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Synthesis of new enantiopure proton-ionizable crown ethers containing a dialkylhydrogenphosphate moiety☆

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Abstract—Seven new enantiopure proton-ionizable crown ethers containing a dialkylhydrogenphosphate moiety were prepared starting from optically active dialkyl-substituted oligoethylene glycols and phosphorus oxychloride followed by mild hydrolysis of the resulting macrocyclic chlorophosphates. Pentaethylene glycols having primary hydroxyl groups gave good yields of 17-crown-6 type ethers. Pentaethylene glycols with secondary hydroxyl groups rendered about the same amount of 17-crown-6 ethers and open chain dihydrogenphosphates in low yields. Tetraethylene glycols are reluctant to undergo macrocyclization with phosphorus oxychloride, especially the ones which contain secondary hydroxyl groups.

1. Introduction

In order for an ion carrier (e.g., a crown ether) to perform a practically useful so-called 'active transport' (i.e., transport against a concentration gradient) across the membrane of an aqueous source phase/lipophilic membrane/aqueous receiving phase system, it should possess a relatively strong ion-binding ability at the source phase/membrane interface, and a relatively weak ion-binding ability at the membrane/receiving phase interface.

A solution for this seemingly contradictory requirement is to engineer into the ion carrier a so-called 'switching mechanism', which enables alternation between strong and weak binding states. These two states can be reversibly interconverted by external forces, such as redox,[1] light,[2] temperature[3] and pH[4] gradients.

Proton-ionizable crown ethers having a pH switching mechanism have attracted the attention of many researchers, because at pH values higher than their pK_a, they are mostly ionized to ligand anions, which increase the cation–ligand complex stability with enhancement of selectivity, and avoid the need for a counteranion in a cation transport through various membrane systems or in solvent extraction.[4–12] The latter factor is of immense importance for practical applications in separations involving hydrophilic aqueous phase anions, such as chloride, nitrate and sulfate.[5] The transport of cations in most of these cases is pH dependent, so the transport can be turned on and off by adjusting the pH. Proton-ionizable macrocyclic carriers should have lipophilic substituents to ensure that they remain in the organic membrane. Without a lipophilic substituent, no transport occurs, because the crown ether leaks into the aqueous phase and is thus unavailable as a carrier.

We have been interested for several years in proton-ionizable crown ethers, in which the proton dissociable group is incorporated into the macroring. In such pH switching ligands, after deprotonation, the negatively charged heteroatom (e.g., oxygen or nitrogen) is in the coordination sphere of the complexed cation.[7–12]

There has always been a strong demand for proton-ionizable macrocyclic ligands with pK_a values, which would allow the transport of cations at relatively low pH values. Such more acidic pH-switched ligands can also be used

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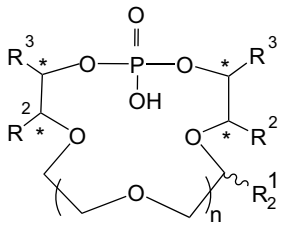


1: n=1, R^1=R^2=R^3=H
rac-**2**: n=1, R^1=octyl, R^2=R^3=H
3: n=2, R^1=R^2=R^3=H
rac-**4**: n=2, R^1=octyl, R^2=R^3=H
rac-**5**: n=2, R^1=decyl, R^2=R^3=H
rac-**6**: n=2, R^1=hexadecyl, R^2=R^3=H
(*S*,*S*)-**7**: n=1, R^1=R^3=H, R^2= *i*Bu
(*S*,*S*)-**8**: n=2, R^1=R^3=H, R^2= Me
(*S*,*S*)-**9**: n=2, R^1=R^2=H, R^3= Me
(*S*,*S*)-**10**: n=2, R^1=R^3=H, R^2= *i*Bu
(*S*,*S*)-**11**: n=2, R^1=R^2=H, R^3= *i*Bu
(*S*,*S*)-**12**: n=2, R^1=R^3=H, R^2= octyl
(*S*,*S*)-**13**: n=2, R^1=R^2=H, R^3= octyl

Figure 1. Schematics of proton ionizable crown ethers containing a dialkylhydrogenphosphate moiety.

to transport certain heavy metal cations, ammonium and primary organic ammonium ions at relatively low aqueous source phase pH.[10–12]

Bradshaw et al. synthesized fairly acidic proton-ionizable crown ethers containing a dialkylhydrogenphosphate moiety **1**–*rac*-**6** (see Fig. 1). These ligands were either achiral **1** and **3** or racemic *rac*-**2**, *rac*-**4**, *rac*-**5** and *rac*-**6**.[11] The water-insoluble macrocycles *rac*-**2**, *rac*-**4**, *rac*-**5** and *rac*-**6** showed an appreciable transport of alkali, alkaline earth and several transition metal cations in a H_2O–CH_2Cl_2–H_2O liquid membrane system.[12]

It is known that natural ion carriers (ionophores), such as valinomycin, monensin, lasalocid, monactin, dinactin, salinomycin, narasin, and nigericin, are optically active compounds and their stereostructure plays a very important role in the selective transport of metal cations through biomembranes.[13,14] Other studies have shown that the chirality of the synthetic host molecules is also an important factor in binding, solvent extraction and transport of metal cations.[15–17]

As an extension of our research for the purpose of finding enantiopure chiral host molecules having enhanced selectivity for both metal ions and the enantiomers of chiral protonated primary amines in binding,[18–20] solvent extraction,[21] membrane transport,[8,9,12] potentiometric[22] and other studies, we prepared macrocycles (*S*,*S*)-**7**–(*S*,*S*)-**13** (see Fig. 1).

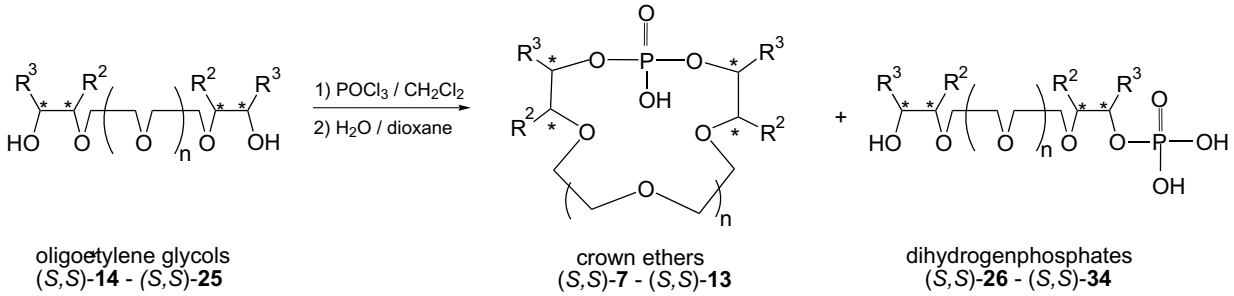
Note that to the best of our knowledge, no enantiopure chiral proton-ionizable crown ethers containing a dialkylhydrogenphosphate moiety have been reported.

Application studies on these new ligands will be reported when that work is finished.

2. Results and discussion

For the preparation of the new enantiopure macrocycles (*S*,*S*)-**7**–(*S*,*S*)-**13**, the reported procedure for obtaining the crown ethers **1**–*rac*-**6**[11] has been thoroughly modified. The intermediate chlorophosphates were obtained by reacting phosphorus oxychloride with the appropriate enantiopure oligoethylene glycols using a high dilution technique which provided higher yields than the reported[11] procedure. Also yields increased when the reaction temperature was raised from the reported −70[11] to −15 °C.

Our optimized general procedure (see Section 4) for macrocyclization was followed by the smooth hydrolysis of the resulting chlorophosphates to the desired crown ethers (*S*,*S*)-**7**–(*S*,*S*)-**13** using a water–dioxane mixture at room temperature (see Scheme 1 and Table 1). Starting from enantiopure pentaethylene glycols (*S*,*S*)-**20**, (*S*,*S*)-**22** and (*S*,*S*)-**24** with primary hydroxyl groups, only crown ethers could be isolated in good yields (see Table 1, entries 7, 9 and 11). Starting from pentaethylene glycols having secondary hydroxyl groups (*S*,*S*)-**21**, (*S*,*S*)-**23** and (*S*,*S*)-**25**, about the same amounts of crown ethers and open chain dihydrogenphosphates could be isolated in low yields (see Table 1, entries 8, 10 and 12). Using tetraethylene glycols (*S*,*S*)-**14**–(*S*,*S*)-**19** as starting materials, except for (*S*,*S*)-**16**, only open chain dihydrogenphosphates could be isolated in low yields (see Table 1, entries 1–6). Starting from tetraethylene glycol (*S*,*S*)-**16**, having primary hydroxyl groups, 3% of crown ether (*S*,*S*)-**7** could be obtained (see Table 1, entry 3).



