Bis[*p*-({2-[(diallylamino)sulfonyl]ethyl}-dimethylsilyl)phenyl] Ether (9): Allyl bromide (0.057 g, 0.47 mmol) was added at room temperature to a mixture of Cs_2CO_3 (0.306 g, 0.94 mmol) and compound **8** (0.310 g, 0.080 mmol) in 20 mL of CH_3CN. The reaction mixture was stirred at room temperature for 12 h. The base was filtered off, and the filtrate was concentrated in vacuo, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.280 g (87%) of the title compound: IR: $\tilde{\nu}$ = 3055 (m), 1966 (w), 1596 (m), 1455 (s), 1104 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 0.15−0.25 (m, 4 H), 2.80−2.90 (m, 2 H), 3.50−3.75 (bs, ≈ 310 H), 3.90−3.95 (m, 12 H), 4.15 (t, J_1 = 4.5 Hz, 4 H), 5.15−5.30 (m, 8 H), 5.60−5.85 (m, 4 H), 6.95 (d, J_2 = 9.0 Hz, 4 H), 7.40 (d, J_2 = 9.0 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.4, 49.6, 49.8, 67.6, 70.0, 70.9, 71.2, 114.9, 119.4, 128.1, 133.3, 135.4, 160.4 ppm. MS (Electrospray): *m*/*z*: *n* = 82: 2137.3 (2 +, 2 H^+); *n* = 88: 1513.2 (3 +, 3 H^+).

Poly(ethylene Glycol)-3400 Bis[*p*-({2-[(2,5-dihydro-1*H*-pyrrol-1-yl)-sulfonyl]ethyl}dimethylsilyl)phenyl] Ether (10): Catalyst $RuCl_2$(=CHPh)$(PCy_3)_2$ (**18a**, 2.0 mg, 2.4 μmol) was added to a solution of compound **9** (0.050 g, 0.012 mmol) in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.040 g (81%) of the title compound: IR: $\tilde{\nu}$ = 3057 (m), 1966 (w), 1594 (m), 1454 (s), 1102 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 2.85−2.95 (m, 4 H), 3.55−3.75 (bs, ≈ 310 H), 3.85 (t, J_1 = 4.0 Hz, 4 H), 4.10−4.20 (m, 12 H), 5.80 (s, 4 H), 6.95 (d, J_2 = 8.5 Hz, 4 H), 7.40 (d, J_2 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ. −2.8, 10.0, 46.2, 55.3, 67.5, 70.0, 70.9, 71.2, 114.9, 126.0, 128.1, 135.3, 160.3 ppm. MS (Electrospray): *m*/*z*: *n* = 68: 1202.4 (3 +, 3 H^+); *n* = 72: 946.0 (4 +, 4 H^+).

***N*-(*tert*-Butoxycarbonyl)-3-pyrroline (11):** CsF (0.076 g, 0.502 mmol) and Boc_2O (0.328 g, 1.51 mmol) were added to a solution of **10** (0.200 g, 0.050 mmol) in 10 mL of DMF. The reaction mixture was stirred overnight at 110 °C, and DMF was removed in vacuo. The residue was dissolved in CH_2Cl_2 and precipitated from ether. The filtrate was concentrated in vacuo and the product was purified on silica gel (hexane/EtOAc, 7:3) to yield 13.5 mg (80%) of the title compound.[78] ^1H NMR ($CDCl_3$, Me_4Si): δ = 1.50 (s, 9 H), 4.15 (d, *J* = 4.5 Hz, 4 H), 5.80 (sl, 2 H) ppm. MS (Electrospray): *m*/*z* = 170 $[M + H]^+$, 339 $[2 M + H]^+$.

