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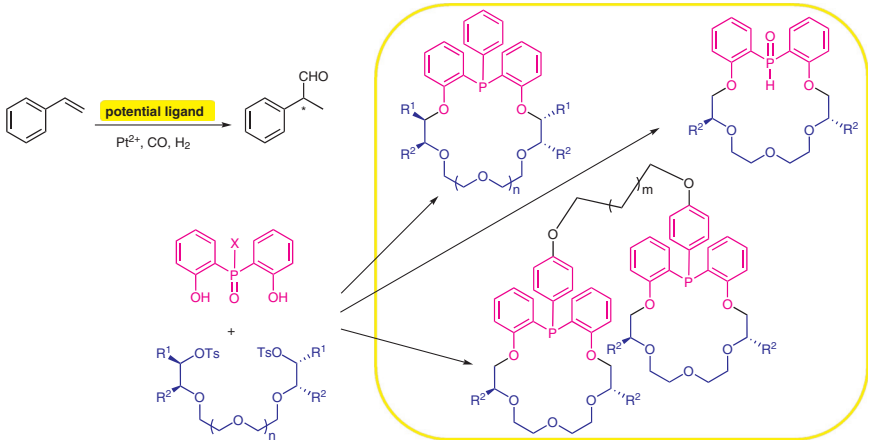
Synthesis of New Chiral Crown Ethers Containing Phosphine or Secondary Phosphine Oxide Units

Hajnalka Szabó-Szentjóbi[a]
István Majoros[a]
Anna Márton[a]
Ibolya Leveles[b,c]
Beáta G. Vértessy[b,c]
Miklós Dékány[d]
Tünde Tóth[a,e]
Péter Huszthy*[a]

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, PO Box 91, 1521 Budapest, Hungary
[b] Department of Applied Biotechnology and Food Science, Budapest University of Technology and Economics, PO Box 91, 1521 Budapest, Hungary
[c] Institute of Enzymology, Research Centre for Natural Sciences, 1117 Budapest, Hungary
[d] Spectroscopic Research Department, Gedeon Richter Plc., Gyömrői út 19-21, 1103 Budapest, Hungary
[e] Institute for Energy Security and Environmental Safety, Centre for Energy Research, P.O. Box 49, 1525 Budapest, Hungary
huszthy@mail.bme.hu



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Abstract The transition-metal complexes of phosphine and secondary phosphine oxide compounds can be used in various catalytic reactions. In this paper, the synthesis and characterization of eight new crown ethers containing trivalent phosphorus in their macroring are reported. These macrocycles are promising candidates as ligands for catalytic reactions.

Key words crown ethers, macrocycles, phosphines, phosphine oxides, catalytic ligands

Trivalent phosphorus ligands, such as phosphines or phosphinites are highly important class of ligands,[1] for the phosphorus exhibits a high affinity toward transition metals, and P(III)-transition-metal complexes are widely applied catalysts in homogeneous catalytic reactions. One of these reactions is the hydroformylation, which can be performed asymmetrically since the discovery of rhodium-BINAPHOS catalysts by Tanaka.[2] Furthermore, chiral phosphine ligands play pivotal roles in transition-metal-catalyzed asymmetric reactions.[3]

Crown ethers are macrocyclic compounds in which the most common repeating units in the macroring are ethyleneoxy moieties, which can wrap and capture various metal cations due to the presence of the lone pairs of oxygen atoms.[4] Phosphacrowns having one or more trivalent phosphorus atoms in the macroring have also been prepared recently.[5] It can be a great advantage to produce crown ether type phosphorus ligands due to the coordinating and capturing effects of the oxygens. In addition, chiral centers can easily be built in the macroring, which makes it possible to apply these ligands in asymmetric catalytic reactions. There are only few applications of phosphinocrowns in catalytic asymmetric reactions including 1,4-addition of arylboronic acids to α,β-unsaturated ketones,[6] or asymmetric hydrogenation of enamides.[7] A few years ago, we reported the synthesis of chiral crown ethers (*R*,*R*)-**1** and (*S*,*S*)-**2** containing a triphenylphosphine moiety (Figure 1),[8] and later the use of their Pd and Rh complexes in asymmetric hydroformylation.[9]

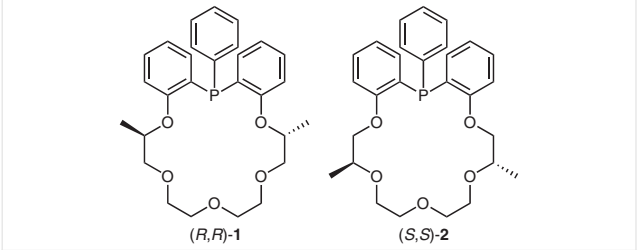

Figure 1 Examples of reported crown ethers containing triphenylphosphine unit

In the present paper, we describe the syntheses of new chiral crown ethers (*S*,*S*)-**3**, (*R*,*R*)-**4**, (*R*,*R*)-**5**, (*S*,*S*)-**6**, (*S*,*S*,*S*,*S*)-**7**, and (*S*,*S*,*S*,*S*)-**8** containing triarylphosphine units, and (*S*,*S*)-**9** and (*S*,*S*)-**10** containing a secondary phosphine oxide moiety (Figure 2). In secondary phosphine oxides, the pentavalent phosphine oxide form is in equilibrium with the

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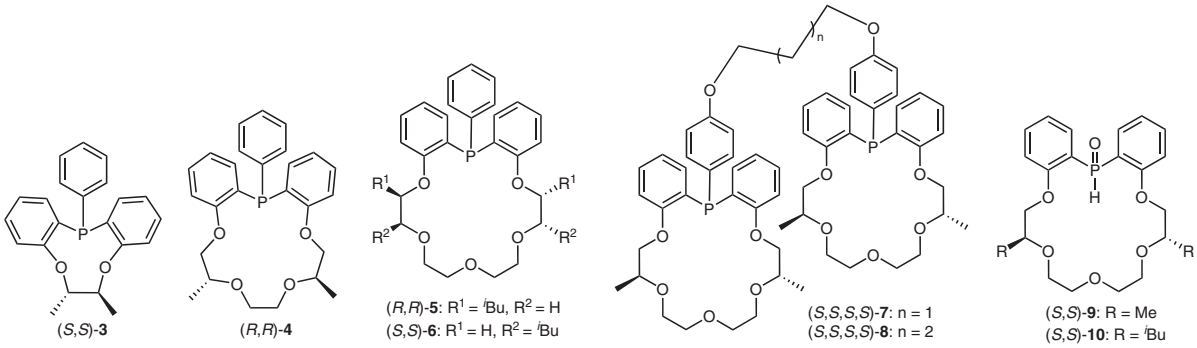


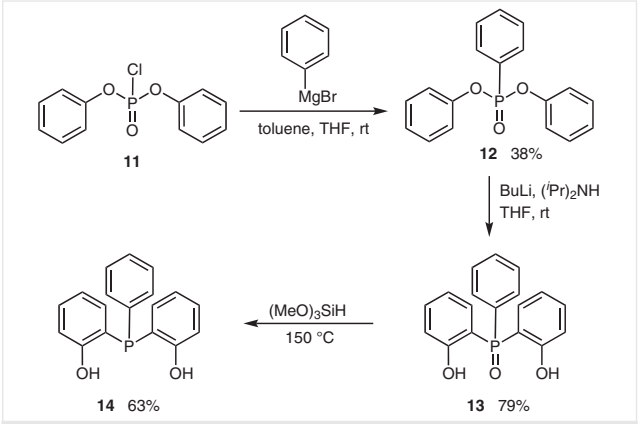
Figure 2 Structures of newly synthesized macrocycles

trivalent phosphinous acid form.[10] In the presence of a transition metal, the equilibrium is in favor of the phosphinous acid form by the coordination of the phosphorus atom[11] giving rise to a suitable family of potential catalysts, which are less sensitive to the oxidation, thus eliminating one of the major disadvantages of phosphine type ligands.[12] Therefore, secondary phosphine oxides (*S*,*S*)-**9** and (*S*,*S*)-**10** are expected to be easier to apply as catalyst ligands.

The aim of the syntheses of the new phosphine ligands was to produce catalytic ligands reaching higher asymmetric induction for hydroformylation reactions than the earlier ones.[9] Our previous results showed that larger groups at the chiral centers rendered higher degree of the enantiomeric recognition.[13] Hopefully in the case of (*R*,*R*)-**5** and (*S*,*S*)-**6** similar trend will be observed.

Better selectivities are also expected from bismacrocycles (*S*,*S*,*S*,*S*)-**7** and (*S*,*S*,*S*,*S*)-**8**. It was observed several times, that bidentate ligands have positive effect on selectivities of catalytic reactions by the chelating effect and the greater conformational stability.

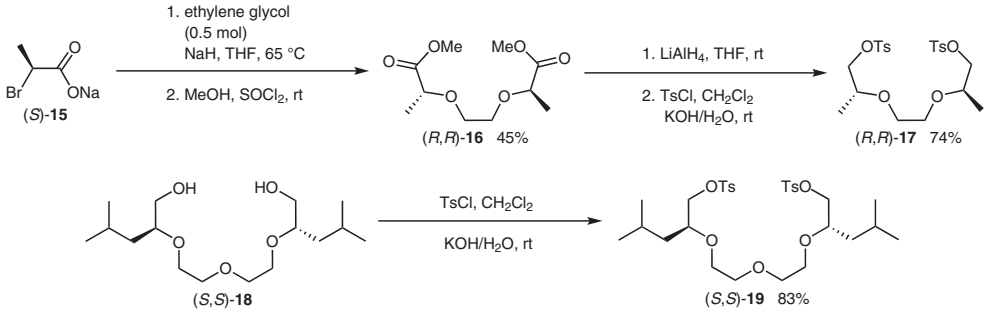
To obtain the target macrocycles, convergent synthetic methods were applied. First, we had to prepare the key intermediates, which were linked to each other in a macrocyclization reaction later (Scheme 3). Phosphine oxide **13**[14] and phosphine **14**[15] (Scheme 1) have been reported (although phosphine **14** is not completely characterized), but we worked out a new, more efficient synthetic pathway to obtain them. Commercially available phosphorochloridate **11** was first transformed into phosponate **12**[16] using phenylmagnesium bromide. Phosphonate **12** was then subjected to an intramolecular rearrangement reaction to give phosphine oxide **13**, which was reduced by trimethoxysilane to obtain phosphine **14**.