Scheme 1. Formation of new enantiopure chiral crown ethers containing a dialkylhydrogenphosphate moiety and open chain dihydrogenphosphates (see also Table 1).

Table 1. Isolated yields (in per cent) of crown ethers and open chain dihydrogenphosphates (see also Scheme 1)

Entry	n	R^2	R^3	Starting oligoethylene glycol	Crown ether	Yield (%)	Dihydrogenphosphate	Yield (%)
1	1	Me	H	(*S*,*S*)-**14**	—	—	(*S*,*S*)-**26**	40
2	1	H	Me	(*S*,*S*)-**15**	—	—	(*S*,*S*)-**27**	36
3	1	*i*-Bu	H	(*S*,*S*)-**16**	(*S*,*S*)-**7**	3	(*S*,*S*)-**28**	31
4	1	H	*i*-Bu	(*S*,*S*)-**17**	—	—	(*S*,*S*)-**29**	22
5	1	Octyl	H	(*R*,*R*)-**18**	—	—	(*R*,*R*)-**30**	36
6	1	H	Octyl	(*S*,*S*)-**19**	—	—	(*S*,*S*)-**31**	31
7	2	Me	H	(*S*,*S*)-**20**	(*S*,*S*)-**8**	61	—	—
8	2	H	Me	(*S*,*S*)-**21**	(*S*,*S*)-**9**	14	(*S*,*S*)-**32**	16
9	2	*i*-Bu	H	(*S*,*S*)-**22**	(*S*,*S*)-**10**	59	—	—
10	2	H	*i*-Bu	(*S*,*S*)-**23**	(*S*,*S*)-**11**	8	(*S*,*S*)-**33**	10
11	2	Octyl	H	(*S*,*S*)-**24**	(*S*,*S*)-**12**	63	—	—
12	2	H	Octyl	(*S*,*S*)-**25**	(*S*,*S*)-**13**	15	(*S*,*S*)-**34**	15

Based on these experimental facts, it can be concluded that the fastest macrocyclization reaction leading to the formation of a 17-membered ring takes place when pentaethylene glycols with primary hydroxyl groups are used. In these cases, only a small amount of by-products is formed. Using pentaethylene glycols with secondary hydroxyl groups, macrocyclization reaction becomes slower. In the studied cases, the formation of a 14-membered ring is very unfavourable, especially when involving secondary hydroxyl groups. As it can be seen from Table 1, entries 2, 4 and 6, no crown ethers, but only open chain dihydrogenphosphates could be isolated, indicating a reluctance for ring closure of the open chain dichloro intermediates.

A close inspection of the IR spectra of our crown ethers and of the open chain dihydrogenphosphates revealed some general differences, which prompted us to obtain a deeper insight into this phenomenon.

Quantum chemical calculations enabled us to interpret the differences between the vibrational spectra of the open chain dihydrogenphosphates and the crown ethers.

Due to the flexible nature of structures **1** and **35** (see Fig. 2), the investigation of only a single conformer is not sufficient. Therefore, a conformational search was carried out using the Monte Carlo technique with the MM3 force field. Conformations having significantly lower energies than the others (eight conformations in the case of **1** and six in the case of **35**) were further optimized at the ab initio B3LYP/6-31+G* level of theory. For conformers having energies within 2 kcal/mol from the most stable one (five in the case of **1** and four in the case of **35**) vibrational frequencies and IR intensities were calculated with the help of second derivative calculations carried out at the same level of theory. As illustrated in Figure 2, the most stable conformations of both **1** and **35** seem to be stabilized by intramolecular hydrogen bonds. These provide a way to interpret the IR spectra of the two structures. According to the calculations in the case of **1**, the P–O–H bending motion of the single hydrogen bridge appears as a sharp peak between 1290 and 1310 cm^{-1} in the vibrational spectra of all stable conformers. The open chain dihydrogenphosphate **35** containing three OH groups has far more possibilities for hydrogen bonding compared to **1**, so the bands corresponding to the OH bending motions appear smeared over the 1100–1400 cm^{-1} region. This finding is in good agreement with the observed IR spectra of the methyl-substituted analogues (*S*,*S*)-**9** and (*S*,*S*)-**32**, while the IR spectra of (*S*,*S*)-**9** exhibit a narrow band at 1280 cm^{-1}, in the case of (*S*,*S*)-**32** the vibration bands appearing in the 1200–1400 cm^{-1} region are merged.

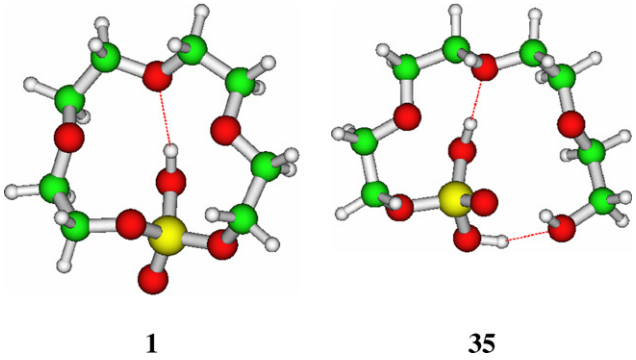


Figure 2. The most stable conformations of 1-hydroxy-2,5,8,11,14-pentaoxa-1-phosphacyclotetradecane-1-oxide **1** and 2-(2-{2-[2-hydroxyethoxy]ethoxy}ethoxy)ethan-2-yl dihydrogenphosphate **35**.

It should be mentioned that with the exception of (*S*,*S*)-**11**, the acidic proton of P–O–H could not be located in the ^1H NMR spectra of crown ethers (*S*,*S*)-**7**–(*S*,*S*)-**13**. In the case of crown ether (*S*,*S*)-**11**, a very broad proton signal centred at 5.05 could be observed.

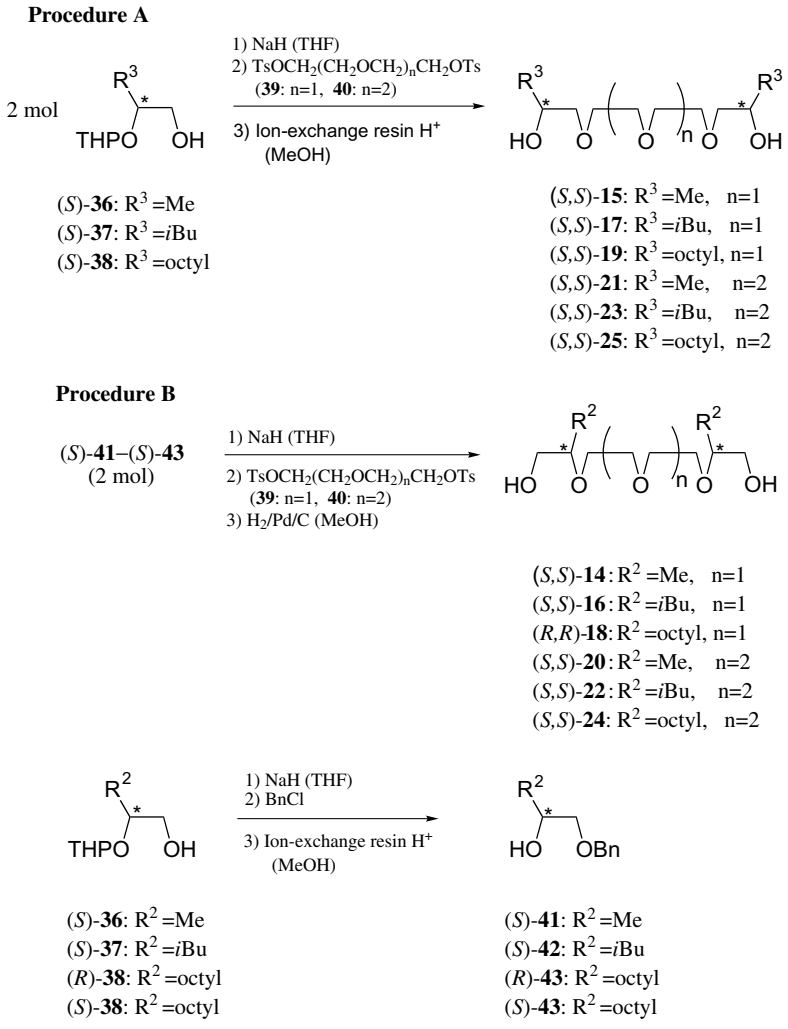
Except for (*S*,*S*)-**14**,[23] (*S*,*S*)-**15**,[24,25] (*S*,*S*)-**17**[26] and (*S*,*S*)-**21**,[24] the enantiopure oligoethylene glycols needed for the preparation of crown ethers (*S*,*S*)-**7**–(*S*,*S*)-**13** have, to the best of our knowledge, not been reported, although some of them, *rac*,*meso*-**18**,[27] *rac*,*meso*-**19**[28] and *rac*,*meso*-**24**,[27] have been prepared as mixtures of *rac* and *meso* compounds. The above mentioned oligoethylene glycols have been synthesized by different procedures than the ones we reported here. Note that the antipodes of (*S*,*S*)-**15** and (*S*,*S*)-**17**, that is, (*R*,*R*)-**15**[25] and (*R*,*R*)-**17**,[29] are also known, but the latter tetraethylene glycols were prepared using procedures different from ours.