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[1-(methoxycarbonyl)-3-butenylamino]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (12): A solution of methyl L-allylglycinate (0.700 g, 5.43 mmol) in 5 mL of THF was added dropwise at 0 °C to a solution of compound **7** (4.25 g, 1.1 mmol) in 20 mL of THF. The mixture was stirred at room temperature for 12 h. THF was removed in vacuo, and the residue was precipitated from *i*PrOH, redissolved in CH_2Cl_2 and precipitated from *i*PrOH. The product was dissolved in CH_2Cl_2, precipitated from ether, filtered, and dried in vacuo to yield 4.0 g (90%) of the title compound: IR: $\tilde{\nu}$ = 3563 (m), 1962 (w), 1746 (m), 1470 (s), 1115 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.15−1.35 (m, 4 H), 2.50 (t, J_1 = 7.0 Hz, 4 H), 2.80−2.95 (m, 4 H), 3.50−3.70 (bs, ≈ 310 H), 3.75 (s, 6 H), 3.85 (t, J_2 = 5.0 Hz, 4 H), 4.10−4.25 (m, 6 H), 4.75 (d, J_3 = 9.0 Hz), 5.10−5.20 (m, 4 H), 5.55−5.80 (m, 2 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, −2.8, 10.4, 38.1, 50.4, 53.0, 55.7, 67.6, 70.0, 70.9, 71.2, 114.9, 120.4, 128.0, 129.8, 131.9, 135.3, 160.4, 172.4 ppm. MS (Electrospray): *m*/*z*: *n* = 75: 2015.1 (2 +, 2 H^+); *n* = 81: 1439.1 (3 +, 2 H^+/Na^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({(allyl)[1-(methoxycarbonyl)-3-butenyl]amino}sulfonyl)ethyl]dimethylsilyl}phenyl) Ether (13a): Allyl bromide (0.148 g, 1.22 mmol) was added at room temperature to a mixture of K_2CO_3 (0.169 g, 1.22 mmol) and compound **12** (0.500 g, 0.122 mmol) in 20 mL of DMF. The mixture was stirred at room temperature for 12 h. Then base was filtered off, and the filtrate was concentrated in vacuo, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.460 g (90%) of the title compound: IR: $\tilde{\nu}$ = 3058 (m), 1964 (w), 1742 (m), 1594 (s), 1116 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.15−1.30 (m, 4 H), 2.40−2.80 (m, 4 H), 2.85−3.00 (m, 4 H), 3.50−3.75 (bs, ≈ 310 H), 3.80−3.90 (m, 8 H), 4.15 (t, J_1 = 4.5 Hz, 4 H), 4.50 (dd, J_2 = 6.5 Hz, J_3 = 9.5 Hz, 2 H), 5.05−5.25 (m, 8 H), 5.65−5.95 (m, 4 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.6, 10.1, 34.9, 48.8, 50.4, 52.6, 60.0, 67.7, 70.1, 70.9, 71.2, 114.8, 118.8, 118.9, 128.2, 134.9, 135.1, 135.3, 160.3, 171.8 ppm. MS (Electrospray): *m*/*z*: *n* = 76: 1393.9 (3 +, 2 H^+/Na^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({(3-butenyl)[1-(methoxycarbonyl)-3-butenyl]amino}sulfonyl)ethyl]dimethylsilyl}phenyl) Ether (13b): 3-Butenyl bromide (0.131 g, 0.97 mmol) was added at room temperature to a mixture of K_2CO_3 (0.135 g, 0.97 mmol) and compound **12** (0.400 g, 0.097 mmol) in 10 mL of DMF. The reaction mixture was stirred at room temperature for 12 h. The base was then filtered off, and the filtrate was concentrated, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.380 g (93%) of the title compound: IR: $\tilde{\nu}$ = 2876 (s), 