Scheme 1 Preparation of key substrates phosphine oxide **13** and phosphine **14**

The other key intermediates were the enantiopure oligoethylene glycol derivatives. The synthesis of triethylene glycol ditosylate (*R*,*R*)-**17** started from the sodium salt of commercially available enantiopure bromopropionic acid (*S*)-**15**, which was subjected to an S_N2 displacement reaction with the sodium salt of ethylene glycol, followed by esterification to furnish diester (*R*,*R*)-**16**. Reduction of the latter diester with lithium aluminum hydride gave the appropriate diol derivative, which was tosylated using potassium hydroxide as a base to obtain ditosylate (*R*,*R*)-**17** (Scheme 2). Tetraethylene glycol ditosylate (*S*,*S*)-**19** was prepared from the reported diol (*S*,*S*)-**18**,[17] which was reacted with tosyl chloride under the same conditions as described for the triethylene glycol ditosylate (*R*,*R*)-**17** (Scheme 2).

With the appropriate intermediates in hand, the next steps in the syntheses of the target compounds were the macrocyclization reactions. It should be noted here that in the ring closing reactions we did not expect appreciable yields, because several side reactions such as oligomerization, elimination, and hydrolysis of the ditosylate starting material can take place. The 9-crown-3 ether type phosphine oxide (*S*,*S*)-**21** was prepared from 2,3-butanediol ditosylate (*R*,*R*)-**20**[18] and phosphine oxide **13** (Scheme 3). The expected product in this reaction by a two to two macrocyclization was an 18-crown-6 ether type bisphosphine oxide compound, which unfortunately was not detected at all. Despite DMF is the most common solvent in these types of macrocyclization reactions, using it as a solvent gave no results, the starting materials were not transformed even



Scheme 2 Preparation of key substrate ditosylates (*R*,*R*)-**17** and (*S*,*S*)-**19**

after a long reaction time. We found that using DMSO as a solvent, except the desired 18-crown-6 ether type bisphosphineoxide, mixtures of several products were obtained, including surprisingly the strained 9-crown-3 ether type phosphine oxide (*S*,*S*)-**21**, the structure of which was analyzed by single-crystal X-ray diffraction method (Figure 3, Table 1).[19]

In order to carry out the synthesis of 15-crown-5 ethers (*R*,*R*)-**22** and 18-crown-6 ethers (*R*,*R*)-**24** and (*S*,*S*)-**25** the macrocyclizations were performed by the reaction of the appropriate ditosylates (*R*,*R*)-**17**, (*S*,*S*)-**23**,[20] and (*S*,*S*)-**19** with phosphine oxide **13** using DMF as a solvent. In the case of (*R*,*R*)-**22**, using K_2CO_3 as a base gave a better yield (31%) than applying Na_2CO_3 (17%) (Scheme 3). This result was unexpected, because the sodium ion is considered to have better template effect than that of potassium ion for facilitating the formation of 15-crown-5 ethers. In the case of (*S*,*S*)-**25**,

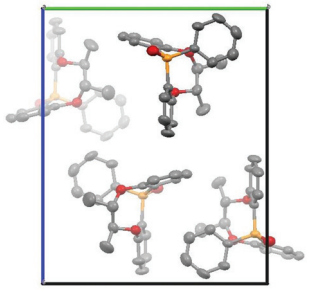
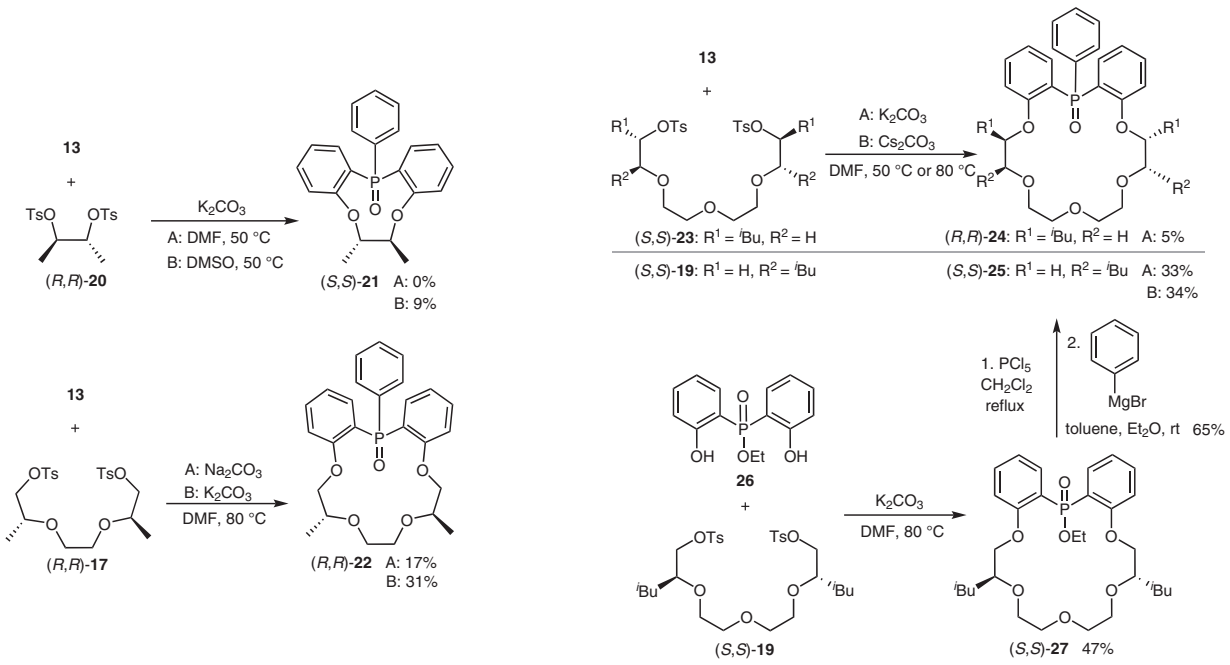


Figure 3 3D unit cell representation of the 9-crown-3 ether (*S*,*S*)-**21**. Atom coloring is as follows: C: gray, O: red, P: yellow.

there was no actual difference in the yield whether using K_2CO_3 or Cs_2CO_3 as a base (Scheme 3). The temperature was 50 °C in the cases of macrocyclizations with secondary ditosylates (*R*,*R*)-**20** and (*S*,*S*)-**23**,[20] and 80 °C with primary



Scheme 3 Macrocyclization reactions

Table 1 Crystal Data and Structure Refinement for (*S*,*S*)-**21**

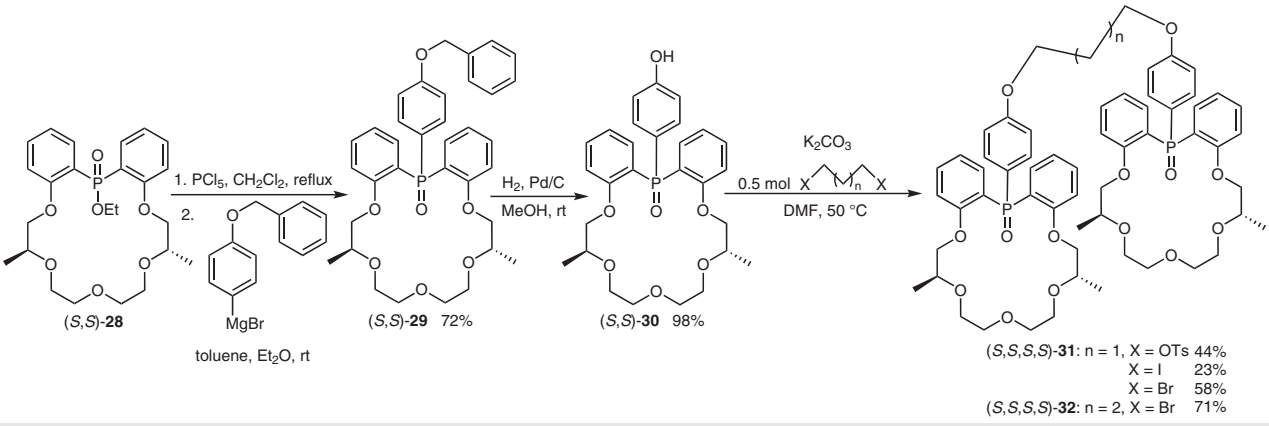
CCDC Number[19d]	1994255	Space group	*P*21 21 21
Formula	$C_{22}H_{21}O_3P$	Hall group	*P*2ac 2ab
Formula weight	364.36	*Z*	4
Wavelength (Å)	1.5418	Density (g/cm^3)	1.275
Temperature (K)	100	Abs. coeff., μ (mm^{-1})	1.429
Unit cell dimensions, a (Å)	8.1646(4)	h,k,l_{max}	10,16,20
b (Å)	13.7657(5)	Data completeness	1.64/0.94
c (Å)	16.8932(6)	Θ_{max}	
α (°)	90	Reflections	0.0736 (2910)
β (°)	90	*R*1/*wR*2	0.2125 (3488)
γ (°)	90	Nref	3701 [2124]
Volume (Å^3)	1898.65(13)		

ditosylates (*R*,*R*)-**17** and (*S*,*S*)-**19**. Applying lower temperature in the former cases was necessary to avoid the racemization and the elimination side reaction. In these cases, the Williamson type ether formation reaction takes place with total inversion of configuration. It is assumed that in the case of formation of (*R*,*R*)-**24**, steric hindrance also contributed to the lower yield.

