Unconventional, Amphiphilic Polymers Based on Chiral Poly(ethylene oxide) Derivatives. I. Synthesis and Characterization[1]

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ABSTRACT: The first representatives of a new class of synthetic, amphiphilic polymers—polyethylene oxide-based (PEO-based) polymers **1**−**3**, (see Figure 2)—are introduced. These polymers are constituted in a similar way as coiled-coil-forming peptides: the polymers possess a regular repeat of apolar (A) residues in a polar (P) sequence of residues. Polymers **1**−**3** can thus be characterized by the formula $[PAPPAPP']_n$ or $[PAPP']_n$, in which P stands for an ethylene oxide unit, P′ stands for a glycate unit, and A stands for a hydrophobically modified ethylene oxide unit. The preparation of **1**−**3** comprises the synthesis and $SnOct_2$-catalyzed ring-opening polymerization of 2-oxo-crown ether monomers *(SS)*-**4**, *(S)*-**5**, and *(S)*-**6**. Alternatively, polymers **1**−**3** have been obtained by the polycondensation of their *ω*-hydroxycarboxylic acid precursors. ^{1}H NMR and ^{13}C NMR analysis as well as electrospray mass spectrometry (ES-MS) verified the integrity of the followed synthetic route and, therefore, confirmed the regular repeat of polar and apolar segments in **1**−**3**. The critical aggregation concentrations (cac's) of **1**−**3** in H_2O at 20 °C were determined by a fluorescence study, using pyrene as an apolar fluorescent probe. The cac's (i) were strongly influenced by the size of the hydrophobic segments in the polymer and by the frequency at which these segments were repeated in the polymer and (ii) varied over a wide concentration range (i.e. polymer **1** displayed a cac of ca. 0.002 mg/mL, whereas polymer **3** showed a cac of ca. 0.15 mg/mL). Thus, tailoring of the cac is possible in these new synthetic, amphiphilic polymers.

Introduction

Amphiphilic polymers are of fundamental scientific interest and find their use in industrial applications. Over the years, many of these polymers, in which hydrophilic (or polar) and hydrophobic (or apolar) segments are combined, have been investigated. Amphiphilic polymers can be obtained by alternating hydrophilic and hydrophobic blocks, as exemplified in frequently studied block copolymers such as polystyrene/poly(sodium acrylate) (PS/PANa), polystyrene/poly(ethylene oxide) (PS/PEO), and poly(ethylene oxide)/poly(propylene oxide) (PEO/PPO/PEO).[2] Other approaches to acquire amphiphilic polymers include the copolymerization of monomers of opposing polarity or the postmodification of polymers.[3] Recently, special architectures have been employed to construct new amphiphiles in general and new amphiphilic polymers in particular;[4] dendrimers and star polymers, for instance, have been used in the synthesis of amphiphiles.[5] All these approaches have added to a better understanding of the structure−property relationship in amphiphilic (macro)molecules, but up to date, no general theory has been put forward to describe the behavior of amphiphiles. Therefore, an increased control over the properties of amphiphiles remains in demand, especially regarding the highly specific functions that are possible for amphiphiles, as exemplified in some vital natural systems (e.g. phospholipid bilayers in cell membranes and enzymes in which hydrophobic microdomains serve as specific receptor sites).

A unique 'ribbon'-type of amphiphilicity is observed in coiled−coil-forming peptides such as myosin.[6] Myosin has a 7_2-repeat of apolar (A) amino acids in a polar (P) sequence of amino acids and can therefore be characterized by the formula $[PAPPAPP]_n$. This typical 7_2-repeat gives rise to α-helical peptides with a hydrophobic ribbon along the surface of the α-helix, causing the association of two peptide macromolecules to a double superhelix—a so-called coiled coil (see Figure 1).

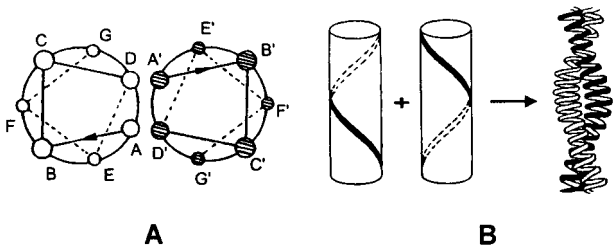

Figure 1. Coiled coil representations. The 'helical wheel' representation (part A) is an end-on-view of two α-helices that build up a coiled coil. In every 'wheel', the repeating unit of seven amino acids is drawn. Positions A and D (and A′ and D′) are occupied by hydrophobic residues such as leucine (Leu), while positions B, C, and D (and B′, C′, and D′) are occupied by hydrophilic, α-helix-stabilizing residues such as serine (Ser). Finally, positions E and G (and E′ and G′) are occupied by lysine (Lys) and glutamic acid (Glu), which at the right pH give salt bridges between the two α-helical units of the coiled coil.[39] The association process is schematically drawn in part B. In H_2O, the apolar ribbons on the surfaces of the amphiphilic α-helices—for simplicity drawn as cylinders—'click' together, thereby deforming the two helices to two left-handed superhelices. After association, the ribbons are buried in the interior of the coiled coil and are thus shielded from the aqueous environment.

To our knowledge, the design of *nonpeptide*, synthetic polymers with a potential 'ribbon'-type of amphiphilicity has never been addressed. A first approach to such synthetic analogues of coiled coils is presented here and involves the synthesis of the chiral, PEO-based polymers shown in Figure 2. The choice of the PEO-based target polymers **1**−**3**—the ester function in the backbone has been introduced for synthetic reasons—is inspired by the solubility and the dominantly hydrophilic behavior of

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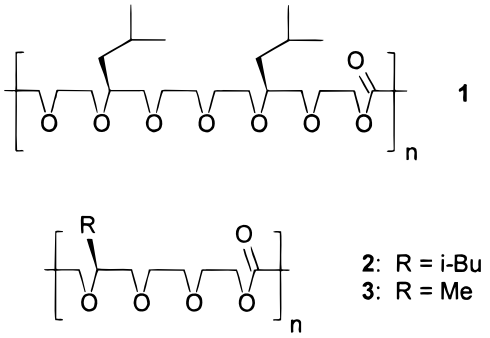


Figure 2. Synthetic coiled-coil analogues based on PEO. Isobutyl side groups are chosen in analogy to the isobutyl side groups of the leucine residues in coiled-coil-forming peptides. The methyl side groups are chosen analogous to the methyl side groups in PEO/PPO/PEO block copolymers. Chirality is introduced in analogy to the chirality present in peptides. Polymer **1** and polymers **2** and **3** can be abbreviated in the formulas $[PAPPAPP']_n$ and $[PPAP']_n$, respectively.

PEO in H_2O and by the 7_2-helical conformation of PEO in dilute aqueous solutions. In contrast, PPO and poly(butylene oxide) (PBO) are hardly soluble in H_2O,[7] whereas PEO/PPO/PEO as well as PEO/PBO/PEO block copolymers show distinct amphiphilic behavior.[8] Therefore, ethylene oxide fragments are regarded as polar (or hydrophilic), whereas alkyl-substituted ethylene oxide fragments are apolar (or hydrophobic). Consequently, stereoregular placing of isobutyl side chains at every second and fifth unit of a seven−unit repeat of ethylene oxides—as shown in polymer **1**—results in a synthetic analogue of coiled−coil-forming polypeptides, in the sense that the design of the primary structure is identical. Polymers **2** and **3**, both having a [PAPPAPP′]-resembling [PPAP′]-repeat in the primary structure, can be used to investigate the structure−property relationship in this type of polymers.

This paper reports on (i) the synthesis of polymers **1**−**3**, (ii) the molecular characterization of **1**−**3** and their precursors by ^1H NMR, ^{13}C NMR, chromatography techniques, and electrospray mass spectrometry (ES-MS) and (iii) experimental evidence for the amphiphilic behavior of macromolecules **1**−**3** in aqueous solutions. This evidence includes the determination of the critical association concentrations (cac's) of **1**−**3** in H_2O at 20 °C by fluorescent-probe measurements, employing pyrene as the fluorescent apolar probe. Whether these synthetic polymers **1**−**3** form well-defined higher structures such as coiled coils will be discussed in the second part of this article sequence.

Results and Discussion

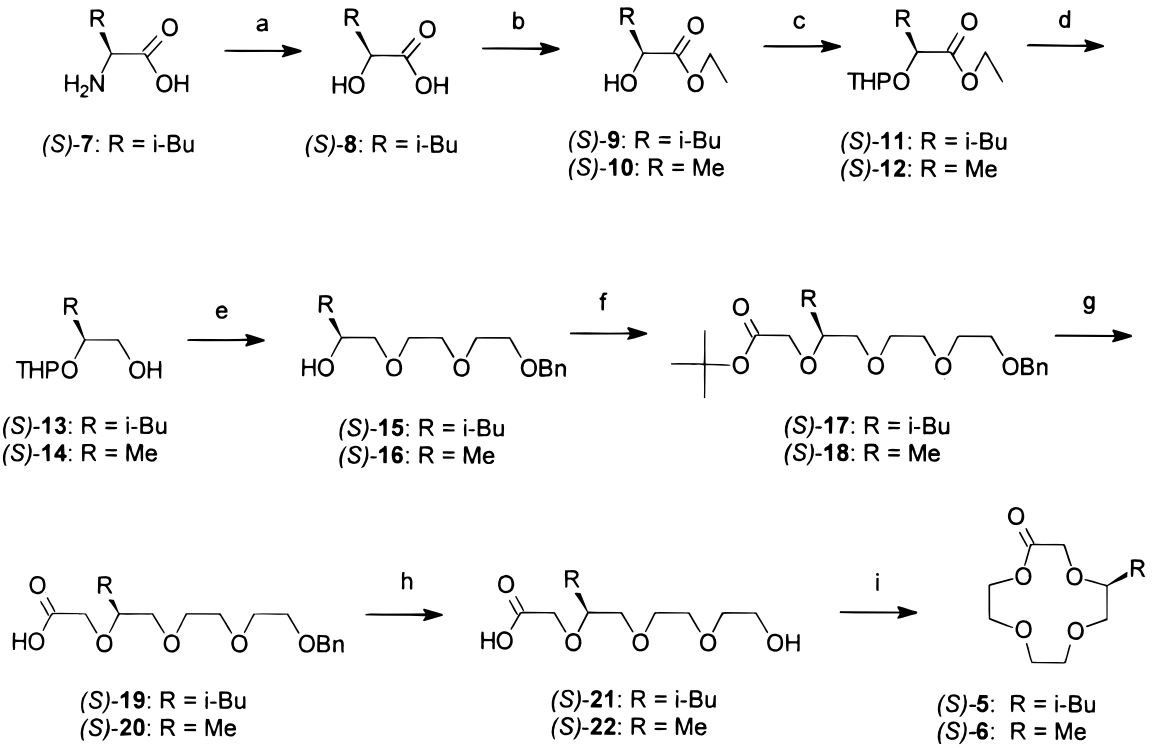
Synthesis of the Alkyl-Modified Oxo-Crown Ethers *(SS)*-4, *(S)*-5, and *(S)*-6. The synthesis of oxo-crown monomers *(SS)*-**4**, *(S)*-**5**, and *(S)*-**6** is shown in Schemes 1−3. The reactions and compounds shown in Scheme 1 have partially been reported in the literature.[9,10]

The chiral and apolar fragments in the final crown ethers—the isobutyl- and methyl-substituted ethylene oxide fragments—have been introduced by starting the syntheses with either *(S)*-leucine or ethyl *(S)*-lactate (both these compounds *(S)*-**7** and *(S)*-**10** are commercially available). Conversion of leucine (*(S)*-**7**) by sequential diazotation ($H_2SO_4/NaNO_2/H_2O$) and esterification with EtOH gave ethyl *(S)*-leucate (**9**). Protection of esters *(S)*-**9** and *(S)*-**10** with 3,4-dihydro-*2H*-pyran (DHP), employing *p*-toluenesulfonic acid (TsOH) as catalyst in Et_2O, yielded the tetrahydropyranoxy (THP) ethyl esters *(S)*-**11** and *(S)*-**12** in almost quantitative yields. Reduction of these compounds using $LiAlH_4$ in Et_2O afforded the THP-monoprotected alkyl-substituted chiral diols *(S)*-**13** and *(S)*-**14**. Williamson syntheses of these primary alcohols with 2-(2-(benzyloxy)ethoxy)-ethyl tosylate (compound **37**)[11] in boiling THF using KOH as base and consecutive removal of the THP group gave the secondary alcohols *(S)*-**15** and *(S)*-**16**. Coupling with *tert*-butyl bromoacetate in *tert*-BuOH, using *tert*-BuOK to create the alkoxide, gave the *tert*-butyl esters *(S)*-**17** and *(S)*-**18** in satisfactory yields of 72% and 78%, respectively. Acid-catalyzed hydrolysis of the *tert*-butyl esters and hydrogenation of the benzyl groups gave the *ω*-hydroxycarboxylic acids *(S)*-**21** and *(S)*-**22** in almost quantitative yields. The final cyclization step was achieved by heating the appropriate *ω*-hydroxycarboxylic acid precursor with the Lewis acid $CoCl_2$ (≫11 mol %) at 250 °C in a Kugelrohr apparatus.[12] An almost pure distillate could be collected, when reduced pressures of 2−3 and 8 mmHg were applied for *(S)*-**21** and *(S)*-**22**, respectively. Chromatography afforded the 2-oxo-12-crown-4 compounds *(S)*-**5** and *(S)*-**6** in yields of 72% and 56%, respectively. For comparison, the high dilution cyclization method of Mukaiyama[13] was used to synthesize compound *(S)*-**5**: the 2-oxo-12-crown-4 product was obtained in an inferior yield of 34% (additionally, 7% dimeric product was isolated).

In Schemes 2 and 3, the synthesis of the larger 2-oxo-21-crown-7 monomer *(SS)*-**4** is shown. Alcohol *(S)*-**13** was coupled with 2-(benzyloxy)ethyl tosylate (compound **34**)[14] in refluxing THF using KOH as base. After workup, the crude product was treated with TsOH in MeOH to remove the THP group. Thus, ether *(S)*-**23** was obtained in a 77% yield. The convenient etherification method to produce *(S)*-**23** (KOH, THF, reflux)—similarly applied in the syntheses of *(S)*-**15** and *(S)*-**16**—was introduced by Selve, who used it for the production of nonionic fluoro surfactants.[15] When these coupling conditions are applied to the reaction of a secondary alcohol with a primary tosylate—as in the syntheses of compounds *(S)*-**24** and *(S)*-**25**—more equivalents of tosylate and longer reaction times have to be employed to reach reasonable yields (40% and 67% for *(S)*-**24** and *(S)*-**25**, respectively). Evidently, more byproducts such as hydrolyzed material are formed in these cases. Standard reaction conditions were used to debenzylate *(S)*-**25** to alcohol *(S)*-**26** and to tosylate *(S)*-**24** to *(S)*-**27**. Finally, ethylene oxide oligomer *(SS)*-**28** could be obtained from alcohol *(S)*-**26** and tosylate *(S)*-**27** in a 68% yield by applying the previously described reaction conditions for Williamson syntheses (KOH, THF, reflux).

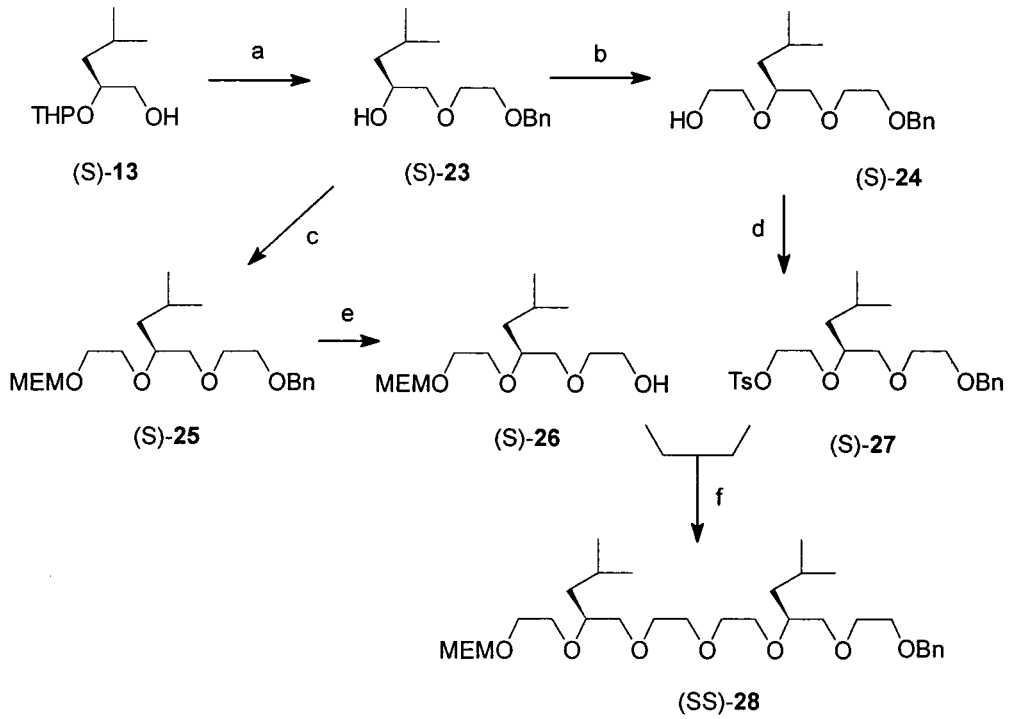
The $ZnBr_2$-catalyzed removal of the methoxyethoxymethylene (MEM) group in compound *(SS)*-**28** was achieved in a poor yield of only 44% (see Scheme 3). The reaction did not proceed to completion, and debenzylation occurred simultaneously (7% *α*,*ω*-diol side-product *(SS)*-**33** was isolated). The primary alcohol *(SS)*-**29** was coupled with *tert*-butyl bromoacetate to introduce an ester function. Sequential hydrolysis of the *tert*-butyl ester and hydrogenation of the benzyl group were conducted using standard reaction conditions. A newly developed and simplified version of a ring closure procedure reported by Corey[16] could be used for the final cyclization to *(SS)*-**4**: at a concentration of 0.03 M, *ω*-hydroxycarboxylic acid *(SS)*-**32** was stirred for 3 days in xylene in the presence of 1.5 mol equiv of dithiodipyr-

Scheme 1



(a) $NaNO_2$, H_2SO_4, H_2O, RT (54%); (b) EtOH, HCl, PhMe, Δ (75%); (c) DHP, TsOH, Et_2O, RT (87%, 95%); (d) $LiAlH_4$, Et_2O, RT (94%, 92%); (e) (1) $TsO(CH_2CH_2O)_2Bn$ (**37**), KOH, THF, Δ and (2) TsOH, MeOH, RT (68%, 73%); (f) $BrCH_2COO$*tert*-Bu, *tert*-BuOK, *tert*-BuOH, RT (72%, 78%); (g) TFA, RT (97%, 93%); (h) Pd/C, H_2, dioxane, RT (100%, 100%); (i) $CoCl_2$, 250 °C, $p \approx 5$ mmHg (72%, 56%). The yields in parentheses refer to the isobutyl- and methyl-substituted compounds, respectively. DHP = 3,4-dihydro-*2H*-pyran; Ts = *p*-toluenesulfonyl; TFA = trifluoroacetic acid.