1967 (w), 1741 (m), 1457 (s), 1113 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 2.30−3.00 (m, 12 H), 3.55−3.80 (bs, ≈ 310 H), 3.70 (s, 6 H), 3.90 (t, J_1 = 5.5 Hz, 4 H), 4.15 (t, J_1 = 5.5 Hz, 4 H), 4.45 (dd, J_2 = 6.5 Hz, J_3 = 9.0 Hz, 2 H), 5.00−5.30 (m, 8 H), 5.60−5.90 (m, 4 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.2, 35.2, 35.5, 46.0, 49.6, 52.7, 60.3, 67.6, 70.1, 70.9, 114.9, 117.5, 119.0, 128.2, 133.7, 135.0, 135.4, 160.4, 171.8 ppm. MS (Electrospray): *m*/*z*: *n* = 73: 2063.1 (2 +, 2 K^+); *n* = 84: 1550.2 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({[1-(methoxycarbonyl)-3-butenyl](4-pentenyl)amino}sulfonyl)ethyl]dimethylsilyl}phenyl) Ether (13c): 4-Pentenyl bromide (0.142 g, 0.97 mmol) was added at room temperature to a mixture of K_2CO_3 (0.135 g, 0.97 mmol) and compound **12** (0.400 g, 0.097 mmol) in 10 mL of DMF. The reaction mixture was stirred at room temperature for 12 h. The base was filtered off, and the filtrate was concentrated, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.360 g (87%) of the title compound: IR: $\tilde{\nu}$ = 2871 (s), 1966 (w), 1741 (m), 1460 (s), 1104 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 1.65−2.30 (m, 8 H), 2.40−2.60 (m, 2 H), 2.70−2.85 (m, 2 H), 2.90−3.00 (m, 4 H), 3.10−3.30 (m, 4 H), 3.55−3.75 (bs, ≈ 310 H), 3.90 (t, J_1 = 5.0 Hz, 4 H), 4.15 (t, J_1 = 5.0 Hz, 4 H), 4.45 (dd, J_2 = 6.5 Hz, J_3 = 9.0 Hz, 2 H), 5.00−5.25 (m, 8 H), 5.65−5.90 (m, 4 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.1, 30.0, 31.4, 35.2, 46.1, 49.6, 52.7, 60.2, 67.6, 70.0, 70.9, 114.8, 115.8, 118.9, 128.2, 133.8, 135.3, 137.7, 160.4, 171.8 ppm. MS (Electrospray): *m*/*z*: *n* = 73: 2077.6 (2 +, 2 K^+); *n* = 77: 1456.8 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({[1-(methoxycarbonyl)-3-butenyl](3-propynyl)amino}sulfonyl)ethyl]dimethylsilyl}phenyl) Ether (13d): Propargyl bromide (0.116 g, 0.97 mmol) was added at room temperature to a mixture of K_2CO_3 (0.135 g, 0.97 mmol) and compound **12** (0.400 g, 0.097 mmol) in 10 mL of DMF. The reaction

mixture was stirred at room temperature for 12 h. The base was filtered off, and the filtrate was concentrated, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.360 g (88%) of the title compound: IR: $\tilde{\nu}$ = 3054 (m), 2360 (w), 1744 (s), 1456 (m), 1109 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.25−1.35 (m, 4 H), 2.20 (t, J_1 = 2.5 Hz, 2 H), 2.50−2.85 (m, 4 H), 3.05−3.15 (m, 4 H), 3.55−3.80 (bs, ≈ 310 H), 3.70 (s, 6 H), 3.85 (t, J_2 = 4.5 Hz, 4 H), 4.10−4.20 (m, 8 H), 4.50 (dd, J_3 = 6.5 Hz, J_4 = 9.0 Hz, 2 H), 5.10−5.25 (m, 4 H), 5.70−5.90 (m, 2 H), 6.95 (d, J_5 = 8.5 Hz, 4 H), 7.40 (d, J_5 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.0, 34.3, 34.5, 50.8, 52.6, 59.6, 67.0, 70.1, 70.9, 73.3, 79.5, 114.9, 119.3, 128.3, 133.4, 135.4, 160.4, 171.3 ppm. MS (Electrospray): *m*/*z*: *n* = 70: 1981.0 (2 +, 2 