The preparation of crown ether (*S*,*S*)-**25** was also accomplished in a different way. First ditosylate (*S*,*S*)-**19** was reacted with phosphinate **26**[21] to obtain macrocycle (*S*,*S*)-**27** containing a phosphinate unit. The latter was transformed to the appropriate phosphinic acid chloride followed by a Grignard reaction with phenylmagnesium bromide adopting a known procedure.[8,22] The overall yield was slightly lower using this procedure.

The syntheses of biscrown ethers (*S*,*S*,*S*,*S*)-**7** and (*S*,*S*,*S*,*S*)-**8** were started from the reported macrocycle (*S*,*S*)-**28**.[23] The latter was reacted with 4-benzyloxyphenylmagnesium bromide using the same method[8,20] as described for (*S*,*S*)-**25** to give (*S*,*S*)-**29**. Removal of the benzyl group of macrocycle (*S*,*S*)-**29** by hydrogenolysis furnished (*S*,*S*)-**30** containing a free phenolic hydroxyl group. To obtain the biscrown ethers (*S*,*S*,*S*,*S*)-**31** and (*S*,*S*,*S*,*S*)-**32** two moles of macrocycle (*S*,*S*)-**30** were coupled with one mole of linkers with different lengths. In order to carry out the synthesis of (*S*,*S*,*S*,*S*)-**31** by S_N2 reaction, different leaving groups of the reagent were tested. Using the ditosylate of propane-1,3-diol (prepared from propane-1,3-diol[24]) gave a better yield (44%), than applying 1,3-diiodopropane (23%) (prepared from ditosylate of propane-1,3-diol by Finkelstein reaction[25]). The highest yield (58%) for the desired bismacrocycle (*S*,*S*,*S*,*S*)-**31** was obtained by the commercially available 1,3-dibromopropane. Based on the latter result, the preparation of biscrown ether (*S*,*S*,*S*,*S*)-**32** was carried out by the reaction of (*S*,*S*)-**30** with 1,4-dibromobutane (Scheme 4).

Based on the LC-MS and ^{1}H NMR analyses of the crude product, in the case of the synthesis of (*S*,*S*,*S*,*S*)-**31**, elimination side reaction of part of the reagent gave the appropriate allyloxy derivative, which decreased the yields.



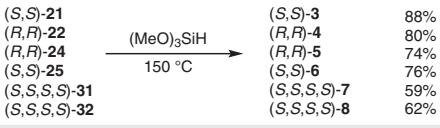
Scheme 4 Preparation of bismacrocycles (*S*,*S*,*S*,*S*)-**31** and (*S*,*S*,*S*,*S*)-**32**

The reduction of the phosphine oxides was carried out in a sealed tube without solvent[8] in all cases. In order to determine which reagent can give the best yield for the deoxygenation reaction, phosphine oxide (*S*,*S*)-**25** was reduced with six different silanes (Table 2).

Table 2 Reduction of (*S*,*S*)-**25** Using Different Silanes

Silane	Yield (%)
$(EtO)_3SiH$	69
$(MeO)_3SiH$	76
$PhSiH_3$	82
Ph_2SiH_2	58
Cl_3SiH	71
TMDS	53

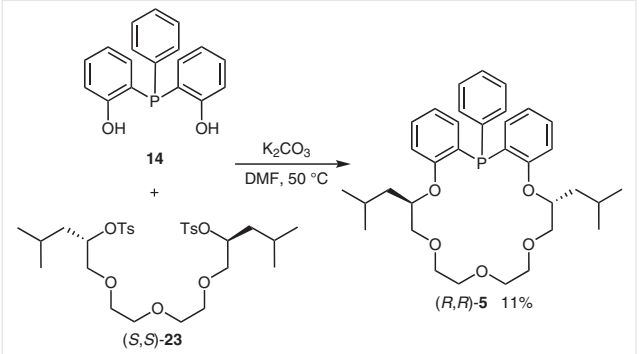
Although using phenylsilane gave the highest yield (82%), but because of its high boiling point, the second best one (trimethoxysilane, 76%) was applied for the reduction of the other phosphine oxides. This way it was easy to get the desired products from the reaction mixtures by evaporating the volatile materials. The deoxygenation reactions gave phosphines (*S*,*S*)-**3**, (*R*,*R*)-**4**, (*R*,*R*)-**5**, (*S*,*S*)-**6**, (*S*,*S*,*S*,*S*)-**7**, and (*S*,*S*,*S*,*S*)-**8** in good to excellent yields (59–88%) (Scheme 5).



Scheme 5 Reduction of crown ethers containing phosphine oxide unit into phosphines

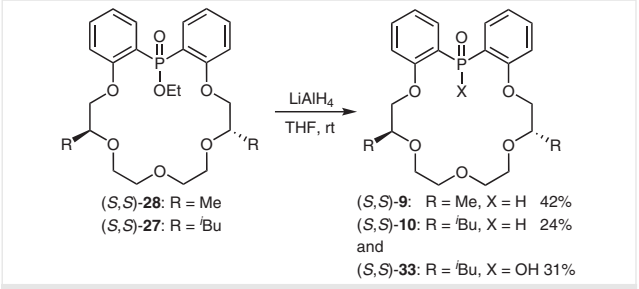
Due to the rather low yield of (*R*,*R*)-**24** (Scheme 3), we tried to obtain its phosphine derivative (*R*,*R*)-**5** by the macrocyclization reaction of phosphine **14** and tetraethylene glycol ditosylate (*S*,*S*)-**23** (Scheme 6). The latter procedure provided a slightly better overall yield of phosphine (*R*,*R*)-**5**. However, it has to be noted that in the purification of the crude product of this reaction we have to use PLC for isolating macrocycle (*R*,*R*)-**5**, because during the column chromatography it underwent oxidation. Because of the fact that during the long reaction time of the macrocyclization, the workup, and purification it was quite complicated to maintain the inert atmosphere, and therefore the direct cyclization process starting from **14** in other cases were not applied.

In order to accomplish the synthesis of secondary phosphine oxides (*S*,*S*)-**9** and (*S*,*S*)-**10**, the appropriate phosphinates (*S*,*S*)-**28** and (*S*,*S*)-**27** were reduced (Scheme 7). As we have already observed,[26] using lithium aluminum hydride as a reducing agent, first phosphine derivatives



Scheme 6 Ring-closing reaction of phosphine **14** and tetraethylene glycol ditosylate (*S*,*S*)-**23**

were obtained, which were oxidized by the air quantitatively to the secondary phosphine oxides during the workup and purification. Surprisingly, during the reduction of (*S*,*S*)-**27**, its hydrolysis was also observed as an undesirable side reaction giving phosphinic acid (*S*,*S*)-**33** as a product. We assume that this hydrolysis is caused by the lithium hydroxide formed from the lithium aluminum hydride in the presence of traces of water.



Scheme 7 Reduction of phosphinates to secondary phosphine oxides

In conclusion, new enantiopure crown ethers (*S*,*S*)-**3**, (*R*,*R*)-**4**, (*R*,*R*)-**5**, and (*S*,*S*)-**6** containing one phosphine unit, (*S*,*S*,*S*,*S*)-**7** and (*S*,*S*,*S*,*S*)-**8** containing two phosphine units, and (*S*,*S*)-**9** and (*S*,*S*)-**10** containing secondary phosphine oxide moiety (Figure 2) were synthesized. We have tried to improve their yields, wherever it was possible. Based on preliminary results[9] we assume that these macrocycles can be suitable catalytic ligands for asymmetric hydroformylation reactions.

All starting materials were purchased from Sigma-Aldrich Corporation unless otherwise noted. Compounds (*S*,*S*)-**18**,[17] (*S*,*S*)-**23**,[20] **26**,[21] and (*S*,*S*)-**28**[23] were prepared as reported. The heating source was an oil bath for the reactions that required heating and for the reactions that needed to be cooled to 0 °C an ice-water bath was used. All reactions were monitored by TLC and visualized by UV lamp (254 nm). Silica gel 60 F_{254} (Merck) plates were used for TLC. Silica gel 60 (70–230 mesh, Merck) was used for column chromatography, and silica gel 60 F_{254} (Merck) plates were used for PLC (preparative layer chroma-

tography). Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well established methods.[27] Evaporations were carried out under reduced pressure. Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin-Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. ^{1}H (500 MHz) and ^{13}C{^{1}H} (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. ^{1}H (300 MHz) and ^{13}C{^{1}H} (75.5 MHz) NMR spectra were recorded on a Bruker 300 Avance spectrometer and it is indicated in each individual case. ^{31}P (121.5 MHz, reference: H_3PO_4) NMR spectra were recorded on a Bruker 300 Avance spectrometer. HRMS analyses were performed on a Thermo Velos Pro Orbitrap Elite (Thermo Fisher Scientific, Bremen, Germany) system. The ionization method was ESI and operated in positive ion mode. The protonated molecular ion peaks were fragmented by CID at a normalized collision energy of 35%. The samples were dissolved in MeOH. Data acquisition and analysis were accomplished with Xcalibur software version 2.2 (Thermo Fisher Scientific). Suitable single crystals for X-ray analysis were obtained from a solution of crown ether (*S*,*S*)-**21** in $CHCl_3$/octane (1:9). X-ray data of a single crystal has been tested and collected on 100 K temperature, on a high flux micro-focus Cu sourced sealed tube SuperNova diffractometer equipped with Eos CCD detector, using monochromated Cu-Kα radiation, λ = 1.5418 Å (Rigaku/Agilent Technologies). CrysAlisPro RED[19a] was used for data processing, and Olex2 for structure solution with direct methods. Final structure is refined with Olex2[19b] and SHELXL9 program packages.[19c] Crystallographic data are presented in Table 1.[19]

Diphenyl phenylphosphonate (12)