Scheme 2

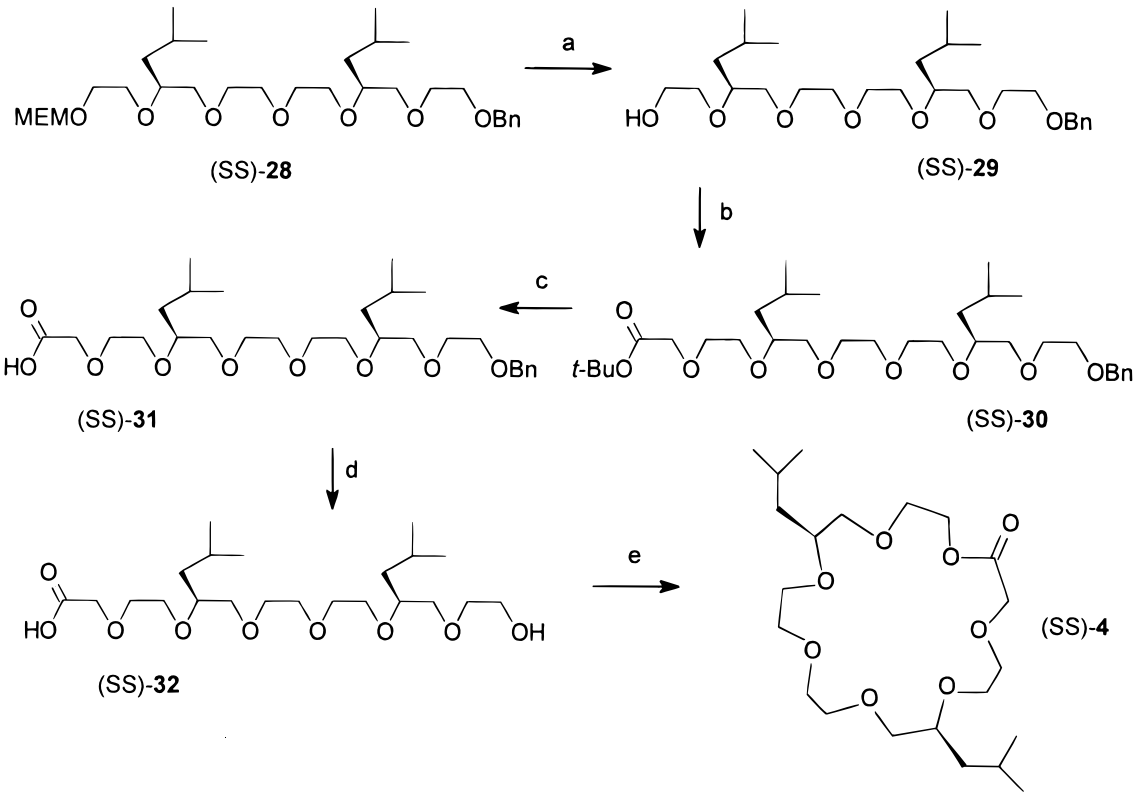


(a) (1) $TsOCH_2CH_2OBn$ (**34**), KOH, THF, Δ and (2) TsOH, MeOH, RT (77%); (b) (1) $THPOCH_2CH_2OTs$ (**35**), KOH, THF, Δ and (2) TsOH, MeOH, RT (40%); (c) $MEMOCH_2CH_2OTs$ (**36**), KOH, THF, Δ (67%); (d) TsCl, pyridine, 4 °C (90%); (e) Pd/C, H_2, MeOH, RT (91%); (f) KOH, THF, Δ (68%). Ts = *p*-toluenesulfonyl; MEM = methoxyethoxymethylene.

idine and PPh_3. Subsequent column chromatography gave 2-oxo-21-crown-7 monomer *(SS)*-**4** in a 50% yield.

The overall yields for the 13-step, 9-step, and 7-step syntheses of the 2-oxo crown ethers *(SS)*-**4**, *(S)*-**5**, and *(S)*-**6** calculated from the starting materials leucine (*(S)*-**7**) and ethyl lactate (*(S)*-**10**) are 2%, 11%, and 26%, respectively. The crown ethers have been characterized by ^1H NMR, ^{13}C NMR, GC-MS, and/or HRMS (high-resolution mass spectrometry) techniques, FTIR, and CD-spectroscopy (the latter two characterization tech-

Scheme 3



(a) $ZnBr_2$, CH_2Cl_2, RT (44%); (b) $BrCH_2COO$*tert*-Bu, *tert*-BuOK, *tert*-BuOH, RT (85%); (c) TFA, RT (94%); (d) Pd/C, H_2, dioxane, H_2O, RT (100%); (e) dithiodipyridine, PPh_3, xylene, RT (50%).

niques have only been applied to the 2-oxo-12-crown-4 ethers). The collected data are in agreement with the assigned structures. As an example, the ^{1}H NMR and ^{13}C NMR spectra of *(S)*-**5** are shown in Figure 3: the ^{1}H NMR spectrum is rather complex due to the chirality of the oxo-crown ether.

Several key compounds were investigated to ensure that the enantiomeric excesses of the starting compounds leucine (*(S)*-**7**) (ee = 97%) and ethyl *(S)*-lactate (*(S)*-**10**) (ee > 99.5%) were preserved in the final oxo-crown ethers.[17] First, ethyl leucate (*(S)*-**9**) was heated at reflux under esterification conditions for 1 week. Subsequent analysis of *(S)*-**9** on a permethylated β-cyclodextrin GC-column did not reveal any signs of racemization. This result implies that not only the esterification to *(S)*-**9** but also the preceding diazotation reaction to *(S)*-**8** are not accompanied by significant racemization.[18] Second, *(2R)*-1,2-propanediol was stirred overnight at 60 °C in dioxane in the presence of KOH. After workup, the diol was analyzed on a permethylated β-cyclodextrin GC-column processed at 100 °C. Comparison with the *(S)*-enantiomer indicated that no (partial) racemization had taken place, proving that the routinely applied reaction conditions for Williamson syntheses on chiral secondary alcohols do not lead to racemization. Finally, the 2-oxo crown ethers *(S)*-**5** and *(S)*-**6** could be analyzed on the—in this research very useful—permethylated β-cyclodextrin capillary GC-column. Assuming that the found contaminations correspond to the *(R)*-enantiomers, expected enantiomeric excesses of ca. 97% and ca. 99.5% were measured for *(S)*-**5** and *(S)*-**6**, respectively.[19]

Preparation of Polymers 1−3. The desired polymers **1**−**3** could be obtained either by ring-opening polymerization of oxo-crown ethers *(SS)*-**4**, *(S)*-**5**, and *(S)*-**6** or by polycondensation of the ω-hydroxycarboxylic acids *(S)*-**32**, *(S)*-**21**, and *(S)*-**22**. All ring opening polymerizations were executed employing stannous 2-ethylhexanoate ($SnOct_2$) as catalyst, applying catalyst/monomer molar ratios ($SnOct_2$/M) higher than 1/60, and using a polymerization temperature of 130 °C. A previous study has shown that these conditions can conveniently be applied to the $SnOct_2$-catalyzed ring-opening polymerization of 2-oxo-12-crown-4.[12a] The polycondensations were performed both with and without the use of a Lewis acid catalyst ($SnOct_2$ was also in these cases chosen as the catalyst). Additionally, lipase-catalyzed polycondensation of monomers *(S)*-**21** and *(S)*-**22** was attempted; in both cases no polymeric material could be obtained (in contrast, successful lipase-mediated polycondensations have been reported for ω-hydroxyalkanoic acids[20]). The results of all successful polymerizations, including some reference polymerizations of the nonsubstituted monomers 2-oxo-21-crown-7 and 2-oxo-12-crown-4,[21] have been summarized in Table 1.

All polymerizations were carried out without solvent. The ring-opening polymerizations were conducted under an argon atmosphere, whereas the polycondensations were performed at reduced pressures (to remove the H_2O that is liberated during reaction). The application of the $SnOct_2$ catalyst in the polycondensations could markedly reduce the polycondensation temperature—compare entries C and D, H and I, and M and N. After reaction times of typically hours—only the ring-opening reactions of the larger 2-oxo-21-crown-7 monomers require reaction times of days (entries B and L)—the reaction mixtures were dissolved in minimum amounts of CH_2Cl_2 and precipitated in hexane or hexane/Et_2O solvent mixtures to yield the polymers as yellowish, sticky oils. The number average molecular weights (M_n)

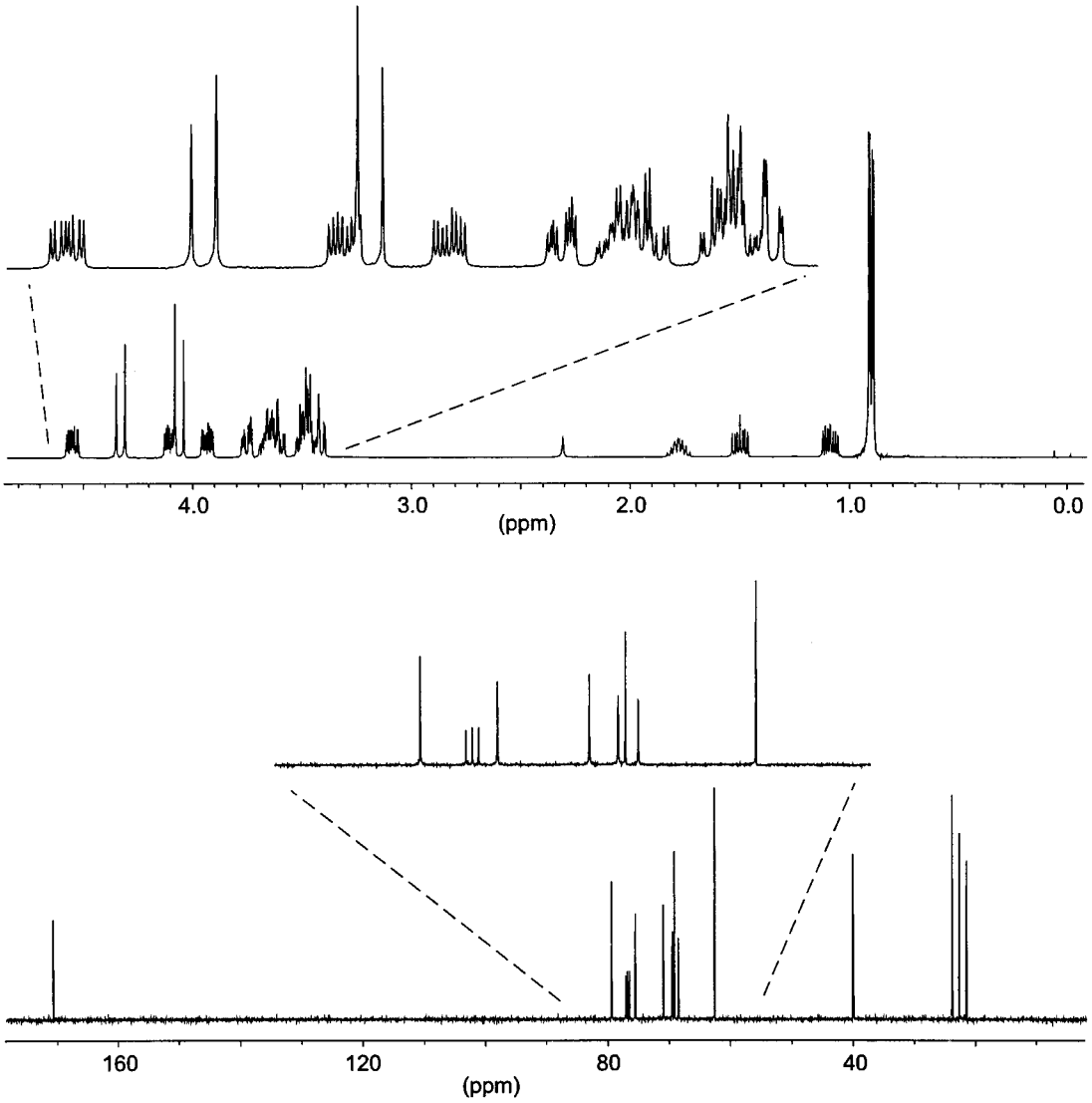


Figure 3. ^{1}H NMR spectrum (upper graph with expansion) and ^{13}C NMR spectrum (lower graph with expansion) of 2-oxo-5-*(S)*-isobutyl-12-crown-4 (*(S)*-**5**) in $CDCl_3$.

Table 1. Polymerization Conditions

polymer	procedure, polymerization type	$SnOct_2$/M molar ratio	T (°C)	t (h)	M_n[a] (kg/mol)	D[a]
1	A, polycondensation	1/37	140	7	3.5*	2.1*
	B, ring opening	1/20	130	100	5.2	1.7
2	C, polycondensation	0	200	5	4.3/3.0*	2.0/2.0*
	D, polycondensation	1/30	135	5	4.0*	1.7*
	E, ring opening	1/56	130	20	2.6	2.2
	F, ring opening	1/23	130	24	7.4/4.6*	2.0/1.9*
	G, ring opening	1/16	130	20	7.9	2.4
3	H, polycondensation	0	200	8	3.2	2.0
	I, polycondensation	1/45	140	4	3.5*	2.4*
	J, ring opening	1/23	130	20	4.1	2.0
	K, ring opening	1/24	130	20	14.9/9.1*	2.1/2.1*
poly(2-oxo-21-crown-7)	L - ring opening	1/25	130	144	11.4	1.9
poly(2-oxo-12-crown-4)	M - polycondensation	0	215	8	11.0/7.7*	2.2/2.1*
	N - polycondensation	1/38	130	6	2.6*	1.8*
	O - ring opening	1/50	130	20	9.0	1.9

[a] The number average molecular weights (M_n's) and molecular weight distributions (D's) were obtained by SEC using polystyrene (PS) standards, except in those entries indicated with an asterix (*) in which polyethylene oxide (PEO) standards were used. The measured M_n is approximately 30−40% lower when PEO standards are used.

of the polymers varied between 2 and 15 kg/mol, and the measured dispersities (D) were always approximately 2. Unfortunately, the molecular weight of the polymers could not be tuned with the applied reaction conditions, probably due to the small scale on which the polymerizations were performed. On the basis of the results shown in Table 1, there is no pronounced preference for a certain polymerization procedure, although the noncatalyzed polycondensations require harsher reaction conditions and the ring-opening polymerizations require longer reaction times, especially in the cases of the larger 2-oxo-21-crown-7 monomers.

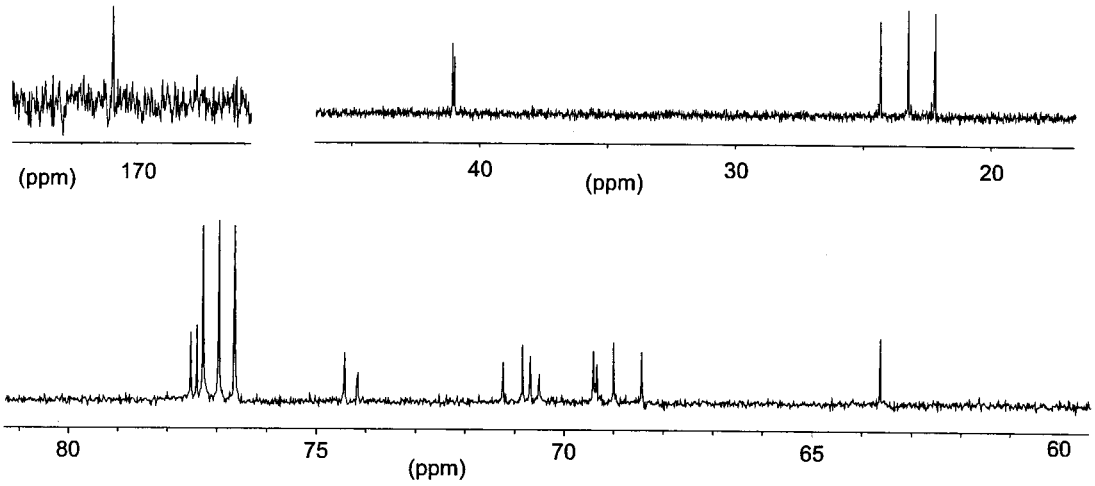


Figure 4. ^{13}C NMR spectrum of polymer **1** in $CDCl_3$: upper left, the carbonyl signal (one carbon atom); upper right, the carbon signals of the isobutyl side groups ($4 \times 2 = 8$ carbon atoms); bottom: all carbon signals associated with the backbone ethylene oxide fragments (13 carbon atoms).