K^+); *n* = 83: 1524.4 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({[1-(methoxycarbonyl)-3-butenyl](2-methylallyl)amino}sulfonyl)ethyl]dimethylsilyl}phenyl) Ether (13e): Methallyl bromide (0.131 g, 0.97 mmol) was added at room temperature to a mixture of K_2CO_3 (0.135 g, 0.97 mmol) and compound **12** (0.400 g, 0.097 mmol) in 10 mL of DMF. The reaction mixture was stirred at room temperature for 12 h. The base was filtered off, and the filtrate was concentrated, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.385 g (94%) of the title compound: IR: $\tilde{\nu}$ = 2882 (s), 2360 (w), 1741 (m), 1466 (s), 1113 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.40 (m, 4 H), 1.75 (s, 6 H), 2.40−2.85 (m, 4 H), 2.85−3.00 (m, 4 H), 3.55−3.80 (bs, ≈ 310 H), 3.85 (t, J_1 = 5.0 Hz, 4 H), 4.15 (t, J_1 = 5.0 Hz, 4 H), 4.90 (t, J_2 = 7.5 Hz, 2 H), 4.95 (d, J_3 = 12.0 Hz, 4 H), 5.05−5.20 (m, 4 H), 5.70−5.85 (m, 2 H), 7.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.1, 20.6, 35.3, 50.0, 52.5, 52.9, 60.4, 67.6, 70.0, 70.9, 114.9, 115.1, 118.7, 128.2, 134.2, 135.3, 141.8, 160.4, 171.4 ppm. MS (Electrospray): *m*/*z*: *n* = 74: 2085.0 (2 +, 2 K^+); *n* = 85: 1547.7 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis(*p*-{[2-({(2-methoxycarbonylallyl)[1-(methoxycarbonyl)-3-butenyl]amino}sulfonyl)ethyl]dimethylsilyl}-phenyl) Ether (13f): Methyl 2-(bromomethyl)acrylate (0.174 g, 0.97 mmol) was added at room temperature to a mixture of K_2CO_3 (0.135 g, 0.97 mmol) and compound **12** (0.400 g, 0.097 mmol) in 10 mL of DMF. The reaction mixture was stirred at room temperature for 12 h. The base was filtered off, and the filtrate was concentrated, dissolved in CH_2Cl_2, and precipitated from ether. The product was filtered off and dried in vacuo to yield 0.370 g (89%) of the title compound. IR: $\tilde{\nu}$ = 2910 (s), 1966 (w), 1740 (s), 1462 (s), 1110 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 2.40−2.80 (m, 4 H), 2.90−3.05 (m, 4 H), 3.55−3.80 (bs, ≈ 310 H), 3.75 (s, 6 H), 3.90 (t, J_1 = 4.5 Hz, 4 H), 4.10−4.20 (m, 8 H), 4.45 (dd, J_2 = 6.5 Hz, J_3 = 8.5 Hz, 2 H), 5.05−5.20 (m, 4 H), 5.60−5.90 (m, 2 H), 6.00 (s, 2 H), 6.35 (s, 2 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.0, 34.8, 46.9, 49.9, 52.4, 52.6, 60.3, 67.6, 70.1, 70.9, 114.9, 118.9, 128.2, 129.1, 133.8, 135.4, 136.8, 160.4, 166.7, 171.5 ppm. MS (Electrospray): *m*/*z*: *n* = 77: 2195.5 (2 +, 2 K^+); *n* = 83: 1564.6 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2-(methoxycarbonyl)-1,2,3,6-tetrahydro-1-pyridyl]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (14a): Catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**18a**, 3.0 mg, 3.8 μmol) was added to a solution of compound **13a** (0.080 g, 0.019 mmol) in 8 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, and then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.067 g (86%) of the title compound. IR: $\tilde{\nu}$ = 3056 (m), 2361 (w), 1742 (m), 1456 (m), 1111 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 2.60 (s, 4 H), 2.85−3.00 (m, 4 H), 3.55−3.80 (bs, ≈ 310 H), 3.70 (s, 6 H), 3.85 (t, J_1 = 5.5 Hz, 4 H), 4.15 (t, J_1 = 5.5 Hz, 4 H), 4.75 (t, J_2 = 2.5 Hz, J_3 = 6.0 Hz, 2 H), 5.60−5.85 (m, 4 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.1, 28.2, 42.8, 48.7, 52.9, 53.4, 67.6, 70.1, 70.9, 114.9, 123.1, 123.9, 128.3, 135.4, 160.3, 171.8 ppm. MS (Electrospray): *m*/*z*: *n* = 77: 2109.1 (2 +, 2 K^+); *n* = 81: 1477.8 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2-(methoxycarbonyl)-2,3,6,7-tetrahydro-1*H*-azepin-1-yl]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (14b): Catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**18a**, 11.0 mg, 13.2 μmol) was added to a solution of compound **13b** (0.280 g, 0.066 mmol) in 16 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.250 g (91%) of the title compound. IR: $\tilde{\nu}$ = 2882 (s), 2358 (w), 1743 (m), 1466 (s), 1112 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.25−1.35 (m, 4 H), 2.30−2.90 (m, 8 H), 2.90−3.00 (m, 4 H), 3.55−3.75 (bs, ≈ 310 H), 3.70 (s, 6 H), 3.85 (t, J_1 = 4.5 Hz, 4 H), 4.15 (t, J_1 = 4.5 Hz, 4 H), 4.80 (dd, J_2 = 3.5 Hz, J_3 = 7.0 Hz, 2 H), 5.70−5.85 (m, 4 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.1, 30.7, 31.4, 44.2, 49.3, 52.6, 59.0, 68.8, 70.0, 70.8, 114.8, 126.6, 128.2, 132.3, 135.3, 160.3, 172.1 ppm. MS (Electrospray): *m*/*z*: *n* = 76: 2101.3 (2 +, 2 K^+); *n* = 71: 1486.9 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2-(methoxycarbonyl)-1,2,3,6,7,8-hexahydroazocin-1-yl]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (14c): Catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**18a**, 10.9 mg, 13.2 μmol) was added to a solution of compound **13c** (0.280 g, 0.066 mmol) in 16 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.265 g (96%) of the title compound. IR: $\tilde{\nu}$ = 2884 (s), 2361 (w), 1741 (m), 1470 (s), 1111 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 1.35−1.55 (m, 2 H), 1.90−2.35 (m, 6 H), 2.50−3.05 (m, 8 H), 3.50−3.85 (bs, ≈ 310 H), 3.70 (s, 6 H), 3.85 (t, J_1 = 5.0 Hz, 4 H), 4.15 (t, J_1 = 5.0 Hz, 4 H), 4.60 (dd, J_2 = 5.0 Hz, J_3 = 7.5 Hz, 2 H), 5.65−5.95 (m, 4 H), 6.90 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.1, 24.6, 29.8, 30.4, 46.5, 48.4, 52.7, 60.6, 67.5, 70.3, 70.9, 114.7, 126.3, 128.2, 134.0. 135.3, 160.2, 172.0 ppm. MS (Electrospray): *m*/*z*: *n* = 77: 2071.1 (2 +, 2 H^+); *n* = 85: 1511.0 (3 +, 2 H^+/K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2-(methoxycarbonyl)-5-vinyl-1,2,3,6-tetrahydro-1-pyridyl]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (14d): Catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**18a**, 11.9 mg, 14.4 μmol) was added to a solution of compound **13d** (0.300 g, 0.072 mmol) in 17 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.250 