Herein we report two general procedures for preparing enantiopure oligoethylene glycols. One was applied to ob-

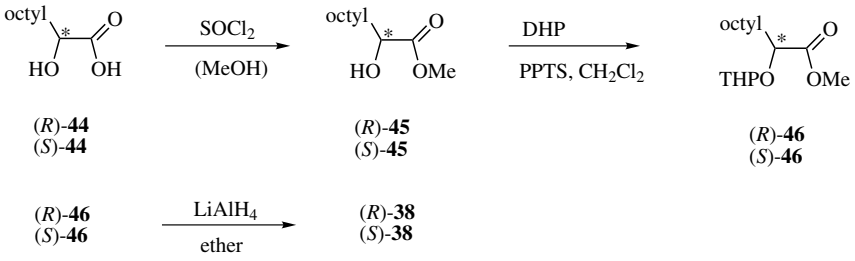
tain the oligoethylene glycols with two secondary hydroxyl groups (Scheme 2, procedure A), and the other one for oligoethylene glycols with two primary hydroxyl groups (Scheme 2, procedure B). In both cases, optically active 2-tetrahydropyranyloxy-alkane-1-ols (*S*)-**36**,[24] (*S*)-**37**,[26,30] (*R*)-**38** and (*S*)-**38** were used as key intermediates. In the case of procedure A the THP-blocked glycols were first deprotonated using a strong base (sodium hydride), after which two moles of the resulting sodium salts were reacted with one mole of diethylene glycol ditosylate **39** or triethylene glycol ditosylate **40** to obtain the bis-tetrahydropyranyl derivatives of the desired oligoethylene glycols. The latter were deblocked by an acidic ion-exchange resin in methanol.

In procedure B the sodium salts of alcohols (*S*)-**36**–(*S*)-**38** were generated, which were then treated with benzyl chloride. On removal of the THP protecting group from the diblocked glycols in the same way as above, the benzyl protected glycols (*S*)-**41**–(*S*)-**43** were obtained. The latter compounds were deprotonated using also sodium hydride. The resulting sodium salts (2 mol) were reacted with 1 mol of ditosylates **39** or **40** to obtain the bis-benzyl derivatives of the desired oligoethylene glycols. The benzyl protecting groups were removed by catalytic hydrogenation. Although the synthesis of (*S*)-**36**[24] and (*S*)-**37**[26,30] has been reported, (*R*)-**38** and (*S*)-**38** are new.

The starting materials for (*R*)-**38** and (*S*)-**38**, that is, (*R*)- and (*S*)-2-hydroxydecanoic acids (*R*)-**44** and (*S*)-**44** (Scheme 3) were obtained by resolution of racemic 2-hydroxydecanoic acid *rac*-**44** with the help of (*R*)- and (*S*)-1-phenylethylamine, respectively, as reported for the *R* enantiomer only.[31] Hydroxy acids (*R*)-**44** and (*S*)-**44** were first treated with thionyl chloride in methanol to give methyl esters (*R*)-**45** and (*S*)-**45** (see Scheme 3). The esters were reacted with an excess of dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) catalyst to give the 2-tetrahydropyranyloxy esters (*R*)-**46** and (*S*)-**46**, which were then reduced to give the THP-blocked glycols (*R*)-**38** and (*S*)-**38**.



Scheme 2. Preparation of enantiopure chiral oligoethylene glycols.



Note: DHP = 3,4-dihydro-2*H*-pyran, PPTS = pyridinium *p*-toluenesulfonate

Scheme 3. Preparation of (*R*)- and (*S*)-2-tetrahydropyranyloxy-decane-1-ol (*R*)-**38** and (*S*)-**38**.

3. Conclusions

The rate of macrocyclization reaction of optically active alkyl-substituted tetra- and pentaethylene glycols, respectively, with phosphorus oxychloride using a high dilution technique depends very much on the constitution of the oligoethylene glycols. The fastest macrocyclization reaction takes place when alkyl-substituted pentaethylene glycols with primary hydroxyl groups are used. Macrocyclization becomes slower when the alkyl-substituted pentaethylene glycols contain secondary hydroxyl groups. Using alkyl-substituted tetraethylene glycols for macrocyclization, especially the ones which have secondary hydroxyl groups, the reaction slows down by a large extent. It has also been shown that general procedures for obtaining enantiopure alkyl-substituted oligoethylene glycols with primary and secondary hydroxyl groups, respectively, could be developed by starting from commercially available and relatively cheap materials.

4. Experimental

4.1. General

Infrared spectra (neat unless otherwise indicated) were recorded on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-500 Avance spectrometer (at 500 MHz for ^1H, 125 MHz for ^{13}C and 202 MHz for ^{31}P spectra). Mass spectra were recorded on a ZQ2000 MS instrument (Waters Corp.) using ESI method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) plates were used for TLC and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Ratios of the solvents for the eluents are given in volumes (mL/mL). Romil Ltd (Cambridge UK) SuperPurity Solvent grade THF stored under argon was used as purchased. All other solvents were dried and purified according to the well established methods.[32] Evaporations were carried out under reduced pressure.

The Monte-Carlo conformational searches were carried out with the help of the Tinker[33] package. For ab initio geometry optimizations and second derivative calculations, the Gaussian98 package was used.[34]

4.2. General procedure for the preparation of crown ethers (*S*,*S*)-7–(*S*,*S*)-13 and open chain dihydrogenphosphates (*S*,*S*)-26–(*S*,*S*)-34 (see also Fig. 1, Scheme 1 and Table 1)

To a vigorously stirred, dry and pure CH_2Cl_2 (200 mL) were simultaneously added a solution of the appropriate oligoethylene glycol (*S*,*S*)-**14**–(*S*,*S*)-**25** (5 mmol) in CH_2Cl_2 (10 mL) and a solution of phosphorus oxychloride (76.6 mg, 5 mmol) in CH_2Cl_2 (10 mL) at −15 °C under Ar in 30 min. After the addition of the two solutions, the resulting reaction mixture was stirred for 1 h at −15 °C, then allowed to warm up to room temperature (rt) and stirred for another 20 h. The solvent was removed and the chlorophosphate was dissolved in dioxane (10 mL). The latter solution was added dropwise to a vigorously stirred mixture of dioxane (10 mL) and water (5 mL) at rt. This was then stirred at room temperature for 10 h. The solvent was removed and the crude product purified by column chromatography on silica gel. Eluents are given for each compound (see below). For yields see also Table 1.

4.2.1. (4*S*,12*S*)-1-Hydroxy-4,12-diisobutyl-2,5,8,11,14-pentaoxa-1-phosphacyclotetradecane 1-oxide (*S*,*S*)-7. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1.3); yield: 3%; $[\alpha]_D^{23} = -8.5$, $[\alpha]_{436}^{23} = -18.1$ (*c* 1.52, CH_2Cl_2); ^1H NMR 0.83 (d, $J = 6.3$ Hz, 12H), 1.11–1.26 (m, 2H), 1.28–1.46 (m, 2H), 1.55–1.75 (m, 2H), 3.40–3.72 (m, 6H), 3.72–4.00 (m, 8H); ^{13}C NMR 22.69, 23.29, 24.60, 40.55, 68.06, 69.11, 70.98, 77.29; ^{31}P NMR 0.35; IR ν_{max} 3296, 2872, 1468, 1368, 1244, 1096, 952, 856 cm^{-1}; MS: 369 $(M+1)^+$. Anal. Calcd for $C_{16}H_{33}O_7P$: C, 52.16; H, 9.03. Found: C, 52.06; H, 9.24.