Diphenyl phosphorochloridate (**11**; 25.0 g, 93 mmol) and toluene (25 mL) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. The mixture was cooled to 0 °C, and phenylmagnesium bromide (140 mmol, 93.5 mL, 1.5 M solution in Et_2O) was added dropwise. After stirring the reaction mixture for 10 min at 0 °C, the temperature was raised to rt, and kept for 3 h. The mixture was poured into a mixture of sat. aq NH_4Cl (300 mL) and CH_2Cl_2 (100 mL). The phases were shaken well, separated, and the organic phase was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1:5) as eluent to give **12** (11.1 g, 38%) as yellow crystals. The product had the same physical properties and spectroscopic data as reported in the literature.[16]

Bis(2-hydroxyphenyl)phenyl-λ^5-phosphanone (13)

To a vigorously stirred solution of freshly distilled pure and anhyd *i*-Pr_2NH (20 mL, 14.5 g, 0.14 mol) in pure and anhyd THF (30 mL) was added 2.5 M *n*-BuLi in hexanes (57 mL, 0.14 mol) at –75 °C under argon over 30 min, and stirring was continued for another 30 min. After the LDA solution had formed, diphenyl phenylphosphonate (**12**; 11.1 g, 35.8 mmol) dissolved in pure and anhyd THF (30 mL) was added over 60 min at –75 °C. The resulting mixture was stirred for 60 min, then it was allowed to warm up to rt and stirred for 4 h. After completion of the reaction, the mixture was added in small portions to a vigorously stirred mixture of CH_2Cl_2 (300 mL), sat. aq NH_4Cl (240 mL), and ice (100 g). The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with H_2O (200 mL), dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by recrystallization from toluene to give **13** (8.77 g, 79%) as a white powder. The product had the same physical properties and spectroscopic data as reported in the literature.[14]

(6*S*,7*S*)-6,7-Dimethyl-13-phenyl-7,13-dihydro-6*H*-dibenzo[*e*,*h*]-[1,4,7]dioxaphospha-13-one [(*S*,*S*)-21]

Phosphanone **13** (1.9 g, 6.13 mmol), butane-2,3-diol ditosylate [(*S*,*S*)-**20**; 2.40 g, 6.13 mmol] and finely powdered anhyd K_2CO_3 (10 g, 72 mmol) were mixed in anhyd DMSO (150 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 50 °C and kept at this temperature until the TLC analysis showed the total consumption of the starting materials (23 days). The solvent was removed, and the residue was dissolved in a mixture of H_2O (30 mL) and CH_2Cl_2 (30 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was first purified by column chromatography on silica gel using MeOH and CH_2Cl_2 mixtures (polarity raised from 1:40 to 1:10) as eluents, and then by recrystallization from CH_2Cl_2/hexane (1:9) to give (*S*,*S*)-**21** (201 mg, 9%) as colorless crystals; mp 258–261 °C; R_f = 0.42 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{25}$ –149.0 (*c* 0.2 CH_2Cl_2).

IR (KBr): 3061, 2969, 2867, 2206, 1589, 1573, 1472, 1440, 1371, 1238, 1183, 1159, 1087, 1075, 958, 835, 821, 755, 729, 637, 549, 521 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.31 (d, *J* = 6.3 Hz, 3 H, CH_3), 3.67–3.79 (m, 1 H), 4.08–4.14 (m, 1 H, OCH), 6.97–7.09 (m, 2 H, ArH), 7.23–7.29 (m, 1 H, ArH), 7.38–7.40 (m, 3 H, ArH), 7.45–7.57 (m, 5 H, ArH), 8.20–8.32 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.10, 18.25 (CH_3), 83.51, 86.39 (OCH), 119.63 (d, *J* = 7.1 Hz, ArC), 123.02 (d, *J* = 11.5 Hz, ArC), 123.75 (d, *J* = 7.1 Hz, ArC), 124.55 (d, *J* = 109 Hz, ArC), 124.86 (d, *J* = 11.1 Hz, ArC), 126.18 (d, *J* = 103 Hz, ArC), 128.00 (d, *J* = 13.0 Hz, ArC), 130.74 (d, *J* = 11.3 Hz, ArC), 131.00 (d, *J* = 2.9 Hz, ArC), 133.80 (d, *J* = 2.5 Hz, ArC), 134.21 (d, *J* = 2.3 Hz, ArC), 134.67 (d, *J* = 6.3 Hz, ArC), 135.68 (d, *J* = 5.8 Hz, ArC), 137.08 (d, *J* = 111 Hz, ArC), 160.07 (d, *J* = 4.0 Hz, ArC), 162.98 (d, *J* = 4.5 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.41.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}O_3P$: 365.1301; found: 365.1284.

(2*R*,2′*R*)-Dimethyl-2,2′-[ethane-1,2-diylbis(oxy)]dipropanoate [(*R*,*R*)-16]

(*S*)-2-Bromopropionic acid (5 g, 32.7 mmol) and anhyd and pure MeOH (50 mL) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. The mixture was cooled to –10 °C, and NaOMe (1.77 g, 32.7 mmol) dissolved in MeOH (50 mL) was added dropwise. The mixture was allowed to warm up to rt and stirred for 1 h, then the solvent was removed. The resulting sodium salt of (*S*)-2-bromopropionic acid was dried over P_2O_5 in a vacuum desiccator. NaH (2.62 g, 60% dispersion in mineral oil, 65.5 mmol), freshly distilled ethylene glycol (1.83 mL, 16.4 mmol), and anhyd and pure THF (100 mL) were placed in a three-necked flask under argon. The reaction mixture was boiled for 1 h, then it was cooled to 0 °C, and the previously prepared sodium salt of (*S*)-2-bromopropionic acid [(*S*)-**15**] was added to it, and the mixture was heated to 65 °C. After stirring the mixture for 24 h, it was cooled to 0 °C and its pH was adjusted to 2 using aq 2 mol/L HCl. This mixture was poured into a mixture of H_2O (30 mL) and CH_2Cl_2 (80 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 80 mL) and Et_2O (2 × 80 mL). The combined organic phases were dried ($MgSO_4$),

filtered, and the solvent was removed. The crude product was a yellow oil, which was placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. It was dissolved in MeOH (75 mL), then the solution was cooled to –30 °C and freshly distilled $SOCl_2$ (6.7 mL, 92 mmol) was added dropwise. The mixture was allowed to warm up to rt and stirred for 2 days, then the solvent was removed. EtOAc (200 mL) and sat. aq Na_2CO_3 (150 mL) were added to the residue. The phases were shaken well and separated. The organic phase was washed with brine (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using acetone/hexane (1:8) as eluent to give (*R*,*R*)-**16** (1.73 g, 45%) as a colorless oil; R_f = 0.34 (acetone/hexane 1:3); $[\alpha]_D^{22}$ +68.76 (*c* 1.03 CH_2Cl_2).

IR (neat): 2988, 2954, 2875, 1748, 1735, 1448, 1436, 1372, 1275, 1206, 1119, 1077, 1043, 978, 856, 754, 659 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.42–1.45 (m, 6 H, CH_3), 3.61–3.66 (m, 2 H, OCH_2), 3.75–3.80 (m, 8 H, OCH_2, OCH_3), 4.08–4.13 (m, 2 H, OCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.65 (CH_3), 51.88 (OCH_3), 69.50 (OCH_2), 75.30 (OCH), 173.68 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{19}O_6$: 235.1176; found: 235.1169.

(2*R*,2′*R*)-[Ethane-1,2-diylbis(oxy)]bis(propane-2,1-diyl)-bis(4-methylbenzenesulfonate) [(*R*,*R*)-17]

$LiAlH_4$ (390 mg, 10.3 mmol) and pure and anhyd THF (5 mL) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. The mixture was cooled to 0 °C, and (*R*,*R*)-**16** (1.0 g, 4.27 mmol) dissolved in THF (15 mL) was added dropwise. The mixture was allowed to warm up to rt and stirred for 24 h. After completion of the reaction, the mixture was worked up using Fieser's method,[28] because of the excellent water solubility of the product. The mixture was cooled to 0 °C, H_2O (390 µL) and 15% aq NaOH (390 µL), then H_2O (1.17 mL) were added to it. The mixture was allowed to warm up to rt and stirred for 15 min, then $MgSO_4$ was added and stirred for another 15 min. The mixture was filtered to remove the solid materials, which were washed with Et_2O. The filtrate was evaporated, then the residue was placed under argon in a three-necked flask and dissolved in CH_2Cl_2 (50 mL). TsCl (2.16 g, 11.3 mmol) and 10% aq KOH (5 mL) were added, and the reaction mixture was stirred for 2 days. H_2O (30 mL) was added to the mixture and the pH was adjusted to 3 using aq 2 mol/L HCl. The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1:6) as eluent, then by recrystallization from MeOH to give (*R*,*R*)-**17** (2.07 g, 74%) as white crystals; mp 97–100 °C; R_f = 0.57 (EtOAc/toluene 1:3); $[\alpha]_D^{23}$ +1.0, $[\alpha]_{365}^{23}$ +4.3 (*c* 5.0 CH_2Cl_2).

IR (KBr): 3422, 2929, 2882, 1598, 1461, 1357, 1324, 1294, 1258, 1189, 1179, 1161, 1121, 1095, 1075, 982, 909, 852, 830, 812, 792, 667, 584, 555, 544 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.3 Hz, 6 H, CH_3), 2.43 (s, 6 H, CH_3), 3.45–3.54 (m, 4 H, OCH_2), 3.63–3.69 (m, 2 H, OCH_2), 3.88–3.95 (m, 2 H, OCH), 7.32–7.34 (m, 4 H, ArH), 7.76–7.78 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.75, 21.67 (CH_3), 69.05, 72,67, 73.54 (OCH, OCH_2), 127.96, 129.88, 133.01, 144.85 (ArC).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{31}O_8S_2$: 487.1455; found: 487.1434.