NMR Analysis of Polymers 1−3. The ^1H NMR and ^{13}C NMR spectra of the polymers **1**−**3** suggest that polymerization is not accompanied by significant degradation or side reactions. As an example the ^{13}C NMR spectrum of polymer **1** is shown in Figure 4: the spectrum accounts for no more than the expected 22 carbons. Molecular weights of the polymers could not be determined by ^1H NMR, since the end group protons could not be detected separately.

ES-MS Characterization of Polymers 1−3. Electrospray mass spectrometry (ES-MS) facilitates the characterization of molecules with masses up to 500 000 Da, explaining its importance in the study of proteins.[22] ES-MS is a mild technique, since it allows pre-existing ions in solution to be transferred to the gas phase with minimum fragmentation. Depending on the mode of measurement, the mass/charge ratio (m/z) of anions or cations can be measured. Polymers **1**−**3** can ideally be characterized in the negative ion mode, since **1**−**3** are macromolecules with a carboxylic end group. Under neutral or basic conditions, the carboxylic acid end groups will be deprotonated and one macromolecule will bear exactly one negative charge. Consequently, m/z values equal to the molecular weight of the polymeric species *minus* one will be measured. Polymers **1**−**3** were analyzed in aqueous mixtures of MeCN, to which CH_3COONH_4 crystals were added to assure deprotonation of the carboxylic end group.

In Figure 5, four ES-MS spectra of polymers **1**, **2**, **3**, and poly(2-oxo-12-crown-4) are shown. It can be seen that only discrete molecular weights are measured. The molecular weights of the repeating units of **1**, **2**, **3**, and poly(2-oxo-12-crown-4) are 434, 246, 204, and 190 Da, respectively, and therefore, the measured discrete values correspond to the deprotonated oligomeric species of the investigated polymers. Thus, these ES-MS results prove the integrity of the synthetic procedure that has been used to obtain polymers **1**−**3**. In particular, it shows that during polymerization no significant degradation, leading to the disruption of the regular repeat of the polar and apolar segments in the polymers, has occurred.

It must be noted that the ES-MS data show a molecular weight distribution different from the distribution determined by SEC (see Table 1). This difference is caused by a lower sensitivity of higher molecular weight species for detection in the negative ion ES-MS mode.[23] Apparently, ES-MS does not characterize the bulk of the material under investigation. This assumption also explains the detection of TFA adducts in the ES-MS characterization of polymer **2** (see Figure 5B); possibly these adducts are sensitive toward detection.

Polymers 1−3: A New Class of Amphiphilic Polymers. The behavior of polymers **1**−**3** was studied in H_2O to investigate the amphiphilic properties of these polymers. In H_2O, transparent solutions were only observed at low concentrations (<0.1, <0.3, and <1.0 mg/mL, for polymers **1**, **2**, and **3**, respectively). At higher concentrations of 1−10 mg/mL, stable turbid solutions were obtained.[24] Turbid solutions of polymer **1** and **3** in H_2O were investigated with dynamic light scattering (DLS). Aggregates with diameters of ca. 300 and ca. 200 nm were found for solutions of **1** and **3**, respectively.[25] The observed behavior of **1**−**3** is reminiscent of the behavior of amphiphilic polymers in H_2O, so further examination of these systems was conducted.

A fluorescent-probe study is a simple and effective way to measure the critical aggregation concentration (cac) of amphiphilic compounds or polymers.[26,27] The basis for such a study is the dependence of the fluorescent behavior of an apolar probe on the polarity of the environment of this probe. A widely applied probe is pyrene. For the polymers discussed here, it was found that the maximum in the excitation spectrum of pyrene shifted from 335 to 338 nm upon association. Thus, I_{338}/I_{335} is a measure for the presence of polymer aggregates. These measures for aggregation—i.e. I_{338}/I_{335} and I_3/I_1 in the exitation and emission spectra of pyrene, respectively—are comparable to previously reported measures for aggregation.[27] In the emission spectrum, such a measure could be found in the I_3/I_1-ratio: the ratio between the third and first vibronic bands in the emission spectrum (I_λ = intensity of fluorescence at wavelength λ).

Aqueous solutions with increasing concentrations of polymers **1**−**3**, poly(2-oxo-12-crown-4), and PEO were investigated with the fluorescent-probe technique using pyrene as the probe.[28] Additionally, the turbidity of the solutions was measured by determination of the absorbance of these solutions at 700 nm. All measurements were conducted at 20 °C, and the results of the experiments are summarized in Figure 6. A clear picture emerges: three regimes can be observed. In the first regime—at low concentrations of polymer—no aggre-

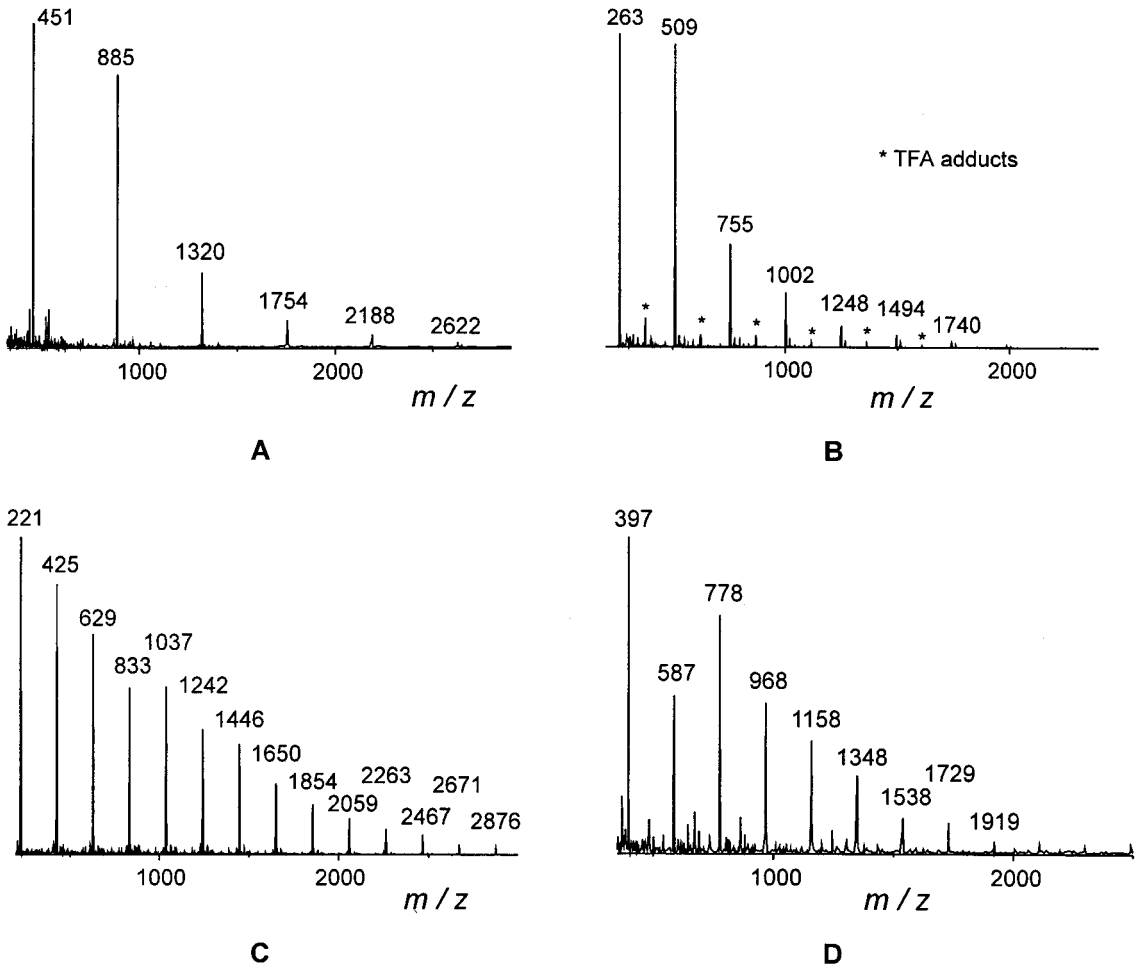


Figure 5. ES-MS spectra of polymers **1**, **2**, and **3** and poly(2-oxo-12-crown-4) in parts A, B, C, and D, respectively.[40] The observed molecular weight/charge ratios *(m/z)* of the oligomeric species obey the formula $m/z = n \cdot \mathrm{FW(monomeric\ unit)} + \mathrm{FW(water)} - 1$, with FW(monomeric unit) = 434, 246, 204, and 190 for **1**, **2**, **3**, and poly(2-oxo-12-crown-4), respectively. The *y*-axes have arbitrary units.

gates of polymer chains exist. This situation changes at the cac of the polymer (the onset of the change in I_{338}/I_{335} or I_3/I_1 ratio). Aggregate formation begins, but the aqueous solutions remain transparent (regime 2). Further increase of the polymer concentration gives the formation of stable turbid solutions, which is the characteristic of regime 3 (in the case of poly(2-oxo-12-crown-4) and PEO this third regime is not observed, because the aqueous solutions remain transparent).

A different cac value was determined for every polymer under investigation (see Table 2, in which all measured cac values have been collected). For polymers **1**−**3**, poly(2-oxo-12-crown-4), and PEO, cac's of 2.1×10^{-3}, 1.3×10^{-2}, 0.15, 0.62, and 1.5 mg/mL were measured. The introduction of hydrophobic segments in a hydrophilic sequence gives polymers with an increased impetus for aggregate formation, as is evident from comparison of the cac values of polymers **1**−**3** with those found for poly(2-oxo-12-crown-4) and PEO. Focusing on the calculated average cac's, it is clear that the cac can be tailored by (i) the frequency at which the alkyl side groups of the polymers repeat and (ii) the size of these alkyl side groups. A slight reduction in the frequency of the repeat of isobutyl groups—compare polymers **1** and **2**—results in a sixfold increase of the cac. Replacement of the isobutyl side groups by methyl side groups—compare polymers **2** and **3**—gives an approximate tenfold increase in the cac. Finally, the influence of molecular weight on the cac value was not noticeable. Comparison of the cac's of two batches of polymer **2** with molecular weights of 4.3 and 2.6 kg/mol, respectively (entries C and E in Table 1), does not show a significant difference in the cac's (see Table 2).

It must be noted that the accuracy of the measured cac values is low: the distribution in the collected data is high, so an error in the average cac of 50% is realistic. However, such an error is inherent to the determination of cac's.[26] Moreover, the size of this error is not dramatic, because the differences between the cac's of the investigated polymers are an order of a magnitude larger.

It is interesting to compare the new amphiphilic polymers **1**−**3** to the amphiphilic PEO/PPO/PEO block copolymers, which are—chemically and in terms of molecular weight—similar. Alexandridis[29] has determined the cac's of these block copolymers, varying the block sizes of both the PPO and the PEO block (see Table 3). It can be seen that the cac values of PEO/PPO/PEO copolymers are considerably higher than the cac values obtained for **1**−**3**. A parallel between both amphiphilic systems is the possibility to adjust the cac value by changing the constitution of the polymer. However, in the case of polymers **1**−**3**, CAC-values can be obtained over a much wider concentration range (compare the fifth columns of Tables 2 and 3).

Another characteristic of PEO/PPO/PEO block copolymers is the formation of cubic, hexagonal, and lamellar (meso)phases in *p*-xylene/H_2O solvent mixtures. Such phases are observed when the solvents are present in only a few weight percent.[30] In a preliminary study,

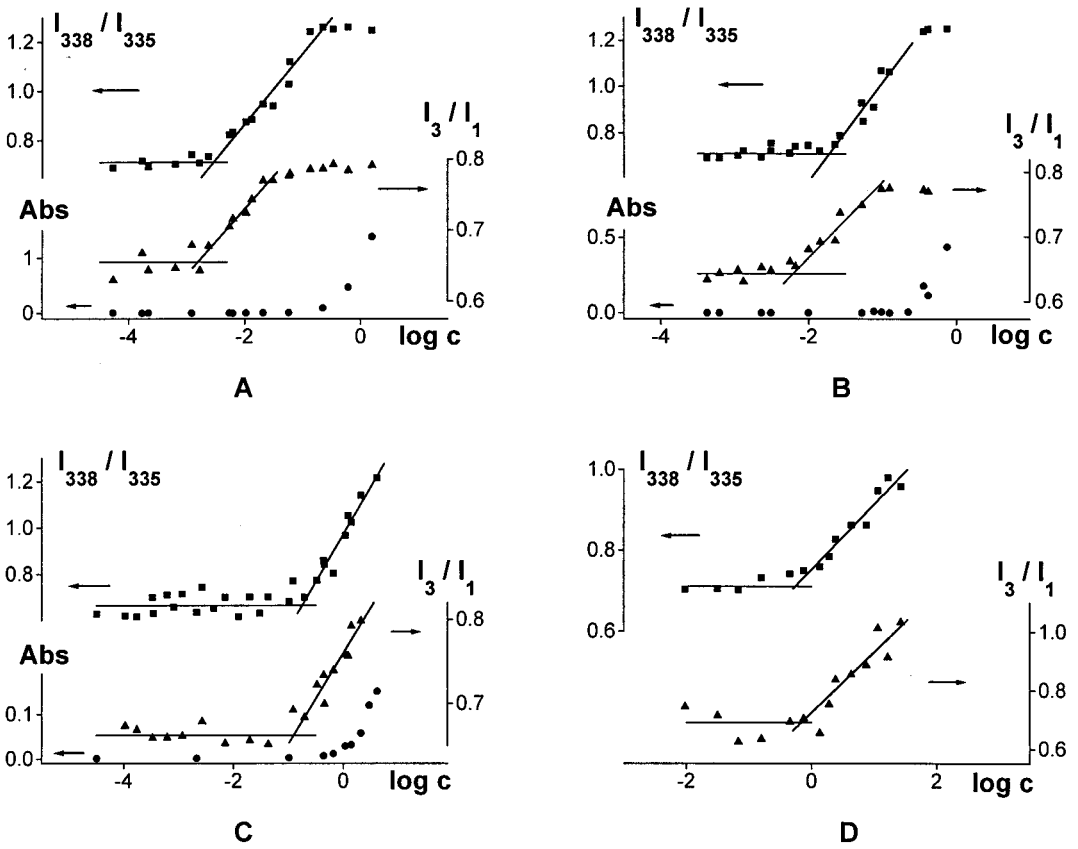


Figure 6. Fluorescent-probe studies on aqueous solutions of polymers **1**−**3** and poly(2-oxo-12-crown-4). Shown are excitation data (λ_{em} = 390 nm; I_{338}/I_{335}; ■), emission data (λ_{ex} = 338 nm; I_3/I_1; ▲), and UV data ($A_{700\ nm}$; ●) at different concentrations of polymer in H_2O at 20 °C. The concentration (log *c*) is calculated in milligrams per milliliter. The results concerning polymers **1**−**3** and poly(2-oxo-12-crown-4) are shown in parts A, B, C, and D, respectively. A pyrene concentration of 4.1×10^{-7} M has been used for all data points.

Table 2. Critical Aggregation Concentrations (cac's) of Polymers in H_2O at 20 °C[a]

polymer (entry)[b]	M_n[c] (kg/mol)	log cac_{em} (mg/mL)	log cac_{ex} (mg/mL)	CAC_{av}[d] (mg/mL)	onset turbidity (mg/mL)
1 (A)	3.5*	−2.81	−2.53	2.1×10^{-3}	≈0.1
2 (C)[e]	4.3	−2.00	−1.67	1.5×10^{-2}	≈0.3
(E)	2.6	−2.21	−1.72	1.1×10^{-2}	
3 (I)	3.5*	−0.91	−0.75	1.5×10^{-1}	≈1.0
poly(2-oxo-12-crown-4) (N)	2.6*	−0.16	−0.26	0.62	*h*
PEO[f]	8.0	*g*	0.18	1.5	*h*

[a] Determined by fluorescence measurements using pyrene as probe: cac's have been derived from both emission and excitation spectra of pyrene at various concentrations of polymer. Applied pyrene concentration: 4.1×10^{-7} M. Emission spectra: λ_{ex} = 338 nm. Excitation spectra: λ_{em} = 390 nm. Absorption measurements at 700 nm produced the turbidity-data. [b] The entry character defines which polymer batch has been used and it refers to the entries in Table 1. [c] Measured by SEC: PS standards or PEO standards (*) were used. [d] The average cac was calculated by taking the average of log cac_{em} and log cac_{ex} (these are the cac's derived from the emission and the excitation spectra, respectively). [e] Here, a pyrene concentration of 1.2×10^{-7} M and a λ_{ex} of 339 nm were applied. [f] Purchased from Sigma Chemicals (Article No. P-2139). [g] No clear onset was visible. [h] The solutions did not become turbid at higher concentrations.

Table 3. Critical Aggregation Concentration Values of PEO/PPO/PEO block copolymers in H_2O at 20 °C[a]

polymer[b]	M_n (kg/mol)	PO units in PPO-block	EO units in PEO blocks	cac (mg/mL)
P103	5.0	60	2 × 17	7
P104	5.9	61	2 × 27	20
P105	6.5	56	2 × 37	22
P123	5.8	69	2 × 19	1.8
F127	12.6	65	2 × 100	40

[a] As determined by Alexandridis.[29] 1,6-Diphenyl-1,3,5-hexatriene was used as the fluorescent probe. [b] The investigated polymers were Pluronic copolymers purchased from BASF.

polymer **2** was investigated at 20 °C under a microscope with crossed polarizers.[31] Varying amounts of *p*-xylene and/or H_2O were added to polymer **2**, but no birefringence was observed. Consequently, the formation of hexagonal or lamellar phases could be excluded for this system.