4.2.2. (4*S*,15*S*)-1-Hydroxy-4,15-dimethyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane-1-oxide (*S*,*S*)-8. Eluent for chromatography: EtOAc/MeOH/H_2O (10:5:2); yield: 61%; $[\alpha]_D^{24} = +26.8$, $[\alpha]_{436}^{24} = +52.3$ (*c* 1.77, CH_2Cl_2); ^1H NMR 1.13 (d, $J = 6.0$ Hz, 6H), 3.55–3.92 (m, 16H), 3.95–4.08 (m, 2H); ^{13}C NMR 15.23, 66.70, 68.44, 69.14, 69.90, 75.04 (d, $J = 6.8$ Hz); ^{31}P NMR 0.85; IR ν_{max} 3392, 2872, 1460, 1376, 1360, 1248, 1104, 968, 856 cm^{-1}; MS: 329 $(M+1)^+$. Anal. Calcd for $C_{12}H_{25}O_8P$: C, 43.94; H, 7.67. Found: C, 43.83; H, 7.79.

4.2.3. (3*S*,16*S*)-1-Hydroxy-3,16-dimethyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-oxide (*S*,*S*)-9. Eluent for chromatography: EtOAc/MeOH/H_2O (10:5:2); yield: 14%; $[\alpha]_D^{23} = +20.1$, $[\alpha]_{436}^{23} = +39.7$ (*c* 2.85, CH_2Cl_2); ^1H NMR 1.23 (d, $J = 6.4$ Hz, 6H), 3.32–3.74 (m, 16H), 4.36–4.53 (m, 2H); ^{13}C NMR 18.73, 69.62, 69.77, 70.01, 70.93, 75.29; ^{31}P NMR −0.15; IR ν_{max} 3280, 2872, 1456, 1356, 1244, 1088, 992, 788 cm^{-1}, MS: 329 $(M+1)^+$. Anal. Calcd for $C_{12}H_{25}O_8P$: C, 43.94; H, 7.67. Found: C, 43.85; H, 7.88.

4.2.4. (4*S*,15*S*)-1-Hydroxy-4,15-diisobutyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-oxide (*S*,*S*)-10. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1); yield: 59%; $[\alpha]_D^{26} = +10.2$, $[\alpha]_{436}^{26} = +21.3$ (*c* 1.49, CH_2Cl_2); ^1H NMR 0.88 (d, $J = 6.6$ Hz, 12H), 1.23–1.31 (m, 2H), 1.39–1.47 (m, 2H), 1.61–1.72 (m, 2H), 3.53–3.79 (m, 14H), 3.81–3.91 (m, 2H), 3.98–4.07 (m, 2H); ^{13}C NMR 22.95, 23.15, 24.86, 39.47, 67.31, 67.55, 69.42, 70.29, 77.93; ^{31}P NMR 0.79; IR ν_{max} 3400, 2872, 1468, 1368, 1248, 1104, 948, 848 cm^{-1}; MS: 413 $(M+1)^+$. Anal. Calcd for $C_{18}H_{37}O_8P$: C, 52.42; H, 9.04. Found: C, 52.33; H, 9.23.

4.2.5. (3*S*,16*S*)-1-Hydroxy-3,16-diisobutyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-oxide (*S*,*S*)-11. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1.4); yield: 8%; $[\alpha]_D^{26} = +7.95$, $[\alpha]_{436}^{26} = +16.3$ (*c* 1.59, CH_2Cl_2); ^1H NMR 0.86 (d, $J = 7.0$ Hz, 6H), 0.88 (d, $J = 6.7$ Hz, 6H),1.16–1.29 (m, 2H), 1.57–1.67 (m, 2H), 1.68–1.81 (m, 2H), 3.39–3.84 (m, 16H), 4.23–4.41 (m, 2H), 5.05 (very br,1H, OH); ^{13}C NMR 22.79, 23.01, 24.47, 42.42, 68.91, 69.15, 69.88, 72.85; 75.10; ^{31}P NMR 0.85; IR ν_{max} 3360, 2872, 1472, 1368, 1240, 1096, 964, 784 cm^{-1}; MS: 413 $(M+1)^+$. Anal. Calcd for $C_{18}H_{37}O_8P$: C, 52.42; H, 9.04. Found: C, 52.28; H, 9.12.

4.2.6. (4*S*,15*S*)-1-Hydroxy-4,15-dioctyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-oxide (*S*,*S*)-12. Eluent for chromatography: EtOAc/MeOH/H_2O (15:2:1); yield: 63%; $[\alpha]_D^{26} = +7.0$, $[\alpha]_{436}^{26} = +14.3$ (*c* 2.50, CH_2Cl_2); ^1H NMR 0.81 (t, $J = 6.3$ Hz, 6H), 1.12–1.31 (m, 24H), 1.36–1.50 (m, 4H), 3.41–3.51 (m, 2H), 3.51–3.73 (m, 12H), 3.77–3.89 (m, 2H), 3.89–4.02 (m, 2H); ^{13}C NMR 14.08, 22.66, 25.40, 29.30, 29.59, 29.90, 30.48, 31.87, 67.07, 67.75, 69.53, 70.33, 79.38; ^{31}P NMR 0.28; IR ν_{max} 3400, 2856, 1468, 1352, 1220, 1096, 952, 856 cm^{-1}; MS: 525 $(M+1)^+$. Anal. Calcd for $C_{26}H_{53}O_8P$: C, 59.52; H, 10.18. Found: C, 59.29; H, 10.25.

4.2.7. (3*S*,16*S*)-1-Hydroxy-3,16-dioctyl-2,5,8,11,14,17-hexaoxa-1-phosphacycloheptadecane 1-oxide (*S*,*S*)-13. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1); yield: 15%; $[\alpha]_D^{24} = +12.1$, $[\alpha]_{436}^{24} = +23.7$ (*c* 1.93, CH_2Cl_2); ^1H NMR 0.87 (t, $J = 7.2$ Hz, 6H), 1.18–1.45 (m, 24H), 1.45–1.60 (m, 2H), 1.64–1.81 (m, 2H), 3.51–3.72 (m, 12H), 3.72–3.86 (m, 4H), 4.26–4.41 (m, 2H); ^{13}C NMR 14.12, 22.70, 25.52, 29.37, 29.67, 29.85, 30.93, 33.38, 68.81, 69.12, 69.68, 74.32, 74.69; ^{31}P NMR −0.63; IR ν_{max} 3250, 2856, 1464, 1360, 1248, 1100, 968, 790 cm^{-1}; MS: 525 $(M+1)^+$. Anal. Calcd for $C_{26}H_{53}O_8P$: C, 59.52; H, 10.18. Found: C, 59.23; H, 10.36.

4.2.8. (2*S*)-2-(2-{2-[(2*S*)-1-Hydroxypropan-2-yloxy]ethoxy}-ethoxy)propyl dihydrogenphosphate (*S*,*S*)-26. Eluent for chromatography: EtOAc/MeOH/H_2O (10:5:2); yield: 40%; $[\alpha]_D^{28} = +24.2$, $[\alpha]_{436}^{28} = +47.3$ (*c* 2.91, CH_2Cl_2);^1H NMR 1.07 (d, $J = 5.5$ Hz, 3H), 1.13 (d, $J = 5.0$ Hz, 3H), 3.36–3.78 (m, 12H), 3.78–4.03 (m, 2H), 6.65 (br s, 3H, OH); ^{13}C NMR 15.99, 16.36, 65.95, 67.42, 67.73, 68.73, 70.52 (br probably two carbon 13 signals together), 74.99, 76.47; ^{31}P NMR −0.04; IR ν_{max} 3392, 2872, 1460, 1376, 1088, 960, 800 cm^{-1}; MS: 303 $(M+1)^+$. Anal. Calcd for $C_{10}H_{23}O_8P$: C, 39.74; H, 7.67. Found: C, 39.61; H, 7.74.

4.2.9. (2*S*)-3-(2-{2-[(2*S*)-2-Hydroxypropoxy]ethoxy}ethoxy)propan-2-yl dihydrogenphosphate (*S*,*S*)-27. Eluent for chromatography: EtOAc/MeOH/H_2O (10:5:2); yield: 36%; $[\alpha]_D^{27} = +11.1$, $[\alpha]_{436}^{27} = +22.6$ (*c* 1.41, CH_2Cl_2); ^1H NMR 1.14 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 5.8$ Hz, 3H), 3.29–3.78 (m, 12H), 3.94–4.08 (m, 1H), 4.38–4.54 (m, 1H), 6.00 (br s, 3H, OH); ^{13}C NMR 18.60, 19.05, 65.87, 69.90 (br probably two carbon 13 signals together), 69.98 (br probably two carbon 13 signals together), 70.39, 75.24, 77.32; ^{31}P NMR 1.80; IR ν_{max} 3312, 2872, 1456, 1376, 1104, 960, 932, 768 cm^{-1}; MS: 303 $(M+1)^+$. Anal. Calcd for $C_{10}H_{23}O_8P$: C, 39.74; H, 7.67. Found: C, 39.56; H, 7.71.