g (83%) of the title compound. IR: $\tilde{\nu}$ = 2875 (s), 2360 (w), 1741 (m), 1456 (m), 1107 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.35 (m, 4 H), 2.70 (s, 4 H), 2.90−3.05 (m, 4 H), 3.50−3.75 (bs, ≈ 310 H), 3.85 (t, J_1 = 5.5 Hz, 4 H), 4.15 (t, J_1 = 5.5 Hz, 4 H), 4.75 (dd, J_2 = 3.0 Hz, J_3 = 5.5 Hz, 2 H), 5.05 (dd, J_4 = 10.0 Hz, J_5 = 21.0 Hz, 2 H), 5.80 (s, 2 H), 6.25 (dd, J_4 = 10.0 Hz, J_5 = 21.0 Hz, 2 H), 6.95 (d, J_6 = 8.5 Hz, 4 H), 7.40 (d, J_6 = 8.5 Hz,

4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.0, 28.4, 41.9, 48.7, 52.9, 53.3, 67.5, 70.0, 70.8, 112.4, 114.8, 124.2, 128.1, 132.9, 135.3, 136.3, 160.3, 171.6 ppm. MS (Electrospray): *m*/*z*: *n* = 73: 2047.1 (2 +, 2 K^+); *n* = 80: 1480.4 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2-(methoxycarbonyl)-5-methyl-1,2,3,6-tetrahydro-1-pyridyl]sulfonyl}ethyl)dimethylsilyl]-phenyl} Ether (14e): Catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**18a**, 7.7 mg, 9.4 μmol) was added to a solution of compound **13e** (0.200 g, 0.047 mmol) in 12 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 183 g (94%) of the title compound. IR: $\tilde{\nu}$ = 2882 (s), 2361 (w), 1742 (m), 1470 (s), 1111 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.30 (m, 4 H), 1.65 (s, 6 H), 2.55 (s, 4 H), 2.90−3.00 (m, 4 H), 3.50−3.75 (bs, ≈ 310 H), 3.80−3.90 (m, 8 H), 4.15 (t, J_1 = 4.5 Hz, 4 H), 4.70 (dd, J_2 = 3.0 Hz, J_3 = 5.5 Hz, 2 H), 5.45 (s, 2 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.0, 20.8, 28.1, 46.1, 48.6, 52.8, 53.2, 67.5, 70.0, 70.9, 114.8, 117.5, 128.2, 131.1, 135.3, 160.3, 172.0 ppm. MS (Electrospray): *m*/*z*: *n* = 76: 2101.2 (2 +, 2 K^+); *n* = 80: 1472.6 (3 +, 3 K^+).

Poly(ethylene Glycol)-3400 Bis{*p*-[(2-{[2,5-bis(methoxycarbonyl)-1,2,3,6-tetrahydro-1-pyridyl]sulfonyl}ethyl)dimethylsilyl]phenyl} Ether (14f): Catalyst $RuCl_2(=CHPh)(Pcy_3)(Imes)$ (**18b**, 13.8 mg, 0.0162 mmol) was added to a solution of compound **13f** (0.350 g, 0.081 mmol) in 20 mL of CH_2Cl_2. The mixture was stirred at room temperature for 14 h, and then precipitated twice from ether. The product was filtered off and dried in vacuo to yield 0.320 g (93%) of the title compound. IR: $\tilde{\nu}$ = 2880 (s), 1750 (m), 1716 (m), 1467 (s), 1110 (s) cm^{-1}. ^1H NMR ($CDCl_3$, Me_4Si): δ = 0.30 (s, 12 H), 1.20−1.35 (m, 4 H), 2.60−2.85 (m, 4 H), 2.90−3.05 (m, 4 H), 3.55−3.75 (bs, ≈ 310 H), 3.65 (s, 6 H), 3.75 (s, 6 H), 3.85 (t, J_1 = 5.5 Hz, 4 H), 4.15 (t, J_1 = 5.5 Hz, 4 H), 4.40 (d, J_2 = 15.0 Hz, 2 H), 4.80 (d, J_3 = 5.5 Hz, 2 H), 6.95 (d, J_4 = 8.5 Hz, 4 H), 6.95−7.05 (m, 2 H), 7.40 (d, J_4 = 8.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, Me_4Si): δ = −2.8, 10.0, 28.4, 41.6, 48.9, 52.2, 52.4, 53.0, 67.5, 69.9, 70.8, 114.8, 127.4, 127.9, 135.2, 135.3, 160.3, 165.1, 170.9 ppm. MS (Electrospray): *m*/*z*: *n* = 74: 2101.5 (2 +, 2 K^+); *n* = 92: 1642.1 (3 +, 3 H^+).