Finally, the viscosities of aqueous solutions of polymers **1**−**3** were measured at concentrations both higher and lower than the determined cac.[32] This was done to investigate whether aggregation would give a significant increase in viscosity, as for example observed for the so-called associative thickeners.[27b,33] In the case of polymers **1**−**3**, no such increase was measurable. In fact, for all solutions, the observed viscosities were equal to the viscosity of H_2O.

Conclusion

PEO-based polymers that possess a regular repeat of hydrophobically modified ethylene oxide units exhibit amphiphilic behavior in aqueous solutions. The first representatives of such PEO-based synthetic am-

phiphilic polymers—polymers **1**—**3**—have been introduced in this paper. With a fluorescent-probe study, the cac's (critical aggregation concentrations) of **1**—**3** at 20 °C have been determined. Aggregation of the polymers was strongly promoted by the presence of the hydrophobic units, as was evident from a comparison of the cac's of **1**—**3** with the cac's of PEO and poly(2-oxo-12-crown-4): polymers lacking hydrophobic units. Additionally, the cac was dependent on both the size of the hydrophobic unit and the frequency at which such a unit was repeated in the polymer. It appears that tailoring of the cac of these amphiphilic polymers over a wide concentration range is possible (cac's of ca. 0.002 mg/mL and ca. 0.15 mg/mL were measured for **1** and **3**, respectively).

The next paper will discuss the possibilities of the introduced polymers for the formation of well-defined higher structures. Optical rotatory dispersion (ORD) spectroscopy and transmission electron microscopy will be used to examine the ordering and assembly processes of polymers **1**—**3** in aqueous solutions.

Experimental Section

General. Compounds *(S)*-**8**, *(S)*-**9**, *(S)*-**11**, *(S)*-**12**, *(S)*-**13**, *(S)*-**14**, **34**, and **37** have been described previously.[9,10,11,14] For **34** and **37** new reaction routes have been used. Commercially available compounds employed in the syntheses were used without further purification, except tosyl chloride, which was recrystallized from hexane. The applied KOH had a purity > 85%. The used solvents were dried if necessary: Et_2O was dried on $CaCl_2$ and stored on sodium wire. Dioxane was distilled from $LiAlH_4$, CH_2Cl_2 from CaH_2 or P_2O_5, pyridine from KOH, and PhMe from CaH_2; all were stored on activated molsieves (heated at 90 °C under vacuum for 24 h). THF was immediately used after distillation from Na.

Thin-layer chromatography (TLC) was performed on Merck 5735 Kieselgel 60F glass plates or on neutral type (type E) alumina 60 F254 (type E) aluminum plates. The TLC plates were air-dried, scrutinized under a UV lamp, and, if necessary, either sprayed with a *p*-anisaldehyde solution and developed using a heat gun or sprayed with an aqueous KI/I_2 solution.[34] Kieselgel 60 (0.040—0.063 mm mesh, Merck 9385), Merck flash silica gel 60 (particle size 0.040—0.063 mm), or Merck alumina (63—200 mm) were used to perform column chromatography. A 25 m WCOT fused silica capillary column coated with a 0.25 mm thick CP Chirasil DEX CB (permethylated β-cyclodextrin) stationary phase was used to determine the optical purities of several compounds (the column was installed in a PE Auto System GC). Helium was used as carrier gas. The determination of the optical purity of L-leucine was achieved on a chiral Daicel CR (+) HPLC column (the measurement was carried out at DSM Research Holland).

GC-MS was performed on a HP 5790 GC with an OV-1 column (a fused silica capillary column coated with a 0.33 mm thick poly(dimethylsiloxane) film) and an HP 5970A MSD. Size exclusion chromatography (SEC) analyses were conducted at 40 °C with stabilized THF as solvent and an eluent rate of 1 mL/min. The SEC apparatus was equipped with two Shodex KF 80-M (linear) columns and a differential refractive index detector (Waters 410). Molecular weights were determined with polystyrene or polyethylene oxide calibration standards.

Elemental analyses were carried out on a PE 240. Differential scanning calometry measurements were performed on a PE DSC-2, applying two heating and cooling runs.

^{1}H-NMR spectra were taken on an AM-400 Bruker spectrometer at 400 MHz or on a Gemini Varian 300 MHz spectrometer. TMS was used as internal standard. ^{13}C-NMR spectra were taken on the Bruker spectrometer at 101 MHz with the solvent as standard. In some cases, inverse-gated decoupled ^{13}C NMR was conducted to be able to integrate the carbon peaks. UV/vis measurements were performed on a PE UV/Vis Spectrophotometer Lambda 2B. Optical rotations were measured on a JASCO DIP 370 digital polarimeter. CD spectra were taken on a JASCO J-600 spectropolarimeter. Infrared spectra were taken on a Perkin Elmer 1605 FTIR-spectrometer with wavenumbers between 4400 and 450 cm^{-1}. Dynamic light scattering (DLS) measurements were conducted on a Malvern 4700C with a PCS-100 spectrometer (λ = 488 nm) at an angle of 90° (spherical shaped aggregates were assumed).

ES-MS Measurements. Electrospray MS (ES-MS) was performed on a Perkin Elmer/Sciex API-300 MS/MS (PE-Sciex, Foster City). The compounds or polymers were dissolved in polar solvents or polar solvent mixtures (such as typically MeCN/H_2O). Measurements were performed on solutions with concentrations of approximately 0.2 mg of polymer/mL. A few crystals of CH_3COONH_4 were added to the aqueous solutions of the polymers to create a sufficiently basic medium for carboxylate formation. Care was taken that the solutions remained clear and did not phase separate.

Fluorescent-Probe Measurements. Fluorescence measurements were performed on a PE LS 50B luminescence spectrometer. The aqueous polymeric solutions that have been subjected to measurements were prepared as follows. Stock solutions of the polymers in Me_2CO were weighed in precision flasks of 10 mL and to every flask 150 mL of a 2.7×10^{-5} M pyrene stock solution in Me_2CO was added. The Me_2CO was removed *in vacuo* at room temperature. Finally, 10 mL of H_2O was added to each flask and the aqueous solutions were stirred for 15 h at 4 °C. The flasks were wrapped in aluminum foil to prevent the pyrene from degrading. In the luminescence spectrometer, the cuvettes were kept at 20 °C with a thermostat bath. For the excitation measurements, slits of 6 and 4 nm and, for the emission measurements, slits of 4.25 and 3 nm were used for the emission and excitation slits, respectively.

Poly(8*(S)*,17*(S)*-diisobutyl-2-oxo-21-crown-7) (1). Procedure A: ω-Hydroxycarboxylic acid *(SS)*-**32** (210 mg, 0.46 mmol) and 25 μL of a 0.50 M $SnOct_2$ solution in PhMe were transferred to a Schlenk flask (1/37 mol equiv of $SnOct_2$). The mixture was stirred and was allowed to polymerize for 7 h at 140 °C and 0.04 mbar. Precipitation in hexane gave a viscous, yellowish, clear oil. Yield: 160 mg (80%). SEC: M_n = 3.5 kg/mol, D = 2.1 (PEO standards). DSC: T_g = −44 °C (ΔC_p = 0.87 J·g^{-1}·K^{-1}).

Procedure B: 2-Oxo-21-crown-7 (*(SS)*-**4**) (23 mg, 0.053 mmol) and 17 μL of a 0.158 M $SnOct_2$ solution in PhMe were transferred to a Schlenk flask (1/20 catalyst/monomer ratio). The PhMe was evaporated at 30 mbar and 40 °C. Thereafter, the mixture was stirred at 130 °C under an argon atmosphere for 4 days. The sticky product was dissolved in a minimum amount of CH_2Cl_2 and precipitated in 5 mL of ice-cold hexane. A yellowish, clear, oily polymer (8 mg, 35%) was obtained. SEC: M_n = 5.2 kg/mol, D = 1.7 (PS standards).

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.3 (2H, m, CH_2CH_2CO), 4.2 (2H, s, $COCH_2O$), 3.9—3.5 (20H, m, further backbone protons), 1.75 (2H, m, $CH_2CH(CH_3)_2$), 1.45 (2H, m, $CH'H''CH(CH_3)_2$), 1.25 (2H, m, $CH'H''CH(CH_3)_2$), 0.90 (12H, m, 4 × CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5 (CO), 77.6, 77.5, 74.5, 74.2, 71.3, 70.9, 70.8, 70.6, 69.4(2), 69.1, 68.5, 63.7 (backbone carbons), 41.2, 41.1, 24.5(2), 23.3(2), 22.4, 22.3 (isobutyl carbons).

Poly(5*(S)*-isobutyl-2-oxo-12-crown-4) (2). Procedure C: ω-Hydroxycarboxylic acid *(S)*-**21** (0.8 g, 3.03 mmol) was transferred to a flask and was rotated for 5 h in a Kugelrohr apparatus. The temperature was gradually raised to 200 °C, and a vacuum of 0.1 mbar was maintained. The obtained oil was precipitated from CH_2Cl_2 in hexane to give a viscous, yellowish, clear oil. Yield: 330 mg (45%). SEC: M_n = 4.3 kg/mol, D = 2.0 (PS standards); M_n = 3.0 kg/mol, D = 2.0 (PEO standards).

Procedure D: ω-Hydroxycarboxylic acid *(S)*-**21** (500 mg, 1.89 mmol) was transferred to a flask, and 125 μL of a 0.50 M $SnOct_2$ solution in PhMe was added (1/30 mol equiv of $SnOct_2$). The flask was rotated for 5 h in a Kugelrohr apparatus. The temperature was kept at 135 °C, and a vacuum of 0.6 mbar was maintained. The obtained oil was precipitated from CH_2Cl_2 in hexane to afford a viscous, yellowish, clear oil. Yield:

340 mg (73%). SEC: M_n = 4.0 kg/mol, D = 1.7 (PEO standards). DSC: T_g = −34 °C (ΔC_p = 1.12 J·g^{-1}·K^{-1}).

Procedure E: Oxo-crown ether *(S)*-**5** (310 mg, 1.26 mmol) and 45 μL of a 0.50 M $SnOct_2$ solution in PhMe were mixed in a Schlenk flask (56/1 monomer/catalyst ratio), after which the PhMe was removed by evaporation *in vacuo*. The mixture was stirred, and polymerization was carried out for 20 h at 130 °C under an atmosphere of argon. Dissolution in a minimum amount of CH_2Cl_2 and precipitation in hexane/Et_2O (4/1) gave a yellowish, viscous oil. Yield: 210 mg (68%). SEC: M_n = 2.6 kg/mol, D = 2.2 (PS standards).

Procedure F: Oxo-crown ether *(S)*-**5** (220 mg, 0.89 mmol) and 77 μL of a 0.50 M $SnOct_2$ solution in PhMe were mixed in a Schlenk flask (23/1 monomer/catalyst ratio), after which the PhMe was removed by evaporation *in vacuo*. The mixture was stirred, and polymerization was carried out for 24 h at 130 °C under an atmosphere of argon. Dissolution in a minimum amount of CH_2Cl_2 and precipitation in hexane/Et_2O (4/1) gave a yellowish, viscous oil. Yield: 125 mg (57%). SEC: M_n = 7.4 kg/mol, D = 2.0 (PS standards); M_n = 4.6 kg/mol, D = 1.9 (PEO standards).

Procedure G: Oxo-crown ether *(S)*-**5** (100 mg, 0.41 mmol) and 50 μL of a 0.50 M $SnOct_2$ solution in CH_2Cl_2 were mixed in a Schlenk flask (16/1 monomer/catalyst ratio), after which the CH_2Cl_2 was removed by evaporation *in vacuo*. The mixture was stirred, and polymerization was carried out for 20 h at 130 °C under an atmosphere of argon. Dissolution in a minimum amount of CH_2Cl_2 and precipitation in hexane gave a yellowish, viscous oil. Yield: 80 mg (80%). SEC: M_n = 7.9 kg/mol, D = 2.4 (PS standards).

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.3 (4H, m, CH_2CH_2-CO and $COCH_2O$), 3.7−3.4 (9H, m, further backbone protons), 1.75 (1H, m, $CH_2CH(CH_3)_2$), 1.4 (1H, ddd, ^2J = 14.0 Hz, ^3J = 8.5 Hz, ^3J = 5.9 Hz, $CH'H''CH(CH_3)_2$), 1.25 (1H, ddd, ^2J = 14.0 Hz, ^3J = 8.1 Hz, ^3J = 4.8 Hz, $CH'H''CH(CH_3)_2$), 0.9 (6H, dd, ^3J = 7.0 and 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8 (CO), 78.0, 75.0, 70.6, 70.4, 69.0, 67.7, 63.6 (backbone carbons), 40.9, 24.3, 23.2, 22.3 (isobutyl carbons).

Poly(5*(S)*-methyl-2-oxo-12-crown-4) (3). Procedure H: ω-Hydroxycarboxylic acid *(S)*-**22** (300 mg 1.36 mmol) was transferred to a flask, that was rotated for 8 h in a Kogelrohr apparatus. The temperature was gradually increased to 200 °C, and a vacuum of 10 mmHg was maintained. The obtained oil was precipitated from CH_2Cl_2 in Et_2O/hexane (1/1) to give a viscous oil. The oil was dissolved in MeCN, and active carbon was added. Filtration and evaporation gave 250 mg (90%) of a clear, viscous oil. SEC: M_n = 3.2 kg/mol, D = 2.0 (PS standards).

Procedure I: ω-Hydroxycarboxylic acid *(S)*-**22** (500 mg, 2.25 mmol) and 100 μL of a 0.50 M $SnOct_2$ solution in PhMe were transferred to a Schlenk flask (1/45 mol equiv of $SnOct_2$). The mixture was stirred and was allowed to polymerize for 4 h at 140 °C and 0.03 mbar. Precipitation from CH_2Cl_2 in Et_2O/hexane (5/1) gave a viscous, yellowish, clear oil. Yield: 330 mg (72%). SEC: M_n = 3.5 kg/mol, D = 2.4 (PEO standards). DSC: T_g = −39 °C (ΔC_p = 0.85 J·g^{-1}·K^{-1}).

Procedure J: Oxo-crown ether *(S)*-**6** (150 mg, 0.74 mmol) and 65 μL of a 0.50 M $SnOct_2$ solution in CH_2Cl_2 were mixed in a Schlenk flask (23/1 monomer/catalyst ratio). Then, the CH_2Cl_2 was removed by evaporation *in vacuo*. The mixture was stirred, and polymerization was carried out for 20 h at 130 °C under an atmosphere of argon. Dissolution in a minimum amount of CH_2Cl_2 and precipitation in hexane gave a yellowish, viscous, clear oil. Yield: 140 mg (93%). SEC: M_n = 4.1 kg/mol, D = 2.0 (PS standards).

Procedure K: Oxo-crown ether *(S)*-**6** (240 mg, 1.18 mmol) and 100 μL of a 0.50 M $SnOct_2$ solution in PhMe were mixed in a Schlenk flask (24/1 monomer/catalyst ratio). Thereafter, the PhMe was removed by evaporation *in vacuo*. The mixture was stirred, and polymerization was carried out for 20 h at 130 °C under an atmosphere of argon. Dissolution in a minimum amount of CH_2Cl_2 and precipitation in hexane/Et_2O (4/1) gave a yellowish, viscous, clear oil. Yield: 210 mg (88%). SEC: M_n = 9.1 kg/mol, D = 2.1 (PEO standards); M_n = 14.9 kg/mol, D = 2.1 (PS standards). ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.3 (2H, m, CH_2CH_2CO), 4.25 (2H, s, $COCH_2O$), 3.8−3.45 (9H, m, further backbone protons), 1.2 (3H, d, ^3J = 6.6 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5 (CO), 75.1(2), 70.3, 70.1, 68.6, 66.6, 63.3 (backbone carbons), 16.6 (methyl carbon).

Poly(2-oxo-21-crown-7). Procedure L: This procedure comprises the ring-opening polymerization of 2-oxo-21-crown-7 at 130 °C during 144 h using $SnOct_2$ as catalyst (25/1 monomer/catalyst ratio). SEC: M_n = 11.4 kg/mol, D = 1.9 (PS standards). See ref 12a for details on the monomer and the polymerization procedure.

Poly(2-oxo-12-crown-4). See ref 12a for details on the monomers and on the polymerization procedures.

Procedure M: [2-(2-{2-Hydroxyethoxy}-ethoxy)-ethoxy]acetic acid (2.7 g, 13.0 mmol) was transferred to a flask, that was rotated in a Kugelrohr apparatus for 8 h. The temperature was gradually raised to 215 °C, while a vacuum of 2 mbar was maintained. The residue was dissolved in a minimum amount of CH_2Cl_2 and precipitated in Et_2O. The polymer was obtained as a brown, sticky oil. Yield: 1.95 g (66%). SEC: M_n = 7.7 kg/mol, D = 2.1 (PEO standards); M_n = 11.0 kg/mol, D = 2.2 (PS standards). DSC: T_g = −42 °C (ΔC_p = 0.96 J·g^{-1}·K^{-1}).

Procedure N: [2-(2-{2-Hydroxyethoxy}ethoxy)ethoxy]acetic acid (380 g, 1.83 mmol) and 95 μL of a 0.50 M $SnOct_2$ solution in PhMe were transferred to a flask (38/1 monomer/catalyst ratio). The flask was rotated at 130 °C for 6 h. A vacuum of 10 mbar was maintained. The residue was dissolved in a minimum amount of CH_2Cl_2 and precipitated in Et_2O. The polymer was obtained as a yellowish, sticky oil. Yield: 280 mg (80%). SEC: M_n = 2.6 kg/mol, D = 1.8 (PEO standards).

Procedure O: This procedure comprises the ring-opening polymerization of 2-oxo-12-crown-4 at 130 °C during 20 h using $SnOct_2$ as catalyst (50/1 monomer/catalyst ratio). SEC: M_n = 9.0 kg/mol, D = 1.9 (PS standards).