(7*R*,12*R*)-7,12-Dimethyl-19-phenyl-6,7,9,10,12,13-hexahydro-19*H*-19λ^5-dibenzo[*k*,*n*][1,4,7,10,13]tetraoxaphosphacyclopentadecin-19-one [(*R*,*R*)-22]

Phosphanone **13** (0.64 g, 2.06 mmol), triethylene glycol ditosylate (*R*,*R*)-**17** (1.0 g, 2.06 mmol), and finely powdered anhyd Na_2CO_3 (5.3 g, 50 mmol) or K_2CO_3 (6.9 g, 50 mmol) were mixed in anhyd and pure DMF (100 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 80 °C and kept at this temperature until TLC analysis showed the total consumption of the starting materials (11 days). The solvent was removed and the residue was dissolved in H_2O (30 mL) and CH_2Cl_2 (30 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using MeOH and CH_2Cl_2 mixtures (polarity raised from 1:30 to 1:10) as eluents to give (*R*,*R*)-**22** [using Na_2CO_3: 316 mg (17%), using K_2CO_3: 576 mg (31%)] as a white powder; mp 115–119 °C; R_f = 0.28 (CH_2Cl_2/MeOH 30:1); $[\alpha]_D^{28}$ +18.45 (*c* 0.68 CH_2Cl_2).

IR (KBr): 3421, 3063, 2971, 2929, 2869, 2204, 1589, 1575, 1477, 1440, 1374, 1344, 1282, 1238, 1159, 1140, 1108, 1085, 1069, 1045, 1027, 959, 931, 906, 833, 821, 800, 753, 728, 715, 702, 642, 549, 537, 517 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.88–0.96 (m, 6 H, CH_3), 3.39–3.48 (m, 1 H), 3.59–3.67 (m, 2 H), 3.72–3.83 (m, 2 H), 3.87–4.07 (m, 5 H, OCH, OCH_2), 6.64–6.79 (m, 2 H, ArH), 6.86–7.03 (m, 4 H, ArH), 7.19–7.40 (m, 7 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.67, 15.79 (CH_3), 68.80, 69.31, 70.42, 71.68, 75.16, 75.53 (OCH, OCH_2), 112.15 (d, *J* = 6.6 Hz, ArC), 112.46 (d, *J* = 6.6 Hz, ArC), 120.14 (d, *J* = 12.3 Hz, ArC), 127.92 (d, *J* = 12.7 Hz, ArC), 131.01 (d, *J* = 2.7 Hz, ArC), 132.13 (d, *J* = 10.3 Hz, ArC), 132.44 (d, *J* = 2.0 Hz, ArC), 132.97 (d, *J* = 1.7 Hz, ArC), 133.66 (d, *J* = 8.0 Hz, ArC), 133.94 (d, *J* = 8.4 Hz, ArC), 159.83 (d, *J* = 4.6 Hz, ArC), 160.52 (d, *J* = 7.1 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.86.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}O_5P$: 453.1825; found: 453.1805.

(2*S*,10*S*)-2,10-Diisobutyl-3,6,9-trioxaundecane-1,11-diyl-bis(4-methylbenzenesulfonate) [(*S*,*S*)-19]

Tetraethylene glycol derivative (*S*,*S*)-**18**[17] (3.20 g, 10.45 mmol) was placed under argon in a three-necked flask, and dissolved in CH_2Cl_2 (30 mL). TsCl (5.98 g, 31.35 mmol) and 10% aq KOH (10 mL) were added to this mixture and stirred for 3 days. H_2O (40 mL) was added and the pH was adjusted to 3 using aq 2 mol/L HCl. The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel using EtOAc/hexane (1:8) as eluent to give (*S*,*S*)-**19** (4.68 g, 83%) as a colorless oil; R_f = 0.54 (EtOAc/hexane 1:2); $[\alpha]_D^{26}$ –13.7 (*c* 1.0 CH_2Cl_2).

IR (neat): 2955, 2928, 2870, 1598, 1467, 1358, 1307, 1292, 1189, 1175, 1136, 1096, 1020, 975, 946, 913, 836, 813, 789, 690, 665, 553 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.90 (m, 12 H, CH_3), 1.12–1.21 (m, 2 H, CH_2), 1.37–1.46 (m, 2 H, CH_2), 1.64–1.75 (m, 2 H, CH), 2.46 (s, 6 H, CH_3), 3.50–3.70 (m, 10 H), 3.94–4.04 (m, 4 H, OCH, OCH_2), 7.36 (d, *J* = 7.9 Hz, 4 H, ArH), 7.81 (d, *J* = 8.2 Hz, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.67, 22.17, 23.18 (CH_3) 24.28 (CH), 40.66 (CH_2), 69.81, 70.75, 72.07, 76.10 (OCH, OCH_2), 127.97, 129.88, 133.03, 144.84 (ArC).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{47}O_9S_2$: 615.2656; found: 615.2633.

(7*S*,15*S*)-7,15-Diisobutyl-22-ethoxy-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-27]

Ethyl phosphinate **26**[21] (1.07 g, 3.86 mmol), tetraethylene glycol ditosylate (*S*,*S*)-**19** (2.37 g, 3.86 mmol), and finely powdered anhyd K_2CO_3 (13.8 g, 100 mmol) were mixed in anhyd DMF (200 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 80 °C and kept at this temperature until TLC analysis showed the total consumption of the starting materials (12 days). The solvent was removed, and the residue was dissolved in a mixture of H_2O (50 mL) and CH_2Cl_2 (50 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using MeOH/CH_2Cl_2 (1:50) as eluent to give (*S*,*S*)-**27** (996 mg, 47%) as a colorless oil; R_f = 0.14 (CH_2Cl_2/MeOH 40:1); $[\alpha]_D^{25}$ +29.4 (*c* 1.0 CH_2Cl_2).

IR (neat): 2953, 2929, 2868, 1677, 1590, 1577, 1474, 1442, 1386, 1367, 1280, 1242, 1216 1142, 1090, 1023, 950, 832, 755, 732, 711, 566, 555, 516 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.70–0.85 (m, 12 H, CH_3), 1.03–1.09 (m, 1 H, CH_2), 1.12–1.18 (m, 1 H, CH_2), 1.22–1.30 (m, 5 H, CH_2, CH_3), 1.51–1.66 (m, 2 H, CH), 2.84–2.88 (m, 1 H), 2.97–3.08 (m, 3 H), 3.21–3.31 (m, 5 H), 3.41–3.45 (m, 1 H), 3.67–3.76 (m, 2 H), 3.87–3.95 (m, 1 H), 4.02–4.16 (m, 3 H, OCH, OCH_2), 6.92–7.02 (m, 4 H, ArH), 7.37–7.43 (m, 2 H, ArH), 7.84–8.00 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.52 (d, *J* = 6.8 Hz, CH_3), 22.48, 22.51, 23.16, 23.36 (CH_3) 24.57, 24.59 (CH), 40.89, 41.83 (CH_2), 60.37 (d, *J* = 5.6 Hz, OCH_2) 70.18, 70.39, 70.69, 70.80 (OCH_2), 72.32 (OCH), 78.21, 78.38 (OCH_2), 112.37 (d, *J* = 7.5 Hz, ArC), 112.78 (d, *J* = 8.1 Hz, ArC), 120.01 (d, *J* = 58 Hz, ArC), 120.12 (d, *J* = 2.8 Hz, ArC), 120.29 (d, *J* = 1.7 Hz, ArC), 121.89 (d, *J* = 68 Hz, ArC), 133.09 (d, *J* = 1.6 Hz, ArC), 133.41 (d, *J* = 0.5 Hz, ArC), 133.46 (d, *J* = 2.3 Hz, ArC), 135.27 (d, *J* = 7.9 Hz, ArC), 160.40 (d, *J* = 3.3 Hz, ArC), 160.90 (d, *J* = 4.8 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.02.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{46}O_7P$: 549.2981; found: 549.2956.

(7*S*,15*S*)-7,15-Diisobutyl-22-phenyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-25]

Starting from (*S*,*S*)-19

Phosphanone **13** (0.51 g, 1.63 mmol), tetraethylene glycol ditosylate (*S*,*S*)-**19** (1.0 g, 1.63 mmol), and finely powdered anhyd K_2CO_3 (6.9 g, 50 mmol) or Cs_2CO_3 (9.77 g, 30 mmol) were mixed in anhyd and pure DMF (100 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 80 °C and kept at this temperature until the TLC analysis showed the total consumption of the starting materials (10 days). The solvent was removed, then the residue was dissolved in a mixture of H_2O (20 mL) and CH_2Cl_2 (20 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using MeOH/CH_2Cl_2 (1:50) as eluent to give (*S*,*S*)-**25** [using K_2CO_3: 316 mg (33%), using Cs_2CO_3: 328 mg (34%)] as a pale yellow oil; R_f = 0.19 (CH_2Cl_2/MeOH 40:1); $[\alpha]_D^{24}$ +21.6 (*c* 1.0 CH_2Cl_2).