4.2.10. (2*S*)-2-(2-{2-[(2*S*)-1-Hydroxy-4-methylpentan-2-yloxy]ethoxy}ethoxy)-4-methylpentyl dihydrogenphosphate (*S*,*S*)-28. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1.3); yield: 31%; $[\alpha]_D^{23} = -7.3$, $[\alpha]_{436}^{23} = -15.35$ (*c* 2.05, CH_2Cl_2); ^1H NMR 0.83 (d, $J = 6.6$ Hz, 12H), 1.04–1.24 (m, 2H), 1.28–1.44 (m, 2H), 1.51–1.79 (m, 2H), 3.37–3.95 (m, 14H), 6.70 (br s, 3H, OH); ^{13}C NMR 22.51, 22.81, 23.17, 23.43, 24.69, 24.94, 39.91, 39.95, 64.24, 67.53 (br probably two carbon 13 signals together), 68.00, 70.54 (br probably two carbon 13 signals together), 70.88, 79.15; ^{31}P NMR 3.09; IR ν_{max} 3250, 2952, 1464, 1368, 1100, 944, 864, 836 cm^{-1}; MS: 387 $(M+1)^+$. Anal. Calcd for $C_{16}H_{35}O_8P$: C, 49.73; H, 9.13. Found: C, 49.55; H, 9.22.

4.2.11. (2*S*)-1-(2-{2-[(2*S*)-2-Hydroxy-4-methylpentyloxy]-ethoxy}ethoxy)-4-methylpentan-2-yl dihydrogenphosphate (*S*,*S*)-29. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1.2); yield: 22%; $[\alpha]_D^{20} = -9.8$, $[\alpha]_{436}^{23} = -20.5$ (*c* 1.85, CH_2Cl_2); ^1H NMR 0.90 (d, $J = 6.4$ Hz, 6H), 0.91 (d, $J = 6.4$ Hz, 6H), 1.09–1.21 (m, 1H), 1.29–1.41 (m, 2H), 1.51–1.64 (m, 1H), 1.70–1.89 (m, 2H), 3.32–3.40 (m, 1H), 3.41–3.49 (m, 1H), 3.50–3.79 (m, 10H), 3.83–3.92 (m, 1H), 4.28–4.42 (m, 1H), 6.36 (br s, 3H, OH); ^{13}C NMR 22.54, 22.93, 23.43, 23.49, 24.27, 24.53, 42.12, 42.52, 68.10, 69.90 (br probably three carbon 13 signals together), 70.61, 72.54, 74.12, 75.83; ^{31}P NMR 2.52; IR ν_{max} 3224, 2952, 1472, 1368, 1120, 936, 760 cm^{-1}; MS: 387 $(M+1)^+$. Anal. Calcd for $C_{16}H_{35}O_8P$: C, 49.73; H, 9.13. Found: C, 49.59; H, 9.26.

4.2.12. (2*R*)-2-(2-{2-[(2*R*)-1-Hydroxydecan-2-yloxy]ethoxy}ethoxy)decyl dihydrogenphosphate (*R*,*R*)-30. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1); yield: 36%; $[\alpha]_D^{27} = -5.2$, $[\alpha]_{436}^{27} = -10.7$ (*c* 1.74, CH_2Cl_2); ^1H NMR 0.88 (t, $J = 6.5$ Hz, 6H), 1.20–1.55 (m, 28H), 3.40–3.78 (m, 10H), 3.78–4.00 (m, 4H), 6.90 (br s, 3H, OH); ^{13}C NMR 14.28, 14.30, 22.87, 22.90, 25.72, 25.77, 29.58,

29.66, 29.85, 29.98, 30.20, 30.25, 32.11 (br probably two carbon 13 signals together), 32.16 (br probably two carbon 13 signals together), 64.19, 64.23, 67.44, 70.60, 70.65, 70.67, 79.43, 81.00; ^{31}P NMR 1.63; IR ν_{max} 3288, 2928, 1464, 1348, 1104, 936, 828 cm^{-1}; MS: 499 $(M+1)^+$. Anal. Calcd for $C_{24}H_{51}O_8P$: C, 57.81; H, 10.31 . Found: C, 57.64; H, 10.42.

4.2.13. (2*S*)-1-(2-{2-[(2*S*)-2-Hydroxydecyloxy]ethoxy}ethoxy)decan-2-yl dihydrogenphosphate (*S*,*S*)-31. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1); yield: 31%; $[\alpha]_D^{27} = +9.8$, $[\alpha]_{436}^{27} = +20.1$ (*c* 2.29, CH_2Cl_2); ^{1}H NMR 0.84 (t, $J = 6.3$ Hz, 6H), 1.13–1.47 (m, 26H), 1.50–1.68 (m, 2H), 3.18–3.94 (m, 13H), 4.10–4.41 (m, 1H) 6.40 (br s, 3H, OH); ^{13}C NMR 14.23, 14.25, 22.82, 22.86, 25.45, 25.88, 29.54, 29.69, 29.83, 29.96, 30.06, 30.30, 32.08, 32.15, 32.85, 33.66, 69.98, 70.03, 70.07, 73.41, 74.19, 74.22, 75.54 (br probably two carbon 13 signals together); ^{31}P NMR 1.90; IR ν_{max} 3250, 2928, 1464, 1352, 1108, 800 cm^{-1}; MS: 499 $(M+1)^+$. Anal. Calcd for $C_{24}H_{51}O_8P$: C, 57.81; H, 10.31. Found: C, 57.62; H, 10.39.

4.2.14. (2*S*,15*S*)-15-Hydroxy-4,7,10,13-tetraoxahexadecan-2-yl dihydrogenphosphate (*S*,*S*)-32. Eluent for chromatography: EtOAc/MeOH/H_2O (10:5:2); yield: 16%; $[\alpha]_D^{23} = +8.75$, $[\alpha]_{436}^{23} = +16.9$ (*c* 4.16, CH_2Cl_2); ^{1}H NMR 1.07 (d, $J = 6.4$ Hz, 3H), 1.19 (d, $J = 6.2$ Hz, 3H), 3.20–3.71 (m, 16H), 3.87–4.00 (m, 1H), 4.33–4.49 (m, 1H), 7.14 (br s, 3H, OH); ^{13}C NMR 18.78, 19.09, 66.07, 70.22, 70.28 (br probably three carbon 13 signals together), 70.40, 70.58, 75.26, 75.34, 76.91; ^{31}P NMR 2.58; IR ν_{max} 3250, 2864, 1456, 1376, 1350, 1248, 1104, 1000, 932 cm^{-1}; MS: 347 $(M+1)^+$. Anal. Calcd for $C_{12}H_{27}O_9P$: C, 41.62; H, 7.86. Found: C, 41.41; H, 7.95.

4.2.15. (4*S*,17*S*)-17-Hydroxy-2,19-dimethyl-6,9,12,15-tetraoxaeicosan-4-yl dihydrogenphosphate (*S*,*S*)-33. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1.4); yield: 10%; $[\alpha]_D^{23} = -11.4$, $[\alpha]_{436}^{23} = -22.3$ (*c* 2.47, CH_2Cl_2); ^{1}H NMR 0.88 (d, $J = 6.4$ Hz, 6H), 0.90 (d, $J = 6.9$ Hz, 6H), 1.07–1.16 (m, 1H), 1.28–1.45 (m, 2H), 1.46–1.60 (m, 1H), 1.67–1.84 (m, 2H), 3.27–3.38 (m, 1H), 3.40–3.49 (m, 1H), 3.49–3.77 (m, 14H), 3.79–3.89 (m, 1H), 4.24–4.37 (m, 1H), 6.00 (br s, 3H, OH); ^{13}C NMR 22.45, 23.00, 23.40, 23.58, 24.35, 24.58, 42.12, 42.41, 68.13, 70.18, 70.24 (br probably two carbon 13 signals together), 70.26 (br probably two carbon 13 signals together), 70.39, 72.58, 74.18, 76.19; ^{31}P NMR 1.99; IR ν_{max} 3384, 2872, 1472, 1368, 1108, 932 cm^{-1}; MS: 431 $(M+1)^+$. Anal. Calcd for $C_{18}H_{39}O_9P$: C, 50.22; H, 9.13. Found: C, 50.03; H, 9.29.