(8*S*,17*S*)-2-Oxo-8,17-diisobutyl-21-crown-7 (*(SS)*-4). α,ω-Dihydroxycarboxylic acid *(SS)*-**32** (47 mg, 0.10 mmol) was dissolved in 3.5 mL of dry and oxygen-free xylene. PPh_3 (40 mg, 0.15 mmol) and dithiodipyridine (33 mg, 0.15 mmol) were added, and the clear solution was stirred for 3 days (after 1 day the solution had become slightly turbid). The solvent was evaporated, and the residue was treated with hexane. Collection of the hexane phases and evaporation of the solvent gave a crude product that was purified by silica column chromatography. Subsequent elution with PhMe/EtOAc (4/1) and EtOAc gave 23 mg (50%) of the title compound as an oil. ^{1}H NMR ($CDCl_3$): δ = 4.4 (2H, m), 4.25 (2H, dd, ^2J = 16.9 Hz, OCH_2COO), 4.0−3.4 (20H, m), 1.75 (2H, m), 1.45 (2H, m), 1.15 (2H, m), 0.9 (12H, d, ^3J = 6.6 Hz (4×)). ^{13}C NMR ($CDCl_3$): δ = 170.9 (CO), 40.9, 40.7, 24.5 (2×), 23.3, 23.2, 22.4, 22.2 (isobutyl carbons), 77.7, 77.5, 75.7, 75.4, 71.2, 71.0 (2×), 70.5, 69.7, 69.6, 68.9, 68.4, and 63.8 (carbons of the ring). GC-MS (FW = 434): m/z 434 and 435.

(5*S*)-5-Isobutyl-1,4,7,10-tetraoxacyclododecan-2-one *(S)*-5). Two procedures were followed. **Method A** (improved method): Compound *(S)*-**21** (0.357 g, 1.35 mmol) was transferred to a small flask together with $CoCl_2$·$6H_2O$ (45 mg, 0.19 mmol). The blue solution was distilled in a Kugelrohr apparatus (225−240 °C; 2−3 mmHg). During 5 h, 0.285 g of a clear oil was collected. TLC analysis showed that the oil consisted mainly of the title product and contained also a small amount of dimer. Alumina column chromatography with hexane/EtOAc (3/1) gave 240 mg (72%) of a clear oil (R_f = 0.37). **Method B:** Compound *(S)*-**21** (0.346 g, 1.31 mmol) and triethylamine (1.37 mL, 9.85 mmol) were dissolved in 100 mL of dry MeCN. This solution was added to a refluxing MeCN solution (125 mL) containing 2-chloro-6-methylpyridinium iodide (1.25 g, 4.89 mmol). The addition was performed with a mechanical syringe over a period of 9 h at a constant addition rate. During the reaction the color of the solution changed from yellow to brown. After the addition was complete, the solution was heated at reflux for another 0.5 h. Evaporation of the MeCN and coevaporation with MeCN to remove triethylamine yielded a brown sticky semisolid to which EtOAc was added. Collection of the liquid and evaporation of the solvent gave 0.75 g of crude product. Alumina column chromatography with hexane/EtOAc (3/1) yielded 162 mg of

monomer that was slightly contaminated; further elution with EtOAc gave 24 mg of dimer (7%). Distillation (100 °C, 0.03 mbar) of the impure monomer in a Kugelrohr apparatus gave a clear yellowish oil. Yield: 110 mg (34%).

Title Compound: ^{1}H NMR ($CDCl_3$): $\delta = 4.6$ (1H, ddd, $^2J = 12.0$ Hz, $^3J = 7.0$ Hz, $^3J = 2.8$ Hz), 4.35 and 4.10 (2H, dd, $^2J = 16.2$ Hz, OCH_2COO), 4.1 (1H, ddd, $^2J = 12.0$ Hz, $^3J = 5.9$ Hz, $^3J = 3.0$ Hz), 3.95 (1H, ddd, $^2J = 12.0$ Hz, $^3J = 5.9$ Hz, $^3J = 2.6$ Hz), 3.75 (1H, ddd, $^2J = 12.0$ Hz, $^3J = 3.9$ Hz, $^3J = 2.2$), 3.7−3.6 (3H, m), 3.6−3.4 (4H, m), 1.8 (1H, m, $CHCH_2CH(CH_3)_2$), 1.5 (1H, ddd, $^2J = 14.1$ Hz, $^3J = 8.8$ Hz, $^3J = 5.5$ Hz, $CHCH'H''CH(CH_3)_2$), 1.15 (1H, ddd, $^2J = 13.7$ Hz, $^3J = 8.8$ Hz, $^3J = 4.5$ Hz, $CHCH'H''CH(CH_3)_2$), 0.9 (6H, dd, $^3J = 7.0$ and 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): $\delta = 170.9$ (CO), 40.3, 24.1, 22.9, and 21.7 (isobutyl carbons), 79.6, 75.7, 71.1, 69.7, 69.3, 68.7, and 62.8 (carbons of the ring). FTIR (cm^{-1}): $\nu = 2950$, 1760, 1465, 1355, 1290, 1190, 1140, 1050, 915, 870, 825. TLC: R_f (hexane/EtOAc (3/1), alumina) = 0.37, R_f (EtOAc, alumina) = 0.80, R_f (EtOAc, silica) = 0.45, R_f (hexane/EtOAc (3/1), silica) = 0.12. $[\alpha]^{28}_D$ ($c = 3.7$; $CHCl_3$) = +7.8°. GC-MS (FW = 246.3): 246.3 and 247.3. HRMS: calcd, 246.1467; found, 246.1436. GC analysis on a permethylated β-cyclodextrin column showed an ee of 97.6%, a value comparable to the ee of the starting compound *(S)*-leucine (*S*-**7**). CD spectroscopy showed a positive Cotton effect at 220 nm ($g_{220} = 0.005$, MeCN, 20 °C).[35]

Dimer: ^{1}H NMR ($CDCl_3$): $\delta = 4.4$ (4H, dd, $^2J = 16.6$ Hz, OCH_2COO), 4.3 (4H, m), 3.75−3.45 (18H, m), 1.85 (2H, m, $CHCH_2CH(CH_3)_2$), 1.5 (2H, ddd, $^2J = 14.1$ Hz, $^3J = 8.8$ Hz, $^3J = 5.5$ Hz, $CH'H''CH(CH_3)_2$), 1.15 (2H, ddd, $^2J = 12.9$ Hz, $^3J = 8.5$ Hz, $^3J = 4.4$ Hz, $CH'H''CH(CH_3)_2$), 0.9 (12H, dd, $^3J = 6.6$ and 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): $\delta = 171.1$ (CO), 40.9, 24.4, 23.2, and 22.2 (isobutyl carbons), 77.7, 76.2, 70.6, 70.5, 69.1, 68.1, and 63.7 (carbons of the ring). TLC: R_f (hexane/EtOAc (3/1), alumina) = 0.20, R_f (EtOAc, alumina) = 0.80, R_f (EtOAc, silica) = 0.45, R_f (hexane/EtOAc (3/1), silica) = 0.05. GC-MS (FW = 492.6) 492.5 and 493.50.

(5*S*)-5-Methyl-1,4,7,10-tetraoxacyclododecan-2-one (*(S)*-6). Compound *(S)*-**22** (0.526 g, 2.37 mmol) was transferred to a small flask together with $CoCl_2 \cdot 6H_2O$ (51 mg, 0.21 mmol). The blue solution was distilled (225−250 °C, 8 mmHg) in a Kugelrohr apparatus. During 5 h 0.40 g of a clear oil that mainly consisted of the title product was collected. Alumina column chromatography with hexane/EtOAc (3/1) was performed, giving 270 mg (56%) of a pure clear oil ($R_f = 0.30$). ^{1}H NMR ($CDCl_3$): $\delta = 4.45$ (1H, ddd, $^2J = 11.8$ Hz, $^3J = 7.0$ Hz, $^3J = 2.6$ Hz), 4.25 and 4.05 (2H, dd, $^2J = 16.1$ Hz, OCH_2COO), 4.1 (1H, ddd, $^2J = 12.0$ Hz, $^3J = 5.9$ Hz, $^3J = 2.9$ Hz), 3.85 (1H, ddd, $^2J = 11.8$ Hz, $^3J = 5.9$ Hz, $^3J = 2.6$ Hz), 3.8−3.3 (8H, m), 1.05 (3H, d, $^2J = 6.6$ Hz, $OCH(CH_3)CH_2O$). ^{13}C NMR ($CDCl_3$): $\delta = 171.0$ (CO), 16.9 (methyl carbon), 77.0, 76.1, 71.2, 69.8, 68.7 (2), and 63.2 (carbons of the ring). TLC: R_f (hexane/EtOAc (3/1), alumina) = 0.30, R_f (hexane/EtOAc (1/1), alumina) = 0.45. $[\alpha]^{28}_D$ ($c = 4.0$; $CHCl_3$) = +36.9°. FTIR data (cm^{-1}): $\nu = 2950$, 1760, 1465, 1355, 1290, 1190, 1140, 1050, 915, 870, 825. GC-MS (FW = 204.2): 204.25. HRMS: calcd, 204.0998; found, 204.0959. GC analysis on a permethylated β-cyclodextrin column showed an ee of 99.4%, a value comparable to the ee of the starting compound ethyl *(S)*-lactate (*S*-**10**). CD spectroscopy showed a positive Cotton effect at 220 nm (MeCN, 20 °C).

(2*S*)-1-[2-(2-(Benzyloxy)ethoxy)ethoxy]-4-methylpentan-2-ol (*(S)*-15). Compound *(S)*-**13** (5.04 g, 25.0 mmol) and tosylate **37** (11.1 g, 31.7 mmol) were dissolved in 100 mL of dry THF. Finely ground KOH (85%, 6.1 g, 92.6 mmol) was added, and the mixture was heated at reflux for 2 days. A white precipitate (TsOK) was formed. TLC analysis showed the formation of product (R_f (EtOAc, silica) = 0.63). After evaporation of the solvent, the remaining mixture was suspended in H_2O. Extraction with CH_2Cl_2, drying of the collected organic layers with $MgSO_4$, and evaporation of the solvent *in vacuo* yielded 15.2 g of a yellow oil. The oil was dissolved in 75 mL of MeOH, and after the methanolic solution was cooled in an ice bath for 15 min, $TsOH \cdot H_2O$ (0.15 g, 0.9 mmol) was added. TLC analysis (silica) showed that removal of the THP group was complete after 90 min of stirring at room temperature (title product, R_f (EtOAc, silica) = 0.50; DHP, $R_f = 0.60$). $NaHCO_3$ was added to quench the reaction. MeOH was evaporated, and coevaporation with MeOH was performed to remove all DHP. Et_2O/H_2O extraction, drying of the collected Et_2O layers with $MgSO_4$, and evaporation of the solvent yielded 8.4 g of crude oily product. TLC analysis (silica) with EtOAc showed that the oil contained besides the title compound also (2*S*)-4-methyl-1,2-pentanediol ($R_f = 0.22$), tosylate **37** ($R_f = 0.65$), monobenzyl-diethylene glycol ($R_f = 0.30$), and dibenzylated tetraethylene glycol ($R_f = 0.50$). The last contamination could be discriminated from the title compound by TLC analysis (silica) using CH_2Cl_2 as an eluent (R_f values of 0.05−0.10 and 0 for contamination and product, respectively). Distillation in a Kugelrohr apparatus gave three fractions: I (20−165 °C, 0.07 mmHg), low-boiling side products containing monobenzylated diethylene glycol; II (200−210 °C, 0.05 mmHg), title product plus some contamination; III, residue, mainly dibenzylated tetraethylene glycol. Fraction II (5.7 g) was purified by silica column chromatography. Sequential elution with hexane/EtOAc (1/1)—to remove contaminants—and hexane/EtOAc (1/2)—to collect the product—gave 5.0 g (68%) of a clear oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.55 (2H, s, OCH_2Ph), 3.85 (1H, m, $HOCHRCH_2O$), 3.7−3.55 (8H, m), 3.45 (1H, dd, $^2J = 9.9$ Hz, $^3J = 2.9$ Hz, $HOCHRCH'H''O$), 3.25 (1H, dd, $^2J = 9.9$ Hz, $^3J = 8.0$ Hz, $HOCHRCH'H''O$), 2.75 (1H, bs, O*H*), 1.8 (1H, m, $CHCH_2CH(CH_3)_2$), 1.4 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 9.0$ Hz, $^3J = 5.5$ Hz, $CH'H''CH(CH_3)_2$), 1.1 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 8.8$ Hz, $^3J = 4.4$ Hz, $CH'H''CH(CH_3)_2$), 0.95 (6H, dd, $^3J = 6.6$ Hz, $^3J = 7.0$ Hz, $CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): $\delta = 138.1$, 128.2, 127.6, and 127.5 (Ph), 41.8, 24.3, 23.3, and 22.0 (isobutyl carbons), 73.1 (OCH_2Ph), 76.2, 70.5 (3×), 69.3, 68.2. FTIR (cm^{-1}): $\nu = 3464$ (br), 2953, 2867, 1455, 1352, 1105, 739, 698. TLC: R_f (hexane/EtOAc (1/1), silica) = 0.27. $[\alpha]^{26}_D$ ($c = 6.08$; $CHCl_3$) = +1.6°; $[\alpha]^{27}_D$ ($c = 0.98$; $CHCl_3$) = +2.4°; $[\alpha]^{20}_D$ ($\rho = 1$ g/mL; neat) = −4.3°. Elemental analysis for $C_{17}H_{28}O_4$ (FW = 296). Calcd: C, 68.92; H, 9.46. Found: C, 68.56; H, 9.54.

(2*S*)-1-[2-(2-(Benzyloxy)ethoxy)ethoxy]propan-2-ol (*(S)*-16). Compound *(S)*-**14** (5.15 g, 32.2 mmol) and 2-(2-(benzyloxy)ethoxy)ethyl tosylate (**37**) (13.4 g, 38.3 mmol) were dissolved in 120 mL of dry THF. Finely ground KOH (85%, 7.2 g, 109.3 mmol) was added, and the mixture was heated with reflux for 3 days. A white suspension was formed. Silica TLC analysis showed that product was present (R_f (EtOAc, silica) = 0.55). After evaporation of the THF *in vacuo*, the remaining semisolid was suspended in H_2O. Extraction with CH_2Cl_2, drying of the collected organic layers with $MgSO_4$, and evaporation of the solvent yielded 12.9 g of crude oil. The product was dissolved in 90 mL of MeOH, and after cooling of the solution in ice for 15 min, $TsOH \cdot H_2O$ (0.15 g, 0.9 mmol) was added. Stirring for 4 h at room temperature gave complete removal of the THP group (the title product had an R_f value of 0.30, while DHP gave an R_f value of 0.60 (EtOAc, silica)). $NaHCO_3$ was added to quench the reaction. MeOH was evaporated, and coevaporation with MeOH was performed to make sure that all dihydropyran (DHP) was also removed. H_2O/Et_2O extraction, drying of the collected Et_2O layers with $MgSO_4$, and evaporation of the solvent yielded 9.3 g of crude product. The oil contained besides the title compound also (2*S*)-1,2-propanediol (R_f (EtOAc, silica) = 0.08), tosylate **37** (R_f (EtOAc, silica) = 0.65), monobenzylated diethylene glycol (R_f (EtOAc, silica) = 0.30 and R_f (MeCN, silica) = 0.64), and dibenzylated tetraethylene glycol (R_f (EtOAc, silica) = 0.50). Monobenzylated diethylene glycol could be discriminated from the title compound using silica TLC analysis with MeCN as an eluent (title compound $R_f = 0.67$). Distillation in a Kugelrohr apparatus gave three fractions I−III: I (20−150 °C, 0.05 mmHg), low-boiling side products, containing monobenzylated diethylene glycol; II (150−170 °C, 0.05 mmHg), title product plus some contamination; III, residue, mainly dibenzylated tetraethylene glycol. Fraction II (6.5 g) was purified by silica column chromatography. Sequential elution with hexane/EtOAc (1/2)—to remove contaminants (R_f values of 0.33 and 0.60)—and with hexane/EtOAc (1/3)—to collect the product—afforded the pure title compound as a clear oil. The absence of monobenzylated diethylene glycol was confirmed

by TLC analysis (MeCN, silica). Yield: 6.0 g (73%). ^{1}H NMR ($CDCl_3$): δ = 7.4−7.2 (5H, m, Ph), 4.55 (2H, s, OC*H*$_2$ Ph), 3.95 (1H, m, HOC*H*(CH_3)CH_2O), 3.7−3.55 (8H, m), 3.45 (1H, dd, ^2J = 10.0 Hz, ^3J = 3.0 Hz, HOCHRC*H*′H″O), 3.25 (1H, dd, ^2J = 10.0 Hz, ^3J = 8.1 Hz, HOCHRCH′*H*″O), 3.0 (1H, bs, O*H*), 1.1 (3H, d, ^3J = 6.6 Hz, HOCH(C*H*$_3$)CH_2). ^{13}C NMR ($CDCl_3$): δ = 138.0, 128.2, 127.6, and 127.5 (Ph), 18.4 (*C*H_3), 73.1 (O*C*H_2-Ph), 76.9, 70.4 (3×), 69.2, 66.1. TLC: R_f (EtOAc, silica) = 0.30, R_f (hexane/EtOAc (1/2), silica) = 0.20, R_f (MeCN, silica) = 0.67. $[\alpha]^{26}_D$ (c = 6.63, $CHCl_3$) = +13.3°. FTIR (cm^{-1}): ν = 3448 (br), 2867, 1453, 1352, 1290, 1253, 1102, 740, 699.