IR (neat): 3392, 3063, 2954, 2926, 2722, 1589, 1576, 1474, 1440, 1387, 1367, 1354, 1281, 1245, 1188, 1136, 1107, 1085, 1044, 1019, 950, 831, 755, 734, 714, 703, 607, 554, 515 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74–0.86 (m, 12 H, CH_3), 1.05–1.32 (m, 4 H, CH_2), 1.48–1.66 (m, 2 H, CH), 2.70–2.78 (m, 1 H), 3.01–3.08 (m, 1 H), 3.18–3.59 (m, 8 H), 3.72–3.83 (m, 2 H), 4.00–4.18 (m, 2 H, OCH, OCH_2), 6.91–7.07 (m, 4 H, ArH), 7.33–7.52 (m, 6 H, ArH), 7.76–7.83 (m, 1 H, ArH), 7.96–8.03 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.58, 22.64, 23.16, 23.24 (CH_3) 24.64 (CH), 41.00, 41.65 (CH_2), 70.54, 70.91, 70.96, 71.05, 71.79, 73.06, 77.95, 78.62 (OCH, OCH_2), 112.52 (d, *J* = 6.6 Hz, ArC), 113.48 (d, *J* = 6.4 Hz, ArC), 120.68 (d, *J* = 12.4 Hz, ArC), 122.06 (d, *J* = 89 Hz, ArC), 123.49 (d, *J* = 89 Hz, ArC), 128.01 (d, *J* = 12 Hz, ArC), 131.18 (d, *J* = 2.8 Hz, ArC), 132.13 (d, *J* = 10 Hz, ArC), 132.99 (d, *J* = 2.2 Hz, ArC), 133.11 (d, *J* = 2.3 Hz, ArC), 133.25 (d, *J* = 67 Hz, ArC), 134.07 (d, *J* = 25 Hz, ArC), 160.13 (d, *J* = 3.3 Hz, ArC), 161.20 (d, *J* = 2.4 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.82.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{46}O_6P$: 581.3027; found: 581.3000.

Starting from [(*S*,*S*)-27]

To a solution of macrocycle (*S*,*S*)-**27** (0.15 g, 0.27 mmol) in anhyd and pure CH_2Cl_2 (8 mL) was added PCl_5 (71 mg, 0.34 mmol) under argon. The mixture was stirred at reflux temperature for 3 h and then at rt for 15 min. The volatile components were removed and anhyd toluene (5 mL) and anhyd Et_2O (5 mL) were added to the residue under argon. The stirred mixture was cooled to 0 °C and PhMgBr (0.81 mmol, 0.27 mL, 3.0 M in Et_2O) was added dropwise to it. After stirring the reaction mixture for 10 min at 0 °C, the temperature was raised to rt and kept for 24 h. The mixture was poured into ice-water (12 mL) then CH_2Cl_2 (10 mL) was added. The phases were shaken well, separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by PLC on silica gel using MeOH/CH_2Cl_2 (1:40) as eluent to give (*S*,*S*)-**25** (103 mg, 65%), which had the same physical properties and spectroscopic data as the one described above.

(6*R*,16*R*)-6,16-Diisobutyl-22-phenyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*R*,*R*)-24]

Phosphanone **13** (0.70 g, 2.23 mmol), tetraethylene glycol ditosylate (*S*,*S*)-**23**[20] (1.37 g, 2.23 mmol) and finely powdered anhyd K_2CO_3 (8.0 g, 58 mmol) were mixed in anhyd and pure DMF (130 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 50 °C and kept at this value until TLC analysis showed the total consumption of the starting materials (18 days). The solvent was removed, and the residue was dissolved in a mixture of H_2O (30 mL) and CH_2Cl_2 (30 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using MeOH/CH_2Cl_2 (1:50) as eluent to give (*R*,*R*)-**24** (66 mg, 5%) as pale yellow crystals; mp 149–152 °C; R_f = 0.27 (CH_2Cl_2/MeOH 30:1); $[\alpha]_D^{22}$ –52.9 (*c* 0.7 CH_2Cl_2).

IR (KBr): 3063, 2954, 2907, 2865, 1587, 1574, 1472, 1441, 1367, 1275, 1244, 1192, 1139, 1112, 1081, 1066, 1044, 989, 940, 861, 792, 755, 720, 702, 612, 552, 513, 501 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 9 H, CH_3), 0.93–0.95 (m, 3 H, CH_3), 1.04–1.10 (m, 1 H), 1.19–1.29 (m, 2 H), 1.37–1.43 (m, 1 H), 1.62–1.70 (m, 1 H), 1.82–1.90 (m, 1 H, CH, CH_2), 2.97–3.00 (m, 1 H), 3.06–3.10 (m, 1 H), 3.20–3.31 (m, 3 H), 3.43–3.53 (m, 4 H), 3.55–3.59 (m, 1 H), 3.63–3.67 (m, 1 H), 4.44–4.51 (m, 2 H, OCH, OCH_2), 6.86–6.87 (m, 1 H, ArH), 7.00–7.09 (m, 3 H, ArH), 7.20–7.25 (m, 1 H, ArH), 7.36–7.39 (m, 1 H, ArH), 7.42–7.53 (m, 4 H, ArH), 8.02–8.09 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.89, 22.54, 23.03, 23.43 (CH_3) 24.10, 24.30 (CH), 40.40, 41.36 (CH_2), 70.74, 70.83, 71.08, 71.59, 71.96, 73.44, 73.81, 75.25 (OCH, OCH_2), 111.39 (d, *J* = 6.8 Hz, ArC), 112.42 (d, *J* = 6.2 Hz, ArC), 119.62 (d, *J* = 12.9 Hz, ArC), 120.32 (d, *J* = 11.8 Hz, ArC), 121.98 (d, *J* = 89 Hz, ArC), 123.41 (d, *J* = 91 Hz, ArC), 127.85 (d, *J* = 12.4 Hz, ArC), 131.30 (d, *J* = 2.7 Hz, ArC), 132.51 (d, *J* = 109 Hz, ArC), 132.62 (d, *J* = 10.1 Hz, ArC), 132.88 (d, *J* = 6.0 Hz, ArC), 132.88 (d, *J* = 2.6 Hz, ArC), 133.84 (d, *J* = 9.7 Hz, ArC), 134.96 (d, *J* = 6.2 Hz, ArC), 158.45 (d, *J* = 3.7 Hz, ArC), 160.66 (d, *J* = 1.7 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.14.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{46}O_6P$: 581.3027; found: 581.3008.

(7*S*,15*S*)-22-[4-(Benzyloxy)phenyl]-7,15-dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*]-[1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-29]

To a solution of macrocycle (*S*,*S*)-**28** (1.2 g, 2.59 mmol) in anhyd and pure CH_2Cl_2 (40 mL) was added PCl_5 (642 mg, 3.11 mmol) under argon. The mixture was stirred at reflux temperature for 3 h. The volatile components were removed and anhyd and pure toluene (15 mL) and Et_2O (10 mL) were added to the residue under argon. The stirred mixture was cooled to 0 °C and a solution of 4-benzyloxyphenylmagnesium bromide (6.48 mmol, 6.5 mL, 1 M in THF) was added dropwise. After stirring the reaction mixture for 20 min at 0 °C, it was let to warm up to rt and kept stirring at rt for 24 h. The mixture was poured into ice-water (60 mL) and CH_2Cl_2 (50 mL) was added. The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by column chromatography on silica gel using MeOH/CH_2Cl_2 (1:40) as eluent to give (*S*,*S*)-**29** (1.12 g, 72%) as a yellow oil; R_f = 0.44 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{28}$ +29.2 (*c* 0.76, CH_2Cl_2).

IR (neat): 1595, 1588, 1577, 1570, 1501, 1477, 1473, 1466, 1438, 1289, 1274, 1249, 1228, 1175, 1166, 1131, 1111, 1083, 1072, 1065, 1009, 969, 924, 856, 832, 825, 808, 755, 735, 702, 692, 586, 546, 520, 501, 486 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.79–2.85 (m, 1 H), 3.09–3.24 (m, 3 H), 3.33–3.61 (m, 6 H), 3.69–3.74 (m, 1 H), 3.79–3.84 (m, 1 H), 3.96–4.02 (m, 1 H), 4.12–4.17 (m, 1 H, OCH, OCH_2), 5.12 (s, PhCH_2), 6.94–7.07 (m, 6 H, ArH), 7.31–7.49 (m, 8 H, ArH), 7.75–7.83 (m, 1 H, ArH), 7.89–7.97 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.01, 17.40 (CH_3), 69.56, 69.89, 69.93, 70.20, 70.39, 70.92, 70.97, 75.05, 75.47 (OCH, OCH_2), 112.37 (d, *J* = 6.5 Hz, ArC), 112.83 (d, *J* = 6.5 Hz, ArC), 114.49 (d, *J* = 13.7 Hz, ArC), 120.45 (d, *J* = 1.9 Hz, ArC), 120.61 (d, *J* = 2.2 Hz, ArC), 127.44 (s, Bn-ArC), 128.10 (s, Bn-ArC), 128.65 (s, Bn-ArC), 132.88 (d, *J* = 1.7 Hz, ArC), 133.09 (d, *J* = 0.6 Hz, ArC), 133.84 (d, *J* = 0.6 Hz, ArC), 133.96 (d, *J* = 1.2 Hz, ArC), 133.94 (d, *J* = 11.5 Hz, ArC), 136.61 (s, Bn-ArC) 160.12 (d, *J* = 3.1 Hz, ArC), 160.80 (d, *J* = 2.5 Hz, ArC), 161.13 (d, *J* = 3.0 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.15.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{40}O_7P$: 603.2506; found: 603.2484.

(7*S*,15*S*)-22-(4-Hydroxyphenyl)-7,15-dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*]-[1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-30]

To Pd/C catalyst (10% Pd on charcoal, 270 mg) was added MeOH (10 mL) under argon. After argon was exchanged by H_2, the mixture was stirred under atmospheric H_2 for 10 min. A solution of (*S*,*S*)-**29** (1.10 g, 1.82 mmol) in MeOH (40 mL) was added to the prehydrogenated catalyst and this mixture was stirred vigorously until the consumption of H_2 stopped. H_2 was exchanged by argon, and the mixture was filtered using a Celite pad. The solvent was removed to obtain pure (*S*,*S*)-**30** (916 mg, 98%) as a pale yellow solid; mp 145–147 °C; R_f = 0.24 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{29}$ +50.2 (*c* 0.60, CH_2Cl_2).