Methyl Pyridine-2-carboxylate (15a): CsF (0.074 g, 0.484 mmol) was added to a solution of **14a** (0.100 g, 0.0242 mmol) in 5 mL of DMF. The mixture was stirred overnight at 110 °C and DMF was removed in vacuo. The residue was dissolved in CH_2Cl_2 and precipitated from ether. The filtrate was evaporated and the product was purified on silica gel (hexane/EtOAc: 95:5) to yield 3.8 mg (57%) of the title compound:[79] ^1H NMR ($CDCl_3$, Me_4Si): δ = 4.00 (s, 3 H), 7.50 (m, 1 H), 7.90 (td, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1 H), 8.15 (td, J_3 = 1.0 Hz, J_2 = 8.0 Hz, 1 H), 8.75 (m, 1 H) ppm. MS (Electrospray): *m*/*z* = 138 $[M + H]^+$.

Dimethyl Pyridine-2,5-dicarboxylate (15f): CsF (0.072 g, 0.471 mmol) was added to a solution of **14f** (0.100 g, 0.0236 mmol) in 5 mL of DMF. The mixture was stirred overnight at 110 °C and DMF was evaporated. The residue was dissolved in CH_2Cl_2, precipitated from ether, and filtered. The filtrate was evaporated and the product was purified on silica gel (hexane/EtOAc, 9:1) to yield 7.0 mg (76%) of the title compound:[80] ^1H NMR ($CDCl_3$, Me_4Si): δ = 4.00 (s, 3 H), 4.10 (s, 3 H), 8.25 (dd, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 1 H), 8.45 (dd, J_3 = 2.0 Hz, J_2 = 8.0 Hz, 1 H), 9.35 (dd, J_1 = 1.0 Hz, J_3 = 2.0 Hz, 1 H) ppm. MS (Electrospray): *m*/*z* = 196 $[M + H]^+$.

1,2,3,6-Tetrahydropyridine-2-carboxylic Acid Hydrochloride (17a): Compound **14a** (0.100 g, 0.024 mmol) was dissolved in 5 mL of 6 N HCl and stirred at 100 °C for 24 h. The solvent was evaporated. The residue was dissolved in *i*PrOH, and PEG was precipitated at −20 °C and filtered off. The filtrate was evaporated in vacuo to yield 4.4 mg (56%) of the title compound. IR: $\tilde{\nu}$ = 2967 (s), 1744 (m), 1420 (m), 1070 (w), 936 (w) cm^{-1}. ^1H NMR (D_2O, Me_4Si): δ = 2.40−2.55 (m, 1 H), 2.65−2.75 (m, 1 H), 3.70 (s, 1 H), 4.10 (q, *J* = 5.5 Hz, 1 H), 5.70−5.75 (m, 1 H), 5.90−6.00 (m, 1 H) ppm. ^{13}C NMR (D_2O, Me_4Si): δ = 25.1, 42.1, 53.8, 120.0, 124.8, 172.2. HRMS: calcd. for $C_6H_{10}NO_2$ 128.0712, found 128.0699. $[\alpha]_D^{20}$ = −151 (0.185, H_2O).

2,3,6,7-Tetrahydro-1*H*-azepine-2-carboxylic Acid Hydrochloride (17b): Compound **14b** (0.100 g, 0.024 mmol) was dissolved in 5 mL of 6 N HCl and stirred at 100 °C for 24 h. The solvent was evaporated. The residue was dissolved in *i*PrOH, and PEG was precipitated at −20 °C and filtered off. The filtrate was evaporated in vacuo to yield 5.5 mg (64%) of the title compound: IR: $\tilde{\nu}$ = 2792 (s), 1733 (m), 1388 (m), 1116 (w), 975 (m) cm^{-1}. ^1H NMR (D_2O, Me_4Si): δ = 2.45 (s, 2 H), 2.60−2.70 (m, 1 H), 2.75−2.85 (m, 1 H), 3.10−3.20 (m, 1 H), 3.35−3.45 (m, 1 H), 4.15 (dd, J_1 = 2.0 Hz, J_2 = 9.5 Hz, 1 H), 5.75−5.90 (m, 2 H) ppm. ^{13}C NMR (D_2O, Me_4Si): δ = 25.1, 27.5, 44.4, 58.8, 127.6, 131.2, 172.0 ppm. HRMS: calcd. for $C_7H_{12}NO_2$ 142.0868, found 142.0820. $[\alpha]_D^{20}$ = −17 (*c* = 0.475, H_2O).