***tert*-Butyl (1*S*)-{1-[[2-(2-(Benzyloxy)ethoxy)ethoxy]-methyl]-3-methylbutoxy}acetate ((*S*)-17).** Compound *(S)*-**15** (8.5 g, 28.7 mmol) was flushed with PhMe and dissolved in 40 mL of *tert*-BuOH, after which *tert*-BuOK (3.58 g, 32.0 mmol) was added. Short heating to 40 °C gave a clear, yellow solution. After stirring for 1 h, *tert*-butyl bromoacetate (10.7 g, 54.9 mmol) was added dropwise. A precipitate (KBr) immediately formed. The reaction mixture was stirred for another hour before the solvent was evaporated *in vacuo*. CH_2Cl_2/H_2O extraction, drying of the collected organic layers with K_2CO_3, and evaporation of the solvent yielded 15.1 g of crude product. Silica column chromatography with hexane/EtOAc (3/1) afforded a pure clear oil (R_f = 0.23) in a yield of 8.5 g (72%). ^{1}H NMR ($CDCl_3$): δ = 7.4−7.2 (5H, m, Ph), 4.55 (2H, s, OC*H*$_2$Ph), 4.10 (2H, dd, ^2J = 16.2 Hz, OC*H*′*H*″COOtBu), 3.7−3.6 (9H, m), 3.5 (2H, m), 1.8 (1H, m, CH_2C*H*(CH_3)$_2$), 1.4 (9H, s, C(C*H*$_3$)$_3$), 1.4 (1H, ddd, CHC*H*′H″CH(CH_3)$_2$), 1.25 (1H, ddd, ^2J = 13.6 Hz, ^3J = 8.2 Hz, ^3J = 5.2 Hz, CHCH′*H*″-CH-(CH_3)$_2$), 0.95 (6H, dd, ^3J = 6.6 Hz, ^3J = 6.6 Hz, $CHCH_2$CH-(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ = 169.8 (CO), 138.0, 128.1, 127.5, 127.3 (Ph), 80.8 (*C*(CH_3)$_3$), 40.8, 24.1, 23.0, and 22.2 (isobutyl carbons), 27.9 (C(C*H*$_3$)$_3$), 73.0 (O*C*H_2Ph), 77.6, 74.8, 70.5, 70.4 (2×), 69.2, and 68.0. FTIR (cm^{-1}): ν = 2928, 2868, 1750, 1454, 1368, 1300, 1224, 1126, 737, 698. $[\alpha]^{25}_D$ (c = 2.11; $CHCl_3$) = −12.7°.

***tert*-Butyl (1*S*)-2-[2-(2-(Benzyloxy)ethoxy)ethoxy]-1-methylethoxyacetate ((*S*)-18).** Compound *(S)*-**16** (5.75 g, 22.6 mmol) was flushed with PhMe and dissolved in 35 mL of *tert*-BuOH. *tert*-BuOK (2.78 g, 24.8 mmol) was added, which resulted in a clear, yellow solution. After the solution was stirred for 1 h, *tert*-butyl bromoacetate (8.81 g, 45.2 mmol) was added dropwise. A suspension immediately formed. The reaction mixture was stirred for another hour before the solvent was evaporated. Et_2O/H_2O extraction, drying of the collected organic layers with K_2CO_3, and evaporation of the solvent yielded 11.3 g of crude product. Silica column chromatography with hexane/EtOAc (2/1) afforded the pure product (R_f = 0.22) as a clear oil in a yield of 6.5 g (78%). ^{1}H NMR ($CDCl_3$): δ = 7.4−7.2 (5H, m, Ph), 4.55 (2H, s, OC*H*$_2$Ph), 4.1 (2H, dd, ^2J = 16.6 Hz, OC*H*′*H*″COOtBu), 3.75−3.6 (9H, m), 3.55 (1H, dd, ^2J = 10.3 Hz, ^3J = 6.2 Hz, CH(CH_3)C*H*′H″O), 3.45 (1H, dd, ^2J = 10.3 Hz, ^3J = 4.4 Hz, CH(CH_3)CH′*H*″O), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.1 (3H, d, ^3J = 6.2 Hz, CH(C*H*$_3$)). ^{13}C NMR ($CDCl_3$): δ = 170.1 (CO), 138.2, 128.2, 127.6, 127.5 (Ph), 17.1 (*C*H_3), 81.2 (*C*(CH_3)$_3$), 73.1 (O*C*H_2Ph), 28.0 (C(*C*H_3)$_3$), 75.5, 75.2, 70.7, 70.6, 70.5, 69.3, 67.4. FTIR (cm^{-1}): ν = 2975, 2867, 1748, 1454, 1368, 1298, 1250, 1226, 1127, 1028, 940, 850, 737, 699. $[\alpha]^{26}_D$ (c = 1.85; $CHCl_3$) = −6.6°.

(1*S*)-1-[[2-(2-(Benzyloxy)ethoxy)ethoxy]methyl]-3-methylbutoxyacetic Acid ((*S*)-19). Compound *(S)*-**17** (8.5 g, 20.7 mmol) was coevaporated twice with $CHCl_3$ before TFA (23.6 g, 207 mmol) was added dropwise. After 5 h of stirring the reaction was complete and the solvent was evaporated. The product was dissolved in 50 mL of dry Et_2O. The ethereal solution was added dropwise to 100 mL of H_2O, keeping the pH of the aqueous layer at 11−12 by simultaneously adding a 0.4 M NaOH solution. Thereafter, extraction of the aqueous layer with Et_2O was performed to remove possible contamination. Remarkably, the volume ratio of both layers was much bigger than expected. While an aqueous/ethereal layer volume ratio of 3/1 was expected, a ratio of 20/1 was observed. It appeared that the product acted as a surfactant, strongly increasing the solubility of Et_2O in H_2O. The aqueous layer was adjusted to a pH of 2 with an aqueous HCl solution, after which it was extracted with CH_2Cl_2. The collected organic layers were dried ($MgSO_4$) and concentrated to give a clear oil. Yield: 7.1 g (97%). ^{1}H NMR ($CDCl_3$): δ = 7.4−7.2 (5H, m, Ph), 4.55 (2H, s, OC*H*$_2$Ph), 4.3 (1H, d, ^2J = 17.1 Hz, OC*H*′H″COOH), 4.05 (1H, d, ^2J = 17.1 Hz, OCH′*H*″COOH), 3.75−3.45 (11H, m), 1.8 (1H, m, CH_2C*H*(CH_3)$_2$), 1.4 (1H, ddd, ^2J = 13.9 Hz, ^3J = 7.3 Hz, ^3J = 6.2 Hz, CHC*H*′H″CH(CH_3)$_2$), 1.25 (1H, ddd, ^2J = 13.9 Hz, ^3J = 7.7 Hz, ^3J = 5.9 Hz, CHCH′*H*″CH(CH_3)$_2$), 0.95 (6H, dd, ^3J = 6.7 Hz, ^3J = 6.7 Hz, CH_2CH(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ = 172.4 (CO), 137.9, 128.3, 127.7, and 127.6 (Ph), 40.6, 24.3, 23.0, and 22.5 (isobutyl carbons), 73.1 (OCH_2Ph), 79.8, 74.2, 70.7, 70.5, 70.1, 69.3, and 68.4. FTIR (cm^{-1}): ν = 3100, 3063, 3030, 2950, 1763, 1453, 1352, 1247, 1202, 1120, 882, 739, 699. TLC: R_f (EtOAc, silica) = 0−0.10. $[\alpha]^{26}_D$ (c = 2.22; $CHCl_3$) = +17.5°. ES-MS: m/z 353.1 $[M - H^+]^-$.

(1*S*)-{2-[2-(2-(Benzyloxy)ethoxy)ethoxy]-1-methylethoxy}acetic Acid, ((*S*)-20). Compound *(S)*-**18** (6.5 g, 17.7 mmol) was coevaporated twice with $CHCl_3$ before TFA (20.1 g, 176 mmol) was added dropwise. After 3 h of stirring the reaction was complete and the solvent was evaporated. The product was dissolved in 25 mL of dry Et_2O. The ethereal solution was added dropwise to 100 mL of H_2O, keeping the pH of the aqueous layer at 11 by simultaneously adding a 0.4 M NaOH solution. Thereafter, extraction of the aqueous layer with Et_2O was performed to remove possible contamination. The aqueous layer was adjusted to a pH of 2 with an aqueous HCl solution, and the aqueous layer was extracted with CH_2Cl_2. The collected organic layers were dried ($MgSO_4$) and concentrated to give a clear yellowish oil. Yield: 5.1 g (93%). ^{1}H NMR ($CDCl_3$): δ = 7.4−7.2 (5H, m, Ph), 4.55 (2H, s, OC*H*$_2$-Ph), 4.25 (1H, d, ^3J = 16.9 Hz, C*H*′H″COOH), 4.05 (1H, d, ^3J = 16.9 Hz, CH′*H*″COOH), 3.65 (9H, m), 3.5 (2H, m), 1.15 (3H, d, ^3J = 6.3 Hz, CH(C*H*$_3$)). ^{13}C NMR ($CDCl_3$): δ = 172.6 (CO), 137.9, 128.2, 127.6, and 127.4 (Ph), 16.2 (*C*H_3), 73.0 (O*C*H_2-Ph), 76.8, 74.8, 70.5, 70.4, 70.1, 69.2, 67.1. FTIR (cm^{-1}): ν = 3100, 3063, 3030, 2870, 1761, 1453, 1352, 1248, 1204, 1116, 1028, 915, 883, 823, 742, 699. TLC: R_f (EtOAc, silica) = 0−0.10. $[\alpha]^{24}_D$ (c = 2.37; $CHCl_3$) = + 24.3°. ES-MS: m/z 311.0 $[M - H^+]^-$.

(1*S*)-1-[[2-(2-Hydroxyethoxy)ethoxy]methyl]-3-methylbutoxyacetic Acid, ((*S*)-21). Pd/C (10%, 0.10 g) was added to a solution of compound *(S)*-**19** (2.5 g, 7.1 mmol) in 30 mL of dioxane and 0.75 mL of H_2O. Hydrogenation under 50 psi H_2 overpressure during 3 h gave a complete debenzylation. The suspension was filtered, and the remaining solution was coevaporated with MeCN to remove traces of H_2O. A colorless clear oil was collected. Yield: 1.85 g (100%). ^{1}H NMR ($CDCl_3$): δ = 7.3−6.8 (2H, bs, COO*H* and O*H*), 4.3 (1H, d, ^2J = 16.9 Hz, OC*H*′H″COOH), 4.05 (1H, d, ^2J = 16.9 Hz, OCH′*H*″COOH), 3.75−3.45 (11H, m), 1.8 (1H, m, CH_2C*H*(CH_3)$_2$), 1.45 (1H, ddd, ^2J = 14.0 Hz, ^3J = 6.6 Hz, ^3J = 6.6 Hz, CHC*H*′H″CH(CH_3)$_2$), 1.25 (1H, ddd, ^2J = 14.0 Hz, ^3J = 7.7 Hz, ^3J = 5.9 Hz, CHCH′*H*″CH(CH_3)$_2$), 0.95 (6H, dd, ^3J = 6.7 Hz, ^3J = 6.6 Hz, CH_2CH(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ = 172.2 (CO), 40.5, 24.4, 22.9, and 22.5 (isobutyl carbons), 79.5, 74.0, 72.4, 70.6, 69.8, 68.2, 61.5. FTIR (cm^{-1}): ν = 3350 (br), 2953, 1744, 1462, 1359, 1217, 1123, 888, 756, 670. $[\alpha]^{23}_D$ (c = 2.32; MeCN) = +9.1°.

(1*S*)-2-[2-(2-Hydroxyethoxy)ethoxy]-1-methylethoxyacetic Acid ((*S*)-22). Compound *(S)*-**20** (2.5 g, 8.0 mmol) was dissolved in 30 mL of dioxane and 0.75 mL of H_2O. Pd/C (10%, 0.10 g) was added. Hydrogenation under 50 psi H_2 overpressure during 3 h gave a complete debenzylation. The suspension was filtered and the remaining solution was coevaporated with MeCN to remove traces of H_2O. A clear oil was collected. Yield: 1.75 g (100%). ^{1}H NMR ($CDCl_3$): δ = 7.3−6.8 (2H, bs, COO*H* and O*H*), 4.3 (1H, d, ^2J = 17.1 Hz, OC*H*′H″COOH), 4.05 (1H, d, ^2J = 17.1 Hz, OCH′*H*″COOH), 3.8−3.5 (11H, m), 1.2 (3H, d, ^3J = 6.3 Hz, CH(C*H*$_3$)CH_2). ^{13}C NMR ($CDCl_3$): δ = 172.3 (CO), 16.1 (*C*H_3), 76.3, 74.8, 72.2, 70.4, 69.8, 67.0, and 61.3. FTIR (cm^{-1}): ν = 3340 (br), 2910, 1743, 1454, 1354, 1221, 1121, 920, 890. $[\alpha]^{23}_D$ (c = 2.64; MeCN) = +22.4°.

(2*S*)-1-(2-(Benzyloxy)ethoxy)-4-methylpentan-2-ol ((*S*)-23). Alcohol *(S)*-**13** (16.0 g, 79.2 mmol), tosylate **34** (29.0 g, 94.8 mmol), and KOH (85%, 17.7 g, 269 mmol) were heated at reflux in 300 mL of dry THF. After 72 h the reaction was

stopped. THF was evaporated *in vacuo*, the remaining product was suspended in H_2O, and extraction with Et_2O was carried out. The collected organic layers were dried and concentrated to give 29.5 g of crude product, which was dissolved in 200 mL of MeOH. After the solution had been allowed to cool down in an ice bath, $TsOH \cdot H_2O$ (0.3 g, 1.7 mmol) was added. The mixture was stirred at room temperature for 2 h (TLC-analysis showed that the THP group had been removed). The reaction was quenched by the addition of $NaHCO_3$. After removal of MeOH and DHP (by coevaporation with MeOH), H_2O/CH_2Cl_2 extraction was carried out to yield 25 g of crude product. TLC analysis showed that, besides the title product, also compound **34** and (2*S*)-4-methyl-1,2-pentanediol were present. Silica column chromatography was carried out (petroleum ether (40−60 °C)/EtOAc (2/1)) to remove the diol ($R_f = 0.1$) and most of the tosylate, after which distillation (125 °C, 0.01 mmHg) in a Kugelrohr apparatus gave the pure oily title compound. Yield: 15.4 g (77%). ^{1}H NMR ($CDCl_3$): $\delta = 7.3-7.1$ (5H, m, Ph), 4.5 (2H, OCH_2Ph), 3.8 (1H, m), 3.6 (4H, m), 3.45 (1H, dd, $^2J = 9.9$ Hz, $^3J = 3.0$ Hz), 3.2 (1H, dd, $^2J = 9.9$ Hz, $^3J = 8.3$ Hz), 2.7 (1H, bs), 1.75 (1H, m), 1.35 (1H, ddd, $^2J = 13.8$ Hz, $^3J = 8.8$ Hz, $^3J = 5.5$, C*H*′H″CH(CH_3)$_2$), 1.1 (1H, ddd, $^2J = 13.8$ Hz, $^3J = 8.6$ Hz, $^3J = 4.2$ Hz, CH′*H*″CH(CH_3)$_2$), 0.9 (6H, dd, $^3J = 7.0$ Hz (2×), CH_2CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): $\delta = 138.0$, 128.4, 127.8, 127.7 (Ph), 41.8, 24.4, 23.5, 22.1 (isobutyl carbons), 73.2 (*C*H_2Ph), 76.2, 70.6, 69.3, 68.4. FTIR (cm^{-1}): $\nu = 3448$ (br), 3025, 2943, 2861, 1496, 1449, 1355, 1102, 908, 732, 691. TLC: R_f (PhMe/EtOAc (10/1), silica) = 0.15; R_f (PhMe/EtOAc (30/1), silica) = 0.05; R_f (petroleum ether (40−60 °C)/EtOAc (2/1), silica) = 0.35. $[\alpha]^{20}_D$ ($\rho = 1$ g/mL; neat) = −5.7°; $[\alpha]^{20}_D$ ($c = 2.02$; $CHCl_3$) = + 1.8°.

(1*S*)-2-{1-[[2-(Benzyloxy)ethoxy]methyl]-3-methylbutoxy}ethanol ((*S*)-24). *sec*-Alcohol *(S)*-**23** (2.0 g, 7.9 mmol), tosylate **35** (5.0 g, 16.7 mmol), and KOH (85%, 1.85 g, 28.0 mmol) were heated at reflux for 48 h in 20 mL of dry THF. H_2O/Et_2O extraction was carried out after the THF had been evaporated. Drying of the collected organic layers and evaporation of the Et_2O *in vacuo* yielded 4.2 g of crude product, which was dissolved in 40 mL of MeOH. $TsOH \cdot H_2O$ (0.10 g, 0.6 mmol) was added after the methanolic solution was allowed to cool down in an ice bath. The solution was stirred for 1 h at room temperature, which sufficed to complete the THP removal. $NaHCO_3$ was added to quench the reaction. MeOH and DHP were removed by evaporation *in vacuo*, and the resulting semisolid was taken up in H_2O. Extraction with CH_2Cl_2, drying of the organic layers, and removal of the solvent yielded 2.3 g of crude product. Purification of the title compound was only possible *via* repeated column chromatography. Starting compound *(S)*-**23** (R_f (PhMe/EtOAc (3/2), silica) = 0.33; R_f (CH_2Cl_2/MeCN (10/1), silica) = 0.20) could be removed by elution with PhMe/EtOAc (3/2). Monotosylated ethylene glycol (R_f (PhMe/EtOAc (3/2), silica) = 0.30; R_f (CH_2Cl_2/MeCN, (20/1), silica) = 0.14; R_f (CH_2Cl_2/MeCN (10/1), silica) = 0.20−0.40) was difficult to remove. Silica flash column chromatography with CH_2Cl_2/MeCN (20/1) was the best purification method. Kugelrohr distillation could *not* be applied in this work-up procedure.Yield: 0.95 g (40%). ^{1}H NMR ($CDCl_3$): $\delta = 7.3-7.1$ (5H, m, Ph), 4.6 (2H, OCH_2Ph), 3.75−3.65 (9H, m), 3.5−3.4 (2H, m), 3.1 (1H, t, O*H*), 1.75 (1H, m), 1.4 (1H, ddd, $^2J = 13.8$ Hz, $^3J = 8.4$ Hz, $^3J = 5.2$ Hz, C*H*′H″CH(CH_3)$_2$), 1.2 (1H, ddd, $^2J = 13.8$ Hz, $^3J = 8.5$ Hz, $^3J = 4.8$ Hz, CH′*H*″CH(CH_3)$_2$), 0.90 (6H, dd, $^3J = 7.0$ Hz, $^3J = 6.7$ Hz, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): $\delta = 138.1$, 128.3, 127.7, and 127.6 (Ph), 73.2 (O*C*H_2Ph), 41.4, 24.4, 23.3, 22.3 (isobutyl carbons), 77.5, 74.8, 71.9, 70.6, 69.3, 62.3. FTIR (cm^{-1}): $\nu = 3448$ (br), 2955, 2861, 1496, 1454, 1355, 1099, 886, 737, 698. TLC: R_f (PhMe/EtOAc (3/2), silica) = 0.25; R_f (CH_2Cl_2/MeCN (20/1), silica) = 0.09; R_f (CH_2Cl_2/MeCN (10/1), silica) = 0.15; R_f (CH_2Cl_2/MeCN (5/1), silica) = 0.20. $[\alpha]^{26}_D$ ($c = 0.97$; $CHCl_3$) = +1.6°.