IR (KBr): 3064, 2972, 2934, 2874, 1728, 1590, 1575, 1504, 1475, 1441, 1375, 1349, 1281, 1242, 1134, 1109, 1085, 1025, 994, 972, 837, 756, 700, 552, 505 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 6 H, CH_3), 2.87–2.96 (m, 1 H), 3.17–3.25 (m, 3 H), 3.39–3.58 (m, 6 H), 3.70–3.77 (m, 2 H), 3.94–4.00 (m, 2 H, OCH, OCH_2), 5.18 (br s, OH), 6.83–6.97 (m, 6 H, ArH), 7.12–7.20 (m, 1 H, ArH), 7.35–7.42 (m, 2 H, ArH), 7.50–7.65 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.72, 17.13 (CH_3), 69.37, 70.86, 71.64, 72.71, 74.93, 75.07 (OCH, OCH_2), 112.39 (d, *J* = 6.1 Hz, ArC), 112.61 (d, *J* = 7.7 Hz, ArC), 116.35 (d, *J* = 13.6 Hz, ArC), 120.34 (d, *J* = 13.7 Hz, ArC), 120.70 (d, *J* = 11.5 Hz, ArC), 133.04 (d, *J* = 2.3 Hz, ArC), 133.18 (d, *J* = 2.6 Hz, ArC), 133.72 (d, *J* = 0.6 Hz, ArC), 133.66 (d, *J* = 11.8 Hz, ArC), 133.69 (d, *J* = 1.0 Hz, ArC), 160.14 (d, *J* = 2.9 Hz, ArC), 161.02 (d, *J* = 1.8 Hz, ArC), 162.72 (d, *J* = 3.7 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{34}O_7P$: 513.2037; found: 513.2016.

(7*S*,7′*S*,15*S*,15′*S*)-22,22′-{[Propane-1,3-diylbis(oxy)]bis(4,1-phenylene)}bis(7,15-dimethyl-7,9,10,12,13,15,16,22-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one) [(*S*,*S*,*S*,*S*)-31]

Macrocycle (*S*,*S*)-**30** (150 mg, 0.29 mmol), anhyd and pure DMF (5 mL), and finely powdered anhyd K_2CO_3 (300 mg, 1.81 mmol) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. This solution was stirred for 30 min, then cooled to 0 °C, and propane-1,3-diyl-bis(4-methylbenzenesulfonate) (57.6 mg, 0.15 mmol) or 1,3-diiodopropane (44.3 mg, 0.15 mmol), or 1,3-dibromopropane (30.0 mg, 0.15 mmol) dissolved in DMF (8 mL) was added dropwise. The resulting mixture was warmed up to 50 °C and stirred for 3 days. The solvent was removed, and the residue was dissolved in a mixture of H_2O (15 mL) and CH_2Cl_2 (15 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by PLC on silica gel using MeOH/CH_2Cl_2 (1:20) as eluent to give (*S*,*S*,*S*,*S*)-**31** [using propane-1,3-diol-ditosylate: 68.6 mg (44%); using 1,3-diiodopropane: 35.5 mg (23%); using 1,3-dibromopropane: 89.5 mg (58%)] as a pale yellow powder; mp 93–95 °C; R_f = 0.39 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{27}$ +27.3 (*c* 1.1 CH_2Cl_2).

IR (KBr): 3364, 3242, 3066, 2969, 2930, 2873, 1589, 1575, 1501, 1474, 1441, 1374, 1345, 1282, 1241, 1177, 1134, 1109, 1086, 1069, 1045, 1023, 967, 833, 757, 700, 555, 505 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.3 Hz, 6 H, CH_3), 0.98 (d, *J* = 6.4 Hz, 6 H, CH_3), 2.29 (pent, *J* = 6.1 Hz, 2 H, CH_2), 2.78–2.83 (m, 2 H), 3.11–3.15 (m, 4 H), 3.21–3.26 (m, 2 H), 3.37–3.53 (m, 10 H), 3.58–3.62 (m, 2 H), 3.68–3.72 (m, 2 H), 3.80–3.83 (m, 2 H), 3.99–4.02 (m, 2 H), 4.12–4.22 (m, 6 H, OCH, OCH_2), 6.93–7.05 (m, 12 H, ArH), 7.37–7.46 (m, 6 H, ArH), 7.81–7.85 (m, 2 H, ArH), 7.90–7.94 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.03, 17.51 (CH_3), 29.08 (CH_2), 64.26, 69.58, 69.92, 71.23, 71.42, 71.93, 72.95, 75.08, 75.42 (OCH, OCH_2), 112.27 (d, *J* = 6.5 Hz, ArC), 112.83 (d, *J* = 6.2 Hz, ArC), 114.07 (d, *J* = 13.4 Hz, ArC), 115.47 (ArC), 120.44 (d, *J* = 11.3 Hz, ArC), 120.54 (d, *J* = 10.8 Hz, ArC), 122.29 (d, *J* = 108 Hz, ArC), 123.54 (d, *J* = 108 Hz, ArC), 124.88 (d, *J* = 115 Hz, ArC), 128.91 (ArC), 132.77 (ArC), 132.96 (d, *J* = 1.7 Hz, ArC), 133.69, 133.76, 133.80, 133.86, 133.90 (ArC), 159.94 (d, *J* = 3.2 Hz, ArC), 160.82 (d, *J* = 2.3 Hz, ArC), 161.15 (d, *J* = 2.9 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.55.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{59}H_{71}O_{14}P_2$: 1065.4314; found: 1065.4278.

(7*S*,7′*S*,15*S*,15′*S*)-22,22′-{[Butane-1,4-diylbis(oxy)]bis(4,1-phenylene)}bis(7,15-dimethyl-7,9,10,12,13,15,16,22-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one) [(*S*,*S*,*S*,*S*)-32]

Macrocycle (*S*,*S*)-**30** (300 mg, 0.59 mmol), pure and anhyd DMF (10 mL), and finely powdered anhyd K_2CO_3 (500 mg, 3.62 mmol) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. This mixture was stirred for 30 min, and cooled to 0 °C, and 1,4-dibromobutane (65.0 mg, 0.30 mmol) dissolved in anhyd and pure DMF (15 mL) was added dropwise. The resulting mixture was warmed up to 50 °C and stirred for 3 days. The solvent was removed, then the residue was dissolved in a mixture of H_2O (20 mL) and CH_2Cl_2 (20 mL). The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by PLC on silica gel using MeOH/CH_2Cl_2 (1:20) as eluent to give (*S*,*S*,*S*,*S*)-**32** (226 mg, 71%) as a colorless oil; R_f = 0.28 (CH_2Cl_2/ MeOH 20:1); $[\alpha]_D^{27}$ +36.2 (*c* 0.87, CH_2Cl_2).

IR (neat): 3065, 2967, 2930, 2872, 1589, 1574, 1501, 1475, 1441, 1376, 1345, 1281, 1244, 1177, 1134, 1109, 1022, 968, 830, 756, 693, 555, 505 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.3 Hz, 3 H, CH_3), 0.97 (t, *J* = 6.3 Hz, 3 H, CH_3), 1.97–2.01 (m, 4 H), 2.79–2.83 (m, 2 H), 3.10–3.27 (m, 6 H), 3.35–3.53 (m, 10 H), 3.57–3.72 (m, 4 H), 3.78–3.83 (m, 2 H), 3.98–4.16 (m, 8 H, OCH, OCH_2), 6.91–7.06 (m, 12 H, ArH), 7.36–7.47 (m, 6 H, ArH), 7.80–7.95 (m, 6 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.09, 17.58 (CH_3), 25.92 (CH_2), 67.46, 69.63, 69.99, 71.28, 71.47, 71.99, 73.01, 75.13, 75.47 (OCH, OCH_2), 112.44 (d, *J* = 8.1 Hz, ArC), 112.88 (d, *J* = 5.5 Hz, ArC), 114.09 (d, *J* = 13.7 Hz, ArC), 120.44 (d, *J* = 8.1 Hz, ArC), 120.60 (d, *J* = 7.2 Hz, ArC), 122.36 (d, *J* = 94 Hz, ArC), 123.59 (d, *J* = 65 Hz, ArC), 124.98 (d, *J* = 84 Hz, ArC), 132.85 (d, *J* = 15.0 Hz, ArC), 133.76 (d, *J* = 7.0 Hz, ArC), 133.89 (d, *J* = 9.4 Hz, ArC), 159.96 (d, *J* = 2.9 Hz, ArC), 160.87 (d, *J* = 2.1 Hz, ArC), 161.34 (d, *J* = 2.8 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.44.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{60}H_{73}O_{14}P_2$: 1079.4470; found: 1079.4426.

Reduction of Phosphine Oxides; General Procedure

Phosphine oxide and silane (1.5 mL for 100 mg phosphine oxide) were mixed with vigorous stirring in a sealed tube under argon. The temperature of the reaction mixture was raised to 150 °C and kept stirring at this temperature for 3 days. The volatile components were removed, and the crude product was purified by PLC on silica gel as described below for each compound.

(6*S*,7*S*)-6,7-Dimethyl-13-phenyl-7,13-dihydro-6*H*-dibenzo[*e*,*h*]-[1,4,7]dioxaphosphine [(*S*,*S*)-3]

Phosphine (*S*,*S*)-**3** was prepared from phosphine oxide (*S*,*S*)-**21** (180 mg, 0.49 mmol) using trimethoxysilane as a reducing agent. The eluent was EtOAc/hexane (1:8). Phosphine (*S*,*S*)-**3** (150 mg, 88%) was obtained as white crystals; mp 149–152 °C; R_f = 0.50 (EtOAc/hexane 1:4); $[\alpha]_D^{23}$ –123.6 (*c* 0.3 CH_2Cl_2).