4.2.16. (9*S*,22*S*)-22-Hydroxy-11,14,17,20-tetraoxatriacontan-9-yl dihydrogenphosphate (*S*,*S*)-34. Eluent for chromatography: EtOAc/MeOH/H_2O (10:2:1); yield: 15%; $[\alpha]_D^{24} = +8.1$, $[\alpha]_{436}^{24} = +16.6$ (*c* 1.46, CH_2Cl_2); ^{1}H NMR 0.88 (t, $J = 6.3$ Hz, 6H), 1.17–1.49 (m, 26H), 1.53–1.69 (m, 2H), 3.31–3.41 (m, 1H), 3.43–3.85 (m, 16H), 4.15–4.31 (m, 1H), 5.14 (br s, 3H, OH); ^{13}C NMR 14.12, 14.15, 22.71, 22.74, 25.34, 25.73, 29.40, 29.56, 29.68, 29.83, 29.91, 30.16, 31.95, 32.03, 32.73, 33.47, 69.85, 69.95, 69.99, 70.03, 70.18, 73.41, 74.00, 75.53; ^{31}P NMR 2.10; IR ν_{max} 3400, 2928, 1460, 1352, 1104, 804 cm^{-1}; MS: 543 $(M+1)^+$. Anal. Calcd for $C_{26}H_{55}O_9P$: C, 57.54; H, 10.22. Found: C, 57.40; H, 10.31.

4.3. General procedure for the preparation of oligoethylene glycols (*S*,*S*)-15, (*S*,*S*)-17, (*S*,*S*)-19, (*S*,*S*)-21, (*S*,*S*)-23 and (*S*,*S*)-25, procedure A (see also Scheme 2)

To a suspension of NaH (5.6 g, 140 mmol, 60% dispersion in mineral oil) in THF (30 mL) was added dropwise at 0 °C under argon, 2-tetrahydropyranyloxy-alkane-1-ols (*S*)-**36**–(*S*)-**38** (100 mmol) dissolved in THF (140 mL). The reaction mixture was stirred at 0 °C for 10 min, at rt for 20 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0 °C and either diethylene glycol ditosylate **39** or triethylene glycol ditosylate **40** (45 mmol in both cases) dissolved in THF (70 mL) was added dropwise. Stirring was continued at 0 °C for 10 min and then at rt for 4 days. The solvent was removed and the residue taken up in a mixture of ice (50 g), water (100 mL) and ether (300 mL). The mixture was shaken well and separated. The aqueous phase was extracted with ether (2×100 mL). The combined organic phase was shaken with saturated brine (200 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was dissolved in MeOH (500 mL) and Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form) (4 g) was added to this solution. After stirring the mixture at rt for 2 days, the resin was filtered off and washed with MeOH (3×30 mL). The filtrate and washings were combined and the solvent was evaporated. The crude product was purified by column chromatography on silica gel. Eluents are given for each individual compound (see below).

4.3.1. (2*S*,2′*S*)-1,1′-[Oxybis(ethyleneoxy)]di(propane-2-ol) (*S*,*S*)-15. Tetraethylene glycol (*S*,*S*)-**15** prepared according to procedure A was identical in every respect to the one obtained by the reported[24] method. Eluent for chromatography: EtOAc/EtOH (9:1); yield: 70%.

4.3.2. (2*S*,2′*S*)-1,1′-[Oxybis(ethyleneoxy)]bis(4-methylpentane-2-ol) (*S*,*S*)-17. Tetraethylene glycol (*S*,*S*)-**17** prepared according to procedure A was identical in every respect to the one obtained by the reported[26] method. Eluent for chromatography: EtOAc/hexane (1:1); yield: 72%.

4.3.3. (2*S*,2′*S*)-1,1′-[Oxybis(ethyleneoxy)]di(decane-2-ol) (*S*,*S*)-19. Eluent for chromatography: toluene/EtOAc (4:1); yield: 73%; mp: 41–43 °C; $[\alpha]_D^{26} = +14.3$, $[\alpha]_{436}^{26} = +27.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR 0.88 (t, $J = 7$ Hz, 6H), 1.2–1.55 (m, 28H), 3.31 (dd, $J_{gem} = 10.2$ Hz, $J_{vic} = 8.5$ Hz, 2H), 3.54 (dd, $J_{gem} = 10.2$ Hz, $J_{vic} = 2.5$ Hz, 2H), 3.62–3.72 (m, 8H), 3.75–3.82 (m, 2H), 3.92 (br s, 2H, OH); IR (KBr) ν_{max} 3424, 2920, 2848, 1472, 1152 cm^{-1}.

4.3.4. (2*S*,15*S*)-4,7,10,13-Tetraoxahexadecane-2,15-diol (*S*,*S*)-21. Pentaethylene glycol (*S*,*S*)-**21** prepared according to procedure A was identical in every respect to the one obtained by the reported[24] method. Eluent for chromatography: EtOAc/MeOH/H_2O (25:2:2); yield: 67%.

4.3.5. (4*S*,17*S*)-2,19-Dimethyl-6,9,12,15-tetraoxacosane-4,17-diol (*S*,*S*)-23. Eluent for chromatography: EtOAc/hexane/MeOH/H_2O (25:5:2:0.5); yield: 51%; $[\alpha]_D^{26} = +3.3$, $[\alpha]_{436}^{26} = +6.3$ (*c* 2.0, CH_2Cl_2); ^1H NMR 0.91 (d, $J = 6.6$ Hz, 6H), 0.93 (d, $J = 6.6$ Hz, 6H), 1.07–1.17 (m, 2H), 1.34–1.45 (m, 2H), 1.73–1.89 (m, 2H), 3.1 (br s, 2H, OH), 3.29 (dd, $J_{gem} = 9.8$ Hz, $J_{vic} = 8.3$ Hz, 2H); 3.50 (dd, $J_{gem} = 9.8$ Hz, $J_{vic} = 2.7$ Hz, 2H), 3.61–3.72 (m, 12H), 3.82–3.92 (m, 2H); ^{13}C NMR 22.11, 23.43, 24.43, 41.90, 68.25, 70.50, 70.51, 70.54, 76.39; IR ν_{max} 3448, 2952, 2872, 1468, 1112 cm^{-1}.

4.3.6. (9*S*,22*S*)-11,14,17,20-Tetraoxatriacontane-9,22-diol (*S*,*S*)-25. Eluent for chromatography: EtOAc/hexane/MeOH/H_2O (25:5:2:1); mp: 33–34 °C; yield: 56%; $[\alpha]_D^{27} = +7.4$, $[\alpha]_{436}^{27} = +14.7$ (*c* 1.9, CH_2Cl_2); ^1H NMR 0.88 (t, $J = 6.5$ Hz, 6H), 1.20–1.50 (m, 28H), 3.11 (br s, 2H, OH), 3.31 (dd, $J_{gem} = 9.7$ Hz, $J_{vic} = 8.7$ Hz, 2H); 3.52 (dd, $J_{gem} = 9.7$ Hz, $J_{vic} = 2.2$ Hz, 2H), 3.60–3.72 (m, 12H), 3.75–3.82 (m, 2H); ^{13}C NMR 14.31, 22.88, 25.81, 29.49, 29.76, 29.94, 32.09, 33.21, 70.37, 70.71, 70.73, 76.76, 76.18; IR (KBr) ν_{max} 3448, 2928, 2856, 1456, 1368, 1108, 736, 696 cm^{-1}.

4.4. General procedure for the preparation of oligoethylene glycols (*S*,*S*)-14, (*S*,*S*)-16, (*R*,*R*)-18, (*S*,*S*)-20, (*S*,*S*)-22 and (*S*,*S*)-24. Procedure B (see also Scheme 2)

To a suspension of NaH (8.4 g, 210 mmol, 60% dispersion in mineral oil) in THF (45 mL) was added dropwise at 0 °C under argon 1-benzyloxymethyl-alkane-1-ols (*S*)-**41**–(*S*)-**43** (150 mmol) dissolved in THF (200 mL). The reaction mixture was stirred at 0 °C for 10 min, at rt for 20 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0 °C and diethylene glycol ditosylate **39** or triethylene glycol ditosylate **40** (70 mmol in both cases) dissolved in THF (100 mL) was added dropwise. Stirring was continued at 0 °C for 10 min, then at rt for 4 days. The solvent was removed and the residue was taken up in a mixture of ice (70 g), water (150 mL) and ether (450 mL). The mixture was shaken well and separated. The aqueous phase was shaken with ether (2 × 150 mL). The combined organic phase was shaken with saturated brine (300 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The relevant dibenzyl derivative was dissolved in MeOH (800 mL), charcoal added and the resulting suspension stirred at rt for 2 h. This was filtered and hydrogenated in the presence of Pd/C catalyst (3 g, Merck palladium/charcoal; activated, 10% Pd) until the theoretical volume of hydrogen was consumed. After the reaction was completed, the catalyst was filtered off and the solvent evaporated. The crude product was purified by column chromatography on silica gel. Eluents are given for each individual compound (see below).