((2-{[2*(S)*-[2-((2-Methoxyethoxy)methoxy)ethoxy]-4-methylpentyl]oxy}ethoxy)methyl)benzene ((*S*)-25). Tosylate **36** (6.5 g, 21.4 mmol), compound *(S)*-**23** (4.5 g, 17.9 mmol), and KOH (85%, 4.0 g, 60.7 mmol) were heated at reflux for 5 days in 70 mL of dry THF. After 24 h, portions of compound **36** (2.7 g, 8.9 mmol) and KOH (85%, 2.0 g, 30.3 mmol) were added, because the alcohol *(S)*-**23** was still present in the reaction mixture, while most of the tosylate **36** had already reacted. After 72 h and after 4 days, additional portions of tosylate **36** were added (2.7 g and 0.8 g, respectively). Finally, the mixture was worked up by subsequent evaporation of the THF, H_2O/Et_2O extraction of the remaining semisolid, drying of the collected organic layers ($MgSO_4$), and evaporation of the solvent. This yielded 8.7 g of crude product, which could be purified by repeated silica column chromatography using PhMe/EtOAc (5/1) as eluent (tosylate **36** ($R_f = 0.15$) was hardly present in the crude product; other impurities were detected at R_f values > 0.25). Clear oil. Yield: 4.6 g (67%). ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.75 (OCH_2O), 4.55 (2H, OCH_2Ph), 3.85 (1H, m), 3.75−3.5 (14H, m), 3.4 (3H, s, OCH_3), 1.8 (1H, m), 1.5 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 8.5$ Hz, $^3J = 5.5$ Hz, C*H*′H″CH(CH_3)$_2$), 1.25 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 8.5$ Hz, $^3J = 4.4$ Hz, CH′*H*″CH(CH_3)$_2$), 0.9 (6H, dd, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): $\delta = 138.2$, 128.2, 127.6, and 127.5 (Ph), 95.5 (OCH_2O), 73.1 (O*C*H_2Ph), 41.1, 24.3, 23.3, 22.2 (isobutyl carbons), 58.9 (O*C*H_3), 77.5, 74.6, 71.7, 70.7, 69.4, 69.3, 67.3, 66.6. TLC: R_f (PhMe/EtOAc (5/1), silica) = 0.11.

2-{[2*(S)*-[2-((2-Methoxyethoxy)methoxy)ethoxy]-4-methylpentyl]oxy}ethanol ((*S*)-26). Compound *(S)*-**25** (0.75 g, 1.95 mmol) was dissolved in 15 mL of MeOH. Pd/C (10%, 0.10 g) was added after the solution was flushed with nitrogen. The hydrogenation was conducted at 50 psi H_2 overpressure. After 3 h of stirring, the suspension was subjected to centrifugation. Evaporation of the solvent gave 0.52 g (91%) of clear oily product. ^{1}H NMR ($CDCl_3$): $\delta = 4.75$ (OCH_2O), 3.8 (1H, m), 3.75−3.5 (14H, m), 3.4 (3H, s, OCH_3), 2.9−2.6 (1H, bs, O*H*), 1.75 (1H, m), 1.5 (1H, ddd, $^2J = 13.9$ Hz, $^3J = 8.3$ Hz, $^3J = 6.2$ Hz, C*H*′H″CH(CH_3)$_2$), 1.25 (1H, ddd, $^2J = 13.9$ Hz, $^3J = 8.1$ Hz, $^3J = 4.8$ Hz, CH′*H*″CH(CH_3)$_2$), 0.9 (6H, dd, $^3J = 6.6$ and 6.7 Hz, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): $\delta = 95.5$ (OCH_2O), 40.8, 24.4, 23.2, 22.3 (isobutyl carbons), 61.6 (*C*H_2OH), 58.9 (O*C*H_3), 77.4, 74.1, 72.5, 71.7, 69.2, 67.3, 66.7. FTIR (cm^{-1}): $\nu = 3460$ (br), 2943, 2872, 1643, 1461, 1361, 1243, 1126, 1049, 850.

2-{1*(S)*-[[2-(Benzyloxy)ethoxy]methyl]-3-methylbutoxy}-ethyl Tosylate ((*S*)-27). Compound *(S)*-**24** (2.7 g, 9.1 mmol) in 5 mL of pyridine was added dropwise to an ice-cooled solution of TsCl (1.8 g, 9.5 mmol) in 3 mL of pyridine. The solution was stirred overnight at 4 °C. The reaction mixture was poured into 10 mL of ice water, after which Et_2O and a 1 M HCl aqueous solution were added. Extraction with Et_2O was carried out at a pH value of 1−2. Drying of the collected organic layers and evaporation of the solvent yielded 4.0 g of product. Sequential elution on a silica column was carried out with CH_2Cl_2/hexane, (3/2)—to remove the excess TsCl—and with CH_2Cl_2/MeCN (5/1)—to collect the clear oily product. Yield: 3.7 g (90%). ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (2H, d), 7.4−7.2 (7H, m, Ph), 4.55 (2H, OCH_2Ph), 4.1 (2H, m), 3.85 (1H, ddd, $^2J = 11.7$ Hz, $^3J = 5.1$ Hz, $^3J = 4.0$ Hz), 3.7 (1H, ddd, $^2J = 11.7$ Hz, $^3J = 5.9$ Hz, $^3J = 4.6$ Hz), 3.6−3.4 (7H, m), 2.45 (3H, s, PhCH_3), 1.65 (1H, m), 1.35 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 8.6$ Hz, $^3J = 5.3$ Hz, C*H*′H″CH(CH_3)$_2$), 1.15 (1H, ddd, $^2J = 14.0$ Hz, $^3J = 8.8$ Hz, $^3J = 4.4$ Hz, CH′*H*″CH(CH_3)$_2$), 0.85 (6H, dd, $^3J = 6.6$ Hz, $^3J = 7.0$ Hz, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): $\delta = 138.1$, 128.2, 127.8, and 127.5 (Ph), 144.5, 132.9, 129.6, and 127.4 (Ts), 73.0 (O*C*H_2Ph), 40.8, 24.1, 23.2, 22.0 (isobutyl carbons), 21.5 (*C*H_3), 77.6, 74.7, 70.6, 69.6, 69.3, 67.6. FTIR (cm^{-1}): $\nu = 3063$, 3030, 2954, 2867, 1598, 1495, 1452, 1357, 1291, 1177, 1098, 1019, 921, 816, 774, 738, 699, 663. TLC: R_f (CH_2Cl_2/MeCN (5/1), silica) = 0.90; R_f (CH_2Cl_2/hexane (3/2), silica) = 0.10. $[\alpha]^{22}_D$ ($c = 0.99$; $CHCl_3$) = −9.6°.

(4*S*,13*S*)-1-((2-Methoxyethoxy)methoxy)-4,13-diisobutyl-17-(benzyloxy)-3,6,9,12,15−pentaoxaheptadecane *(SS)*-28). Tosylate *(S)*-**27** (2.2 g, 4.89 mmol), alcohol *(S)*-**26** (1.1 g, 3.74 mmol), and KOH (85%, 1.0 g, 15.2 mmol) were heated at reflux in 15 mL of dry THF. After 3 days the solvent was evaporated *in vacuo* and the resulting semisolid was suspended in 15 mL of H_2O. Extraction of the aqueous layer with Et_2O was followed by drying of the collected organic layers ($MgSO_4$). Evaporation of Et_2O gave 2.6 g of crude product. Silica column chromatography using PhMe/EtOAc (1/1) afforded an oily, yellowish product ($R_f = 0.18$). Yield: 1.45 g (68%). (TLC analysis revealed impurities such as the starting

compounds *(S)*-**26** ($R_f = 0.05$) and *(S)*-**27** ($R_f = 0.68$), hydrolyzed *(S)*-**27** (=*(S)*-**24**; $R_f = 0.27$), and the coupled product of *(S)*-**27** and *(S)*-**24** (R_f = 0.55); all R_f -values were measured with PhMe/EtOAc (1/1), silica.) ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.75 (2H, s, OCH_2O), 4.55 (2H, OCH_2Ph), 3.85 (2H, m), 3.7−3.45 (24H, m), 3.4 (3H, s, OCH_3), 1.7 (2H, m), 1.45 (2H, m), 1.25 (2H, m), 0.90 (12H, 4 × d, $^3J = 7.0$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 138.2$, 128.2, 127.5, and 127.4 (Ph), 73.1 (OCH_2Ph), 41.1(2×), 24.3(2×), 23.3(2×), and 22.2(2×) (isobutyl carbons), 58.7 (OCH_3), 95.4 (OCH_2O), 77.4(2×), 74.5, 74.4, 71.6, 70.8, 70.7, 70.6, 70.4, 69.3(2×), 69.2, 67.3, 66.5. FTIR (cm^{-1}): ν = 2955, 2869, 1454, 1366, 1291, 1244, 1201, 1117, 1048, 851, 737, 698. TLC: R_f (PhMe/EtOAc, (1/1), silica) = 0.18; R_f (PhMe/EtOAc (1/2), silica) = 0.27. $[\alpha]^{20}_D$ (c = 3.5; MeCN) = −12.0°.

(4*S*,13*S*)-1-Hydroxy-4,13-diisobutyl-17-(benzyloxy)-3,6,9,-12,15-pentaoxaheptadecane (*(SS)*-29). MEM-ether *(SS)*-**28** (2.0 g, 3.5 mmol) was dissolved in 10 mL of dry CH_2Cl_2, and the resulting solution was added to $ZnBr_2$ (7.3 g, 32.4 mmol). The resulting suspension was stirred for 3 days. Thereafter, the reaction was quenched with a saturated $NaHCO_3$ solution. Extraction with CH_2Cl_2, drying of the collected organic layers, and evaporation of the solvent gave a crude product, which was contaminated with MEM-ether *(SS)*-**28** (R_f (CH_2Cl_2/EtOAc (1/1), silica) = 0.25) and with α,ω-diol *(SS)*-**33** (simultaneous removal of the benzyl group had also occurred). Silica column chromatography was carried out using CH_2Cl_2/EtOAc (1/1) as eluent to yield 0.75 g (44%) of the oily product (R_f = 0.25). α,ω-Diol *(SS)*-**33** was also isolated, using MeCN/MeOH (20/1) as an eluent (R_f = 0.25). Yield: 0.1 g (7%).

Title Compound. ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.55 (2H, OCH_2Ph), 3.85 (2H, m), 3.7−3.45 (20H, m), 3.15 (1H, t, O*H*), 1.75 (2H, m), 1.45 (2H, m), 1.2 (2H, m), 0.90 (12H, 4 × d, $^3J = 7.0$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$): δ = 138.2, 128.3, 127.6, and 127.5 (Ph), 73.1 (OCH_2Ph), 41.3, 41.1, 24.4(2×), 23.3(2×), and 22.2(2×), (isobutyl carbons), 77.5, 77.4, 74.8, 74.4, 71.9, 70.8, 70.7, 70.6, 70.3, 69.4, 69.3, 62.2. FTIR (cm^{-1}): ν = 3470, 2953, 2868, 1586, 1467, 1367, 1110. TLC: R_f (CH_2Cl_2/EtOAc (1/1), silica) = 0.25; R_f (MeCN/MeOH (20/1), silica) = 0.50.

α,ω-Diol *(SS)*-33. ^{1}H NMR ($CDCl_3$): $\delta = 3.8-3.4$ (22H, m), 2.90 (2H, bs, O*H*), 1.65 (2H, m), 1.50 (2H, m), 1.2 (2H, m), 0.90 (12H, d, $^2J = 6.7$ Hz (4×)). ^{13}C NMR ($CDCl_3$): δ = 39.9, 39.7, 24.5, 24.4, 22.8 (2×), 22.6, 22.5 (isobutyl carbons), 61.0, 60.6 (*C*H_2OH, 2×), 76.5, 76.4, 72.9, 72.1, 72.0, 70.2, 69.8, 69.4, 69.2, 67.1. TLC: R_f (CH_2Cl_2/EtOAc (1/1), silica) = 0.05. FTIR (cm^{-1}): ν = 3333, 2952, 2872, 1666, 1587, 1468, 1367, 1260, 1108, 953, 891, 801.

***tert*-Butyl (7*S*,16*S*)-7,16-Diisobutyl-20-(benzyloxy)-3,6,9,-12,15,18-hexaoxaeicosanate (*(SS)*-30).** Alcohol *(SS)*-**29** (0.75 g, 1.55 mmol) was dissolved in 2.5 mL of *tert*-BuOH. *tert*-BuOK (0.18 g, 1.61 mmol) was added, and the suspension was stirred for 1 h, resulting in a clear solution. *tert*-Butyl bromoacetate (0.57 g, 2.92 mmol) was added dropwise. A precipitate immediately formed. The solvent was evaporated *in vacuo* after the suspension was stirred for 0.5 h. The remaining semisolid was suspended in an aqueous NaCl solution, which was extracted with CH_2Cl_2. Drying of the collected organic layers and evaporation of the solvent yielded 1.04 g of crude product, which was slightly contaminated with compound *(SS)*-**29** (R_f (CH_2Cl_2/EtOAc (3/1), silica) = 0.05). Silica column chromatography using CH_2Cl_2/EtOAc (3/1) gave the pure title compound as a clear oil (R_f = 0.30). Yield: 0.82 g (85%). ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.55 (2H, OCH_2Ph), 4.05 (2H, s, OCH_2COOR), 3.8 (2H, m), 3.7−3.4 (20H, m), 1.7 (2H, m), 1.5 (9H, s, C(CH_3)$_3$), 1.45 (2H, m), 1.2 (2H, m), 0.90 (12H, 4 × d, $^3J = 7.0$ Hz, $^3J = 7.0$ Hz, $^3J = 7.0$ Hz, $^3J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$): δ = 138.1, 128.1, 127.4, and 127.3 (Ph), 169.5 (CO), 73.0 (OCH_2Ph), 41.0, 40.9, 24.2(2×), 23.2(2×), and 22.1(2×) (isobutyl carbons), 81.1 (C(*C*H_3)$_3$), 77.3, 77.2, 74.3 (2×), 70.8, 70.7, 70.6, 70.5, 70.3, 69.2 (3×), 68.8. FTIR (cm^{-1}): ν = 2954, 2868, 1749, 1454, 1368, 1298, 1225, 1120, 950, 844, 736, 698. TLC: R_f (MeCN/MeOH (10/1), silica) = 0.6. $[\alpha]^{24}_D$ (c = 2.6; $CHCl_3$) = −16.1°.

(7*S*,16*S*)-7,16-Diisobutyl-20-(benzyloxy)-3,6,9,12,15,18-hexaoxaeicosanoic Acid (*(SS)*-31). Compound *(SS)*-**30** (0.82 g, 1.37 mmol) was dissolved in TFA (1.7 g). Stirring for 1 h resulted in hydrolysis of the *tert*-butyl ester. The solvent was evaporated, and the resulting oil, which still contained significant amounts of the TFA, was dissolved in 10 mL of dry Et_2O. This ethereal solution was added dropwise to H_2O, which was kept at a constant pH of 2 by simultaneous addition of a 0.4 M NaOH solution. After the addition was completed, the aqueous layer was extracted with Et_2O. Drying of the collected organic layers and evaporation of the solvent gave 0.70 g (94%) of oily product. ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.2$ (5H, m, Ph), 4.55 (2H, OCH_2Ph), 4.15 (2H, s, OCH_2COOH), 3.85 (2H, m), 3.7−3.4 (20H, m), 1.75 (2H, m), 1.45 (2H, m), 1.25 (2H, m), 0.90 (12H, 4 × d, $^3J = 7.0$ Hz, $^3J = 7.0$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$): δ = 138.0, 128.1, 127.5, and 127.4 (Ph), 172.5 (CO), 72.9 (OCH_2Ph), 40.9, 40.5, 24.3, 24.2, 23.1, 23.0, and 22.1(2×) (isobutyl carbons), 77.6, 77.3, 74.2 (2×), 71.4, 70.6, 70.5, 70.4, 70.3, 69.2, 69.1, 69.0, 68.4. FTIR (cm^{-1}): ν = 3100, 2955, 2872, 1761, 1454, 1366, 1260, 1104, 876, 799, 737, 698. TLC: R_f (MeCN/MeOH (1/1), silica) = 0.50; R_f (MeCN/MeOH (10/1), silica) = 0. $[\alpha]^{20}_D$ (c = 2.0; MeCN) = −10.3°. ES-MS: m/z 541.4 [M − H$^+$]$^-$.