1,2,3,6,7,8-Hexahydroazocine-2-carboxylic Acid Hydrochloride (17c): Compound **14c** (0.100 g, 0.024 mmol) was dissolved in 5 mL of 6 N HCl and stirred at 100 °C for 24 h. The solvent was evaporated. The residue was dissolved in *i*PrOH, and PEG was precipitated at −20 °C and filtered off. The filtrate was evaporated in vacuo to yield 5.3 mg (58%) of the title compound: IR: $\tilde{\nu}$ = 2795 (s), 1732 (s), 1449 (m), 1202 (s), 875 (s) cm^{-1}. ^1H NMR (D_2O, Me_4Si): δ = 1.65−1.90 (m, 3 H), 2.05−2.35 (m, 5 H), 2.90−3.00 (m, 1 H), 3.65−3.75 (m, 1 H), 4.25−4.35 (m, 1 H), 4.40 (q, *J* = 6.0 Hz, 1 H) ppm. ^{13}C NMR (D_2O, Me_4Si): δ = 24.7, 25.4, 28.6, 31.6, 52.4, 66.3, 69.3, 169.8. HRMS: calcd. for $C_8H_{14}NO_2$ 156.1025, found 156.1028. $[\alpha]_D^{20}$ = −27 (*c* = 0.225, H_2O).

1,2,3,6-Tetrahydropyridine-2,5-dicarboxylic Acid Hydrochloride (17f): Compound **14f** (0.100 g, 0.024 mmol) was dissolved in 5 mL of 6 N HCl and stirred at 100 °C for 24 h. The solvent was evaporated in vacuo. The residue was dissolved in *i*PrOH, and PEG was precipitated at −20 °C and filtered off. The filtrate was evaporated to yield 6.0 mg (61%) of the title compound: IR: $\tilde{\nu}$ = 2956 (s), 1717 (m), 1416 (m), 1197 (m), 950 (w) cm^{-1}. ^1H NMR (D_2O, Me_4Si): δ = 2.65−2.75 (m, 1 H), 3.00 (d, J_1 = 20.0 Hz, 1 H), 3.90 (d, J_2 = 16.5 Hz, 1 H), 4.10 (d, J_3 = 17.0 Hz, 1 H), 4.15 (q, J_4 = 5.0 Hz, 1 H), 7.15 (s, 1 H) ppm. ^{13}C NMR (D_2O, Me_4Si): δ = 25.7, 41.0, 53.1, 124.1, 137.7, 167.5, 171.4. HRMS: calcd. for $C_7H_{10}NO_4$ 172.0610, found 172.0558. $[\alpha]_D^{20}$ = −158 (0.360, H_2O).

L-*N*-Tosyl-4,5-didehydropipecolic Acid (18a): NaOH (1 N, 0.05 mL, 0.092 mmol) and tosyl chloride (8.8 mg, 0.046 mmol) were added with stirring to a solution of **17a** (5.0 mg, 0.031 mmol) in H_2O (1 mL). After the mixture had been stirred for 5 h at room temperature, additional tosyl chloride (2.0 mg, 0.01 mmol) and NaOH (2 N, 0.005 mL, 0.01 mmol) were added again. After 12 h, the mixture was diluted with 2 N NaOH and extracted with ether (3 ×). Dil. HCl was added to the aqueous phase until pH 1. Extraction with CH_2Cl_2 (5 ×), drying, and evaporation yielded 6.0 mg (70%) of the title compound:[11] ^1H NMR ($CDCl_3$, Me_4Si): δ = 2.45 (s, 3 H), 2.60 (s, 2 H), 4.00 (dd, J_1 = 18.0 Hz, J_2 = 30.0 Hz, 2 H), 4.90 (dd, J_1 = 5.0 Hz, J_2 = 8.5 Hz, 1 H,), 5.70 (sl, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 2 H) ppm. Chiral HPLC: t_R = 16.9 min.

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