4.4.1. (2*S*,2′*S*)-2,2′-[Oxybis(ethyleneoxy)]di(propane-1-ol) (*S*,*S*)-14. Tetraethylene glycol (*S*,*S*)-**14** prepared according to procedure B was identical in every respect to the one obtained by the reported[23] method. Eluent for chromatography: EtOAc/MeOH/H_2O (10:1:0.5); yield: 59%.

4.4.2. (2*S*,2′*S*)-2,2′-[Oxybis(ethyleneoxy)]bis(4-methylpentane-1-ol) (*S*,*S*)-16. Eluent for chromatography: EtOAc/hexane (5:4); yield: 62%; $[\alpha]_D^{20} = -6.9$, $[\alpha]_{436}^{20} = -10.7$ (*c* 2.34, CH_2Cl_2); ^1H NMR 0.91 (d, $J = 6.4$ Hz, 12H), 1.07–1.26 (m, 2H), 1.32–1.54 (m, 2H), 1.62–1.82 (m, 2H), 3.38–3.93 (m, 16H), ^{13}C NMR 22.63, 23.10, 24.68, 40.30, 64.91, 68.60, 70.90, 80.22; IR ν_{max} 3408, 2952, 2872, 1468, 1368, 1100, 948 cm^{-1}.

4.4.3. (2*R*,2′*R*)-2,2′-[Oxybis(ethyleneoxy)]di(decane-1-ol) (*R*,*R*)-18. Eluent for chromatography: hexane/acetone (5:1); yield: 84%; $[\alpha]_{365}^{23} = -22.3$ (*c* 1.43, $CHCl_3$); ^1H NMR 0.88 (t, $J = 7.0$ Hz, 6H), 1.20–1.60 (m, 28H), 3.37–3.43 (m, 2H), 3.49 (dd, $J_{gem} = 11.7$ Hz, $J_{vic} = 7.5$ Hz, 2H); 3.60 (dd, $J_{gem} = 11.7$ Hz, $J_{vic} = 2.5$ Hz, 2H), 3.55–3.82 (m, 8H), 4.1 (br s, 2H, OH); ^{13}C NMR 14.03, 22.60, 25.64, 29.21, 29.48, 29.73, 31.08, 31.82, 64.74, 68.69, 70.81, 81.89; IR ν_{max} 3432, 2928, 2856, 1450, 1108 cm^{-1}.

4.4.4. (2*S*,13*S*)-2,13-Dimethyl-3,6,9,12-tetraoxatetradecane-1,14-diol (*S*,*S*)-20. Eluent for chromatography: EtOAc/MeOH/H_2O (10:1:1); yield: 46%; $[\alpha]_D^{25} = +29.5$, $[\alpha]_{436}^{25} = +57.6$ (*c* 2.38, CH_2Cl_2); ^1H NMR 0.94 (d, $J = 6.5$ Hz, 6H), 3.28 (dd, $J_{gem} = 11.5$ Hz, $J_{vic} = 7.0$ Hz, 2H); 3.37 (dd, $J_{gem} = 11.5$ Hz, $J_{vic} = 3.0$ Hz, 2H); 3.42–3.52 (m, 12H); 3.54–3.59 (m, 2H); 3.62 (br s, 2H, OH); ^{13}C NMR 15.99, 65.76, 67.77, 70.11, 70.52, 76.63; IR ν_{max} 3432, 2872, 1460, 1376, 1248, 1096, 1048, 960 cm^{-1}.

4.4.5. (2*S*,13*S*)-2,13-Diisobutyl-3,6,9,12-tetraoxatetradecane-1,14-diol (*S*,*S*)-22. Eluent for chromatography: EtOAc/hexane/MeOH/H_2O (20:5:2:0.5); yield: 62%; $[\alpha]_D^{26} = -4.55$, $[\alpha]_{436}^{26} = -7.1$ (*c* 2.13, CH_2Cl_2); ^1H NMR 0.92 (d, $J = 6.6$ Hz, 12H), 1.09–1.25 (m, 2H), 1.39–1.53 (m, 2H), 1.62–1.79 (m, 2H), 3.41–3.53 (m, 4H), 3.56–3.80 (m, 14H), 3.85 (br s, 2H, OH); ^{13}C NMR 22.60, 23.15, 24.61, 40.45, 64.96, 68.93, 70.32, 71.01, 79.77; IR ν_{max} 3400, 2952, 2872, 1472, 1368, 1100, 952 cm^{-1}.

4.4.6. (2*S*,13*S*)-2,13-Dioctyl-3,6,9,12-tetraoxatetradecane-1,14-diol (*S*,*S*)-24. Eluent for chromatography: EtOAc/hexane/MeOH/H_2O (25:5:2:0.5); yield: 42%; $[\alpha]_D^{27} = +4.5$, $[\alpha]_{436}^{27} = +9.8$ (*c* 1.76, CH_2Cl_2); ^1H NMR 0.83 (t, $J = 7.0$ Hz, 6H), 1.13–1.50 (m, 28H), 3.34 (br s, 2H, OH), 3.41–3.44 (m, 2H), 3.5–3.75 (m, 16H); ^{13}C NMR 14.10, 22.67, 25.67, 29.28, 29.56, 29.81, 31.35, 31.89, 64.72, 69.07, 70.38, 70.99, 81.62; IR ν_{max} 3448, 2928, 2856, 1464, 1348, 1104, 948 cm^{-1}.

4.5. (*S*)-1-(Benzyloxy)propane-2-ol (*S*)-41

Benzyl-blocked glycol (*S*)-**41** was prepared in the same way as described below for (*S*)-**42** (see also Scheme 2) starting from (*S*)-**36**[24] (15.54g, 97 mmol). Yield: 12.74 g (79%). Bp: 130–132 °C (14 mmHg); $[\alpha]_D^{25} = +4.8$ (neat). Compound (*S*)-**41** prepared in this way was identical in every respect to the one obtained by the reported[35] method.

4.6. (*S*)-1-(Benzyloxy)-4-methylpentane-2-ol (*S*)-42

To a suspension of NaH (7.03 g, 175 mmol, 60% dispersion in mineral oil) in THF (50 mL) was added dropwise at 0 °C under argon a solution of alcohol (*S*)-**37**[26,30] (19.64 g, 97 mmol) in THF (130 mL). The reaction mixture was

stirred at 0 °C for 10 min, then at rt for 20 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0 °C and benzyl chloride (13.5 mL, 14.79 g, 117 mmol) dissolved in THF (20 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, at rt for 20 min and then at 50–55 °C for 16 h. The solvent was removed and the residue was taken up in a mixture of ice (50 g), water (100 mL), saturated aqueous $NaHCO_3$ solution (50 mL) and ether (200 mL). The aqueous phase was extracted with ether (4 × 50 mL). The combined organic phase was shaken with saturated brine (100 mL), dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was dissolved in MeOH (400 mL) and Amberlite® IR-120 strong acidic ion-exchange resin (H^+ form) (6 g) was added to this solution. After stirring the mixture at rt for 2 days, the resin was filtered off and washed with MeOH (3 × 30 mL). The filtrate and washings were combined and the solvent was evaporated. The crude product was purified by distillation to give (*S*)-**42** (15.46 g, 77%); bp: 116–118 °C (0.76 mmHg); $[\alpha]_{365}^{26} = -2.4$ (*c* 3.79, CH_2Cl_2); ^{1}H NMR 0.90 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 1.12–1.19 (m, 1H), 1.37–1.44 (m, 1H), 1.73–1.85 (m, 1H), 2.45 (br s, 1H, OH), 3.29 (dd, $J_{gem} = 9.4$ Hz, $J_{vic} = 8.2$ Hz, 1H); 3.47 (dd, $J_{gem} = 9.4$ Hz, $J_{vic} = 3.1$ Hz, 1H), 3.85–3.92 (m, 1H), 4.54 (s, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR 22.22, 23.56, 24.57, 42.20, 68.66, 73.46, 75.28, 127.87, 127.89, 128.58, 138.17; IR ν_{max} 3432, 2952, 2888, 2872, 1456, 1368, 1104, 736, 696 cm^{-1}.