(7*S*,16*S*)-7,16-Diisobutyl-20-hydroxy-3,6,9,12,15,18-hexaoxaeicosanoic Acid (*(SS)*-32). The benzyl-protected precursor *(SS)*-**31** (250 mg, 0.46 mmol) was dissolved in 9 mL of dioxane and 1 mL of H_2O. A catalytic amount of Pd/C (10%) was added to the solution, and hydrogenation at 50 psi H_2 overpressure was carried out during 3 h. Filtration and evaporation of the solvents gave the clear, oily title compound in a quantitative yield (210 mg). ^{1}H NMR ($CDCl_3$): δ = 5.3 (2H, bs, O*H* and COO*H*), 4.1 (2H, s, CH_2COOH), 3.8−3.4 (22H, m), 1.7 (2H, m), 1.4 (2H, m), 1.2 (2H, m), 0.90 (12H, 4 × d, ^3J = 6.6 Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz, $^3J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$): δ = 172.3 (CO), 40.6, 40.5, 24.6, 24.5, 23.2, 23.1, 22.5, and 22.4 (isobutyl carbons), 78.0, 77.5, 74.3, 74.0, 72.5, 71.8, 70.8, 70.6, 70.5, 69.1 (2×), 69.0, 61.6.

(4*S*,13*S*)-4,13-Diisobutyl-17-hydroxy-3,6,9,12,15-pentaoxaheptadecanol (*(SS)*-33). Details concerning α,ω-diol *(SS)*-**33** can be found in the experimental discussion of compound *(SS)*-**29**.

2-(Benzyloxy)ethyl Tosylate (34).[14] A 2 L flask was charged with 500 mL of *tert*-butanol, and *tert*-BuOK (56.2 g, 0.50 mol) was added in portions. The suspension was stirred and heated to 50 °C to dissolve all the butoxide. The resulting solution was added dropwise to a stirred solution of ethylene glycol (62.5 g, 1.01 mol). After the addition was complete, the solution was stirred for 1 h. The solvent was evaporated *in vacuo* to yield a sticky, brown substance to which 200 mL of dioxane, tetrabutylammonium chloride (2.8 g, 2 mol %), and benzyl chloride (63.3 g, 0.50 mol) were added. The suspension was mechanically stirred at 55−65 °C overnight, after which the dioxane was evaporated. The residue was dissolved in a mixture of 500 mL of H_2O and 300 mL of Et_2O. The pH of the H_2O layer was adjusted to 6 by the addition of an aqueous 1 M H_2SO_4 solution. The Et_2O layer was removed, and two extractions with 300 mL of Et_2O were conducted. The collected Et_2O layers were washed with 100 mL of H_2O, dried with $MgSO_4$, and concentrated. The brown oily residue was purified by distillation (80 °C, 0.1 mmHg) to give monobenzylated glycol. Yield: 44.7 g (59%). The spectroscopic data were in agreement with those found in the literature.[36] ^{1}H NMR ($CDCl_3$): $\delta = 7.4-7.3$ (5H, m, Ph), 4.55 (2H, s, OCH_2Ph), 3.7 (2H, t, CH_2OH), 3.55 (2H, t, CH_2-CH$_2$OH), 2.7 (1H, bs, O*H*). ^{13}C NMR ($CDCl_3$): δ = 137.7, 128.3, 127.7, 127.6 (Ph), 73.0 (OCH_2Ph), 71.3 (*C*H_2CH$_2$OH), and 61.6 (*C*H_2OH). TLC: R_f (hexane/EtOAc (1/1), silica) = 0.30; R_f (hexane/EtOAc (3/1), silica) = 0.13. Monobenzylated glycol (125.3 g, 0.82 mol), TsCl (157.8 g, 0.83 mol), and 500 mL of CH_2Cl_2 were mixed in a 2 L flask. The solution was cooled to 0 °C in a salt ice bath. Freshly powdered KOH (85%, 185.9 g, 2.82 mol) was added in small portions, while keeping the temperature of the suspension below 5 °C. The mixture was stirred overnight at 4 °C, after which it was poured into 300 mL of CH_2Cl_2 and 700 mL of ice water. The CH_2Cl_2 layer was removed, and the H_2O layer was extracted with CH_2Cl_2. The collected organic layers

were washed with 200 mL of H_2O, dried with $MgSO_4$, and concentrated to yield 255 g (97%) of pure product. ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (2H, d, Ts), 7.4−7.25 (7H, m, Ph and Ts), 4.5 (2H, s, OCH_2Ph), 4.2 (2H, t, $^3J = 4.7$ Hz, CH_2OTs), 3.7 (2H, t, $^3J = 4.7$ Hz, CH_2CH$_2$OTs), 2.45 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 144.7$, 132.8, 129.7 127.8 (Ts), 137.5, 128.3, 127.7, 127.5 (Ph), 73.0 (*C*H$_2$Ph), 21.5 (Ph*C*H$_3$), 69.2, 67.4.

2-(Tetrahydropyran-2-yloxy)ethyl Tosylate, (35). TsCl (15 g, 78.7 mmol) was added to an ice-cooled mixture of ethylene glycol (19 g, 306 mmol) and 35 mL of pyridine. The clear solution was stirred at 4 °C overnight, after which the reaction mixture was poured into 80 mL of ice water. Ether and a 1 M HCl solution were added, so that the H_2O layer became acidic (pH = 2). Separation of the two layers, further extraction of the aqueous layer with Et_2O, drying of the collected organic layers ($MgSO_4$), and evaporation of the solvent yielded crude product. Silica column chromatography with sequentially PhMe/EtOAc (10/1)—to remove the ditosylated side product (R_f (PhMe/EtOAc (10/1), silica) = 0.35)—and EtOAc—to collect the product—afforded the monotosylated glycol as a clear oil in a yield of 8.1 g (48%). The spectroscopic data of this compound were in agreement with those found in the literature.[37] ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (2H, d, Ts), 7.35 (2H, d, Ts), 4.1 (2H, t, TsOCH_2), 3.8 (2H, t, CH_2OH), 3.0 (1H, bs, O*H*), 2.45 (3H, s, PhCH_3). ^{13}C NMR ($CDCl_3$): $\delta = 145.0$, 132.3, 129.8, 127.8 (Ts), 71.6 (*C*H$_2$CH$_2$OH), 60.3 (*C*H$_2$OH), and 21.5 (Ph*C*H$_3$). TLC: R_f (PhMe/EtOAc (10/1), silica) = 0.10; R_f (EtOAc, silica) = 0.60. Monotosyl ethylene glycol (20 g, 92.6 mmol) and DHP (8.9 g, 106 mmol) were dissolved in 40 mL of dry Et_2O. A catalytic amount of TsOH·H_2O (0.10 g) was added to the ice-cooled ethereal solution, and the mixture was stirred for 24 h. Subsequently, the reaction mixture was washed with a saturated $NaHCO_3$ solution. The Et_2O layer was dried with $MgSO_4$ and concentrated to afford a clear oil. Yield: 26.9 g (97%). ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (2H, d, Ts), 7.35 (2H, d, Ts), 4.55 (1H, t, OC*H*RO of the THP group), 4.2 (2H, m, TsOCH_2), 3.85 (1H, m), 3.75 (1H, m), 3.65 (1H, m), 3.45 (1H, m), 2.45 (3H, s, CH_3Ph), 1.8−1.4 (6H, m). ^{13}C NMR ($CDCl_3$): $\delta = 144.7$, 132.3, 129.7, 127.9 (Ts), 98.6 (OCHRO of the THP group), 21.5 (Ph*C*H$_3$), 30.1, 25.2, 15.2 (OCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$CHO$_2$ of the THP group), 69.3, 64.6, and 61.8. TLC: R_f (PhMe/EtOAc (5/1), silica) = 0.35.

2-((2-Methoxyethoxy)methoxy)ethyl Tosylate (36). Monotosyl ethylene glycol (described in the experimental preparation of compound **35**) (1.0 g, 4.6 mmol) was stirred in 10 mL of ice-cooled CH_2Cl_2. Sequentially, diisopropylamine (0.9 g, 7.0 mmol) and MEMCl (0.85 g, 6.8 mmol) were added. After 15 min the ice bath was removed and the reaction mixture was stirred overnight (after 3 h the reaction was not yet complete). The mixture was diluted with 30 mL of CH_2Cl_2, before it was washed sequentially with a 1 M HCl solution (10 mL), with a saturated $NaHCO_3$ solution (5 mL), and with H_2O (5 mL). The organic layer was dried with $MgSO_4$ and was concentrated. Silica column chromatography with CH_2Cl_2/EtOAc (10/1) gave 1.2 g (85%) of product. ^{1}H NMR ($CDCl_3$): $\delta = 7.8$ (2H, d, Ts), 7.35 (2H, d, Ts), 4.7 (2H, s, OCH_2O), 4.2 (2H, t, TsOCH_2), 3.8 (2H, t), 3.65 (2H, t), 3.55 (2H, t), 3.35 (2H, t), 2.45 (3H, s, PhCH_3). ^{13}C NMR ($CDCl_3$): $\delta = 144.8$, 132.9, 129.8, 127.9 (Ts), 95.4 (O*C*H$_2$O), 21.6 (Ph*C*H$_3$), 58.9 (O*C*H$_3$), 71.6, 69.1, 66.8, 65.1.

2-(2-(Benzyloxy)ethoxy)ethyl Tosylate (37).[11] Diethylene glycol (369.5 g, 3.49 mol), benzyl chloride (67.9 g, 0.54 mol), and 300 mL of a 1:1 (w/w) NaOH/H_2O solution were transferred to a 2 L flask. The mixture was heated at reflux for 24 h. The solution, which had adopted a deep brown color, was poured into 700 mL of H_2O, and the resulting mixture was extracted with Et_2O (4 × 400 mL). The collected organic layers were dried ($MgSO_4$) and concentrated. The residue was distilled (100 °C, 0.01 mmHg) and gave a slightly yellow clear oil (benzyl diethylene glycol). Yield: 86.3 g (82%). The spectroscopic data of the compound were in agreement with those found in the literature.[15,38] ^{1}H NMR ($CDCl_3$): $\delta = 7.4$−7.3 (5H, m, Ph), 4.55 (2H, s, OCH_2Ph), 3.8−3.55 (8H, m), 2.85 (1H, t, O*H*). ^{13}C NMR ($CDCl_3$): $\delta = 137.6$, 128.3, 127.7, 127.6 (Ph), 73.1 (O*C*H$_2$Ph), 72.4, 70.3, 69.3, and 61.6 (*C*H$_2$OH). TLC: R_f (hexane/EtOAc (1/1), silica) = 0.10. The alcohol (207.6 g 1.06 mol), TsCl (202.8 g, 1.06 mol), and 500 mL of CH_2Cl_2 were mixed in a 2 L flask. The solution was cooled in a salty ice bath. Freshly powdered KOH (85%, 237.5 g, 3.60 mol) was added in small portions, while keeping the temperature of the suspension below 5 °C. The mixture was stirred overnight at 4 °C and was then poured into 300 mL of CH_2Cl_2 and 700 mL of ice water. The CH_2Cl_2 layer was separated, and the H_2O layer was extracted with 150 mL of CH_2Cl_2. The collected organic layers were washed with 200 mL of H_2O, dried with $MgSO_4$, and concentrated to yield 361 g (97%) of pure title product. The spectroscopic data of the compound were in agreement with those found in the literature.[11] ^{1}H NMR ($CDCl_3$): $\delta = 7.85$ (2H, d, Ts), 7.4−7.25 (7H, m, Ph and Ts), 4.55 (2H, s, OCH_2Ph), 4.2 (2H, t), 3.7 (2H, t), 3.6−3.5 (4H, m), 2.45 (3H, s, PhCH_3). ^{13}C NMR ($CDCl_3$): $\delta = 138.0$, 128.4, 127.7, 127.6 (Ph), 144.7, 132.9, 129.8, 127.9 (Ts), 73.2 (O*C*H$_2$-Ph), 21.6 (Ph*C*H$_3$), 70.8, 69.3, 69.2, and 68.8. TLC: R_f (EtOAc, silica) = 0.65.

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References and Notes

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(20) O'Hagan, D.; Zaidi, N. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2389. Khani, D.; Gutman, A. L.; Kohn, D. H. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1221. Wallace, J. S.; Morrow, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **1989**, *27*, 2553 and 3271. Binns, F.; Roberts, S. M.; Taylor, A.; Williams, C. F. *J. Chem. Soc. Perkin Trans. 1* **1993**, 899.

(21) In ref 12a, the synthesis and polymerization of these oxo-crown ethers has been described.

(22) Whitehouse, C. M.; Yamashita, M.; Fenn, J. B.; Dreyer, R. N. *Anal. Chem.* **1985**, *57*, 675.

(23) PPO is a polymeric test material for ES-MS measurements. Also for this polymer, only species with molecular weights lower than 3000 Dalton can be detected adequately.

(24) Turbid aqueous solutions of polymer **1** (1−5 mg/mL), acquired by overnight stirring of **1** in H_2O, did not phase separate on standing. Centrifugation for 2 min at a rotation rate of 3400 rpm resulted in a solution that still was turbid. Centrifugation for 10 min at 4300 rpm gave a white precipitate in a clear solution. Stirring gave an immediate restoration of the turbid solution ($A_{700\ nm} \gg 1$).

(25) The concentrations of the aqueous solutions were 0.8 and 3.7 mg/mL for solutions of polymers **1** and **3** (entries A and I in Table 1), respectively.

(26) The cac's of cationic, anionic, and nonionic surfactants obtained with the fluorescent-probe technique were in agreement with cac's obtained with other techniques: Kalyanasundaram, K.; Thomas, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 2039.

(27) For examples of the application of fluorescent techniques in polymer characterization, see: (a) M*acromolecular complexes in chemistry and biology;* Dubin, P., Bock, J., Davies, R. M., Schulz, D. N., Thies. C., Eds.; Springer-Verlag: Berlin, 1994. Wilhelm, M.; Zhao, C.-L.; Wang, Y.; Xu, R.; Winnik, M. A.; Mura, J.-L.; Riess, G.; Croucher, M. D. *Macromolecules* **1991**, *24*, 1033. Astafieva, I.; Zhong, X. F.; Eisenberg, A. *Macromolecules* **1993**, *26*, 7339. (b) Yekta, A.; Xu, B.; Duhamel, J.; Adiwidjaja, H., Winnik, M. A. *Macromolecules* **1995**, *28*, 956. Yekta, A.; Duhamel, J.; Brochard, P.; Adiwidjaja, H.; Winnik, M. A. *Macromolecules* **1993**, *26*, 1829. Alami, E.; Almgren, M.; Brown, W.; François, J. *Macromolecules* **1996**, *29*, 2229.

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(31) For this study entry C from Table 1 was used ($M_n = 4.3$, $D = 2.0$, determined with SEC, applying PS standards).

(32) These viscosity measurements were executed with Ubelohdes ($k = 0.01$; type 53010/I).

(33) Walderhaug, H.; Hansen, F. K.; Abramsén, S.; Persson, K.; Stilbs, P. *J. Phys. Chem.* **1993**, *97*, 8336. *Water-soluble polymers*; Glass, J. E., Ed.; Advances in Chemistry Series; American Chemical Society: Washington, D.C., 1986; Vol. 213. *Polymers in aqueous media*; Glass, J. E., Ed.; Advances in Chemistry Series; American Chemical Society: Washington, D.C., 1989; Vol. 223. ACS Symposium Series; *Polymers as rheology modifiers;* Schulz, D. N., Glass, J. E., Eds.; ACS Symposium Series; American Chemical Society: Washington, D.C., 1991; Vol. 462.

(34) Kirchner, J. G. *Techniques of chemistry: Thin layer chromatography*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1978, Vol. XIV, pp 203−204 and 225. KI/I_2 liquid: I_2 is dissolved in an aqueous 10% KI solution until a 5% iodine concentration is reached. The solution is deep brown and may contain undissolved I_2. Spray the solution on a TLC plate. In most cases a brown fixation is observed, but when compounds are dilute, gray fixations are possible. *p*-Anisaldehyde liquid: Mix 1 mL of *p*-anisaldehyde, 5 mL of sulfuric acid, 5 mL of glacial acid, and 90 mL of EtOH. Spray the liquid on the TLC plate and heat it. After 0.5 min spots appear. In most cases a purple fixation is observed. Other colors are also possible: molecules bearing a THP protecting group, for instance, give a green-black fixation. Tosylates generally give white fixations.

(35) The *g* value is the dissymmetry factor of a Cotton effect; it is defined as the ratio between the difference in specific absorbance of right and left circularly polarized light and the specific absorbance, $g = \Delta\epsilon/\epsilon$). See: Eliel, E. L.; Wilen, S. H. *Stereochemistry of organic compounds;* Wiley: New York, 1994.

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(39) Systems without salt bridges are also known to form coiled coils. Recently, it has been argued that the salt bridges ('charge−charge' interactions) between residues E and G′ and between E′ and G do not necessarily contribute favorably to the dimerization of α-helices and may be unfavorable relative to the alternative 'neutral−charge' interactions. Lumb, K. J.; Kim, P. S. *Science* **1995**, *268*, 436. Lavigne, P.; Sönnichsen, F. D.; Kay, C. M.; Hodges, R. S.; Lumb, K. J.; Kim, P. S. *Science* **1995**, *271*, 1137.

(40) Entries A, E, H, and N (see Table 1) have been used for parts A, B, C, and D, respectively, so every mode of polymerization —ring-opening polymerization and polycondensation either with or without $SnOct_2$ catalyst—is represented in these ES-MS-measurements. For the methyl-substituted polymer (entry H), no CH_3COONH_4 salt was added to the investigated solution.

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