4.7. (*R*)-1-(Benzyloxy)decane-2-ol (*R*)-43

Benzyl-blocked glycol (*R*)-**43** was prepared in the same way as described above for (*S*)-**42** (see also Scheme 2) starting from (*R*)-**38** (20.26 g, 78 mmol). The crude product was purified by distillation to give (*R*)-**43** (17.84 g, 87%); bp: 147–151 °C (0.05 mmHg); $[\alpha]_D^{25} = -5.29$ (*c* 2.57, CH_2Cl_2). Compound (*R*)-**43** prepared in this way was identical in every respect to the one obtained by the reported[36] method.

4.8. (*S*)-1-(Benzyloxy)decane-2-ol (*S*)-43

Compound (*S*)-43 was prepared in the same way as described above for (*S*)-42 (see also Scheme 2) starting from (*S*)-**38** (10.13 g, 39 mmol). The crude product was purified by distillation to give (*S*)-**43** (8.51 g, 83%); bp: 146–150 °C (0.05 mmHg); $[\alpha]_D^{25} = +5.2$ (*c* 2.48, CH_2Cl_2); ^{1}H NMR 0.88 (t, $J = 7.0$ Hz, 3H), 1.25–1.49 (m, 14H), 2.44 (br s, 2H, OH), 3.31 (dd, $J_{gem} = 9.5$ Hz, $J_{vic} = 8.0$ Hz, 1H), 3.49 (dd, $J_{gem} = 9.5$ Hz, $J_{vic} = 3.0$ Hz, 1H), 3.72–3.82 (m, 1H), 4.54 (s, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR 14.12, 22.68, 25.54, 29.27, 29.54, 29.69, 31.89, 33,18, 70.43, 73.32, 74.71, 127.73, 128.44, 138.05; IR ν_{max} 3448, 2928, 2856, 1456, 1368, 1108, 736, 696 cm^{-1}.

4.9. Methyl (*R*)-2-hydroxydecanoate (*R*)-45

To a stirred mixture of (*R*)-2-hydroxydeconoic acid (*R*)-**44** (47.9 g, 0.254 mol) in dry and pure methanol (210 mL) was added very slowly at −10 °C and under Ar, $SOCl_2$ (23 mL). After the addition of $SOCl_2$, the reaction mixture was stirred at −10 °C for 10 min. It was then allowed to warm up to rt and stirring was continued for another 4 h. The volatile materials were removed and the residue was purified by distillation under reduced pressure to give (*R*)-**45** (48.1 g, 93%) as a colourless oil. Bp: 61–62 °C (0.02 mmHg), 153–156 °C (22 mmHg); $[\alpha]_D^{22} = -3.07$ (neat); n_D^{25}: 1.4370. Reported[37] values for its antipode (*S*)-**45**: bp: 152–155 °C (22 mmHg); $[\alpha]_D^{22} = +3.0$ (neat); n_D^{25}: 1.4371.

4.10. Methyl (*S*)-2-hydroxydecanoate (*S*)-45

Compound (*S*)-**45** was prepared in the same way as described above for (*R*)-**45** starting from (*S*)-**44** (38.3 g, 0.203 mol). The crude product was purified by distillation under reduced pressure to give (*S*)-**45** (38.0 g, 92%) as a colourless oil. Bp: 60–61 °C (0.02 mmHg), 150–153 °C (22 mmHg); $[\alpha]_D^{22} = -3.0$ (neat); n_D^{25}: 1.4368. Reported[37] values: bp: 152–155 °C (22 mmHg); $[\alpha]_D^{22} = +3.0$ (neat); n_D^{25}: 1.4371.

4.11. Methyl (*R*)-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]decanoate (*R*)-46

To a mixture of methyl ester (*R*)-**45** (33.0 g, 163 mmol) and dihydropyran (DHP) (22 mL, 20,33 g, 242 mmol) in dry CH_2Cl_2 (240 mL) was added pyridinium *p*-toluenesulfonate (PPTS) catalyst (0.9 g) and one drop of pyridine. After stirring the reaction mixture at rt for 80 h, it was poured into a mixture of CH_2Cl_2 (200 mL) and ice-water (250 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic phase was shaken with saturated $NaHCO_3$ (80 mL), water (80 mL), dried over $MgSO_4$, filtered and the solvent was removed. The residue was purified by distillation under reduced pressure to give (*R*)-**46** (mixture of two diastereomers) as a colourless oil. Yield: 43.4 g (93 %), bp: 80–90 °C (0.02 mmHg); $[\alpha]_{365}^{22} = +85.6$ (*c* 2.13, THF); ^{1}H NMR 0.88 (t, $J = 7$ Hz, 6H), 1.2–1.9 (m, 40H), 3.45–3.91 (m, 4H), 3.73 (s, 6H), 4.00 (dd, $J = 7.3$, 5.9 Hz, 1H), 4.32 (dd, $J = 6.6$, 6.0 Hz 1H), 4.65 (t, $J = 3.5$ Hz, 1H), 4.66 (t, $J = 3.5$ Hz, 1H); ^{13}C NMR 14.05, 18.98, 19.24, 22.61, 25.01, 25.21, 25.37, 25.46, 29.15, 29.19, 29.27, 29.28, 29.34, 30.33, 30.34, 31.80, 32.68, 32.99, 51.72, 51.69, 62.50, 62.17, 73.81, 77.59, 97.04, 99.84, 173.57; IR: ν_{max} 2928, 2856, 1752, 1456, 1440, 1200, 1128, 1028 cm^{-1}.

4.12. Methyl (*S*)-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]decanoate (*S*)-46

Compound (*S*)-**46** was prepared in the same way as described above for (*R*)-**46** starting from (*S*)-**45** (48 g, 0.237 mol). The crude product was purified by distillation to give (*S*)-**46** (mixture of two diastereomers) as a colourless oil. Yield: 65.0 g (95%), bp: 78–90 °C (0.02 mmHg); $[\alpha]_{365}^{27} = -88.6$ (*c* 1.00, THF).

4.13. (*R*)-2-[(Tetrahydro-2*H*-pyran-2-yl)oxy]decane-1-ol (*R*)-38

To a well stirred suspension of $LiAlH_4$ (7.2 g, 190 mmol) in ether (280 mL) at 0 °C was slowly added (*R*)-**46** (43 g, 150 mmol) dissolved in ether (60 mL). The mixture was stirred at rt for 22 h. When the reduction was completed, the

mixture was cooled in an ice–salt bath and saturated NH_4Cl (7 mL), 15% NaOH solution (5 mL) and water (5 mL) were added very slowly. The resulting mixture was stirred at rt for 3 h. The precipitate was filtered and washed with ether (3×50 mL).The filtrate and washings were combined and shaken with saturated brine (50 mL), dried over $MgSO_4$ and the solvent was removed to give crude (*R*)-**38** (38.4 g, 99%) as a mixture of two diastereomers, which was used without further purification; $R_f = 0.48$, 0.34 (silica TLC, hexane/EtOAc 9:3); yield: 38.4 g (99%); $[\alpha]_{365}^{23} = +45.1$ (*c* 1.04, THF); ^{1}H NMR 0.88 (t, $J = 7$ Hz, 6H), 1.2–1.9 (m, 40H), 2.31 (t, $J = 6.2$ Hz, 1H, OH), 3.43–4.04 (m, 10H), 3.96 (dd, $J = 9.5$, 2.5 Hz, 1H, OH), 4.44–4.48 (m, 1H) 4.73–4.77 (m, 1H); ^{13}C NMR 14.09, 20.15, 21.29, 22.65, 25.03, 25.35, 25.62, 25.63, 29.23, 29.26, 29.49, 29.73, 29.54, 31.13, 31.48, 31.59, 31.86, 31.93, 64.06, 66.24, 63.33, 65.09, 77.76, 83.67, 97.75, 101.77; IR ν_{max} 3432, 2928, 2856, 1456, 1136, 1076, 1024 cm^{-1}.

4.14. (*S*)-2-[(Tetrahydro-2*H*-pyran-2-yl)oxy]decane-1-ol (*S*)-38

Compound (*S*)-**38** was prepared in the same way as described above for (*R*)-**38** starting from (*S*)-**46** (59.8 g, 209 mmol). The crude product (*S*)-**38** (50.2 g, 93%, as a mixture of two diastereomers) was used without further purification; $R_f = 0.61$, 0.45 (silica TLC, CH_2Cl_2/acetone 10:0.3); $[\alpha]_{365}^{23} = -50.5$ (*c* 1.00, THF).

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