IR (KBr): 3140, 3058, 2965, 2867, 2052, 1901, 1795, 1583, 1570, 1469, 1440, 1384, 1376, 1271, 1236, 1130, 1091, 1073, 1029, 945, 837, 762, 613, 540, 497, 468 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.48 (d, *J* = 6.3 Hz, 3 H, CH_3), 4.07–4.18 (m, 2 H, OCH), 6.90–6.93 (m, 2 H, ArH), 6.99–7.04 (m, 2 H, ArH), 7.11–7.14 (m, 1 H, ArH), 7.19–7.22 (m, 1 H, ArH), 7.26–7.29 (m, 1 H, ArH), 7.34–7.37 (m, 1 H, ArH), 7.43–7.46 (m, 3 H, ArH), 7.72–7.75 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.46, 18.54 (CH_3), 84.62, 87.22 (OCH), 120.36 (d, *J* = 2.1 Hz, ArC), 123.60 (d, *J* = 3.1 Hz, ArC), 123.70 (d, *J* = 8.7 Hz, ArC), 128.66 (d, *J* = 8.9 Hz, ArC), 129.27, 129.80, 130.92, 133.79 (d, *J* = 0.8 Hz, ArC), 133.92 (d, *J* = 13.5 Hz, ArC), 135.98, 136.29, 161.25 (d, *J* = 6.1 Hz, ArC), 164.90 (d, *J* = 16.3 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –19.26.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}O_2P$: 349.1335; found: 349.1352.

(7*R*,12*R*)-7,12-Dimethyl-19-phenyl-6,7,9,10,12,13-hexahydro-19*H*-19λ^5-dibenzo[*k*,*n*][1,4,7,10,13]tetraoxaphosphacyclopentadecine [(*R*,*R*)-4]

Phosphine (*R*,*R*)-**4** was prepared from phosphine oxide (*R*,*R*)-**22** (300 mg, 0.66 mmol) using trimethoxysilane. The eluent was CH_2Cl_2/MeOH (80:1). Phosphine (*R*,*R*)-**4** (230 mg, 80%) was obtained as white crystals; mp 124–126 °C; R_f = 0.60 (CH_2Cl_2/MeOH 30:1); $[\alpha]_D^{21}$ –107.1 (*c* 0.7 CH_2Cl_2).

IR (KBr): 3140, 3056, 2969, 2926, 2871, 2532, 2052, 1959, 1915, 1823, 1791, 1704, 1583, 1572, 1470, 1440, 1385, 1375, 1346, 1321, 1273, 1226, 1131, 1092, 1073, 1027, 924, 910, 858, 835, 818, 762, 689, 609, 524, 506, 496, 469, 425, 413 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 1.07–1.10 (m, 6 H, CH_3), 2.87–3.21 (m, 4 H) 3.52–3.72 (m, 4 H), 4.00–4.18 (m, 2 H, OCH, OCH_2), 6.94–7.03 (m, 3 H, ArH), 7.06–7.11 (m, 1 H, ArH), 7.39–7.47 (m, 5 H, ArH), 7.53–7.61 (m, 1 H, ArH), 7.69–7.77 (m, 1 H, ArH), 8.05–8.12 (m, 2 H, ArH).

^{13}C NMR (75 MHz, CD_3CN): δ = 15.86, 16.42 (CH_3), 68.41 (d, *J* = 1.9 Hz), 69.39 (d, *J* = 6.1 Hz), 72.33 (d, *J* = 1.3 Hz), 73.24, 74.45 (d, *J* = 1.2 Hz), 75.46 (OCH, OCH_2), 111.80 (d, *J* = 1.5 Hz, ArC), 112.15 (d, *J* = 2.2 Hz, ArC), 120.96 (d, *J* = 8.0 Hz, ArC), 125.46 (d, *J* = 13.8 Hz, ArC), 126.58 (d, *J* = 15.5 Hz, ArC), 128.50, 128.60 (d, *J* = 1.1 Hz, ArC), 133.52 (d, *J* = 0.8 Hz, ArC), 133.81, 134.06 (d, *J* = 2.2 Hz, ArC), 134.09, 136.95 (d, *J* = 14.3 Hz, ArC), 160.09 (d, *J* = 17.3 Hz, ArC), 161.33 (d, *J* = 18.8 Hz, ArC).

^{31}P NMR (121.5 MHz, CD_3CN): δ = –32.73.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}O_4P$: 437.1876; found: 437.1854.

(6*R*,16*R*)-6,16-Diisobutyl-22-phenyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecine [(*R*,*R*)-5]

Starting from (*R*,*R*)-24

Phosphine (*R*,*R*)-**5** was prepared from phosphine oxide (*R*,*R*)-**24** (60 mg, 0.10 mmol) using trimethoxysilane. The eluent was CH_2Cl_2/MeOH (120:1). Phosphine (*R*,*R*)-**5** (43 mg, 74%) was obtained as a pale yellow oil; R_f = 0.38 (CH_2Cl_2/MeOH 120:1); $[\alpha]_D^{25}$ –312.5 (*c* 0.2 CH_2Cl_2).

IR (neat): 3059, 3010, 2954, 2906, 2865, 1723, 1581, 1569, 1469, 1438, 1367, 1298, 1269, 1239, 1196, 1141, 1116, 1090, 1065, 1041, 998, 990, 939, 817, 794, 753, 725, 698, 612, 550, 499, 492 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68–0.70 (m, 6 H, CH_3), 0.85–0.89 (m, 6 H, CH_3), 1.10–1.55 (m, 6 H, CH, CH_2), 3.45–3.69 (m, 12 H, OCH_2), 4.47–4.55 (m, 2 H, OCH), 6.81–6.97 (m, 6 H, ArH), 7.30–7.48 (m, 7 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.16, 22.65, 22.99, 23.20 (CH_3), 23.98, 24.52 (CH), 38.71, 40.16 (CH_2), 70.29, 71.10, 71.12, 71.86, 72.08, 73.55, 75.07, 76.16 (OCH, OCH_2), 111.27 (d, *J* = 2.2 Hz, ArC), 111.48 (d, *J* = 2.1 Hz, ArC), 120.11 (d, *J* = 1.9 Hz, ArC), 120.73 (d, *J* = 4.6 Hz, ArC), 128.34 (d, *J* = 8.0 Hz, ArC), 129.01, 130.17, 130.56, 133.65, 134.64 (d, *J* = 20.2 Hz, ArC), 135.38 (d, *J* = 10.5 Hz, ArC), 159.68 (d, *J* = 6.5 Hz, ArC), 159.85 (d, *J* = 10.5 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –21.35.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{46}O_5P$: 565.3078; found: 565.3058.

Starting from (*S*,*S*)-23

Phosphine **14** (152 mg, 0.52 mmol), tetraethylene glycol ditosylate (*S*,*S*)-**23**[20] (319 mg, 0.52 mmol) and finely powdered anhyd K_2CO_3 (2.0 g, 14.5 mmol) were mixed in anhyd and pure DMF (30 mL) under argon. The temperature of the vigorously stirred reaction mixture was raised to 50 °C and kept at this value until TLC analysis showed the total consumption of the starting materials (6 days). The solvent was removed, and the residue was dissolved in a mixture of H_2O (15 mL) and CH_2Cl_2 (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by PLC using MeOH/CH_2Cl_2 (1:50) as eluent to give (*R*,*R*)-**5** (32 mg, 11%), which had the same physical properties and spectroscopic data as described above.

(7*S*,15*S*)-7,15-Diisobutyl-22-phenyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecine [(*S*,*S*)-6]

Phosphine (*S*,*S*)-**6** was prepared from phosphine oxide (*S*,*S*)-**25** (50 mg, 0.08 mmol) using different silanes. The eluent was CH_2Cl_2/MeOH (100:1). Phosphine (*S*,*S*)-**6** was obtained [using triethoxyisilane: 34 mg (69%), using trimethoxysilane: 37 mg (76%); using phenylsilane: 40 mg (82%); using diphenylsilane: 28 mg (58%); using trichlorosilane: 35 mg (71%); using TMDS: 26 mg (53%)] as a pale yellow oil; R_f = 0.21 (CH_2Cl_2/MeOH 80:1); $[\alpha]_D^{23}$ +115.6 (*c* 0.86 CH_2Cl_2).

IR (neat): 3433, 3141, 3060, 3012, 2954, 2926, 2867, 2721, 1900, 1583, 1573, 1473, 1438, 1386, 1367, 1276, 1241, 1132, 1103, 1070, 1026, 950, 840, 751, 729, 697, 619, 531, 498, 479 cm^{-1}.

^{1}H NMR (500 MHz, $CDBr_3$): δ = 0.71–0.79 (m, 12 H, CH_3), 0.88–0.94 (m, 1 H, CH_2), 1.01–1.28 (m, 3 H, CH_2), 1.48–1.52 (m, 2 H, CH), 3.48–3.69 (m, 10 H), 3.99–4.21 (m, 3 H), 4.32–4.35 (m, 1 H, OCH, OCH_2), 6.85–6.92 (m, 1 H, ArH), 7.05–7.09 (m, 3 H, ArH), 7.20–7.31 (m, 2 H, ArH), 7.60–7.81 (m, 7 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.25, 22.29, 23.17, 23.25 (CH_3) 24.46 (CH), 40.98, 41.48 (CH_2), 69.93 (d, *J* = 2.8 Hz), 70.03 (d, *J* = 4.4 Hz), 70.35, 70.72 (d, *J* = 4.9 Hz), 71.09 (d, *J* = 1.0 Hz), 72.47, 73.35(OCH, OCH_2), 110.82 (d, *J* = 1.3 Hz, ArC), 11.98 (d, *J* = 2.0 Hz, ArC), 120.81 (d, *J* = 0.9 Hz, ArC), 121.27 (d, *J* = 0.9 Hz, ArC), 128.37 (d, *J* = 7.8 Hz, ArC), 128.92 (d, *J* = 1.0 Hz, ArC), 130.28 (d, *J* = 14.5 Hz, ArC), 132.22 (d, *J* = 10.4 Hz, ArC), 133.45 (d, *J* = 95 Hz, ArC), 134.52 (d, *J* = 21.2 Hz, ArC), 160.59 (d, *J* = 5.1 Hz, ArC), 160.71 (d, *J* = 3.9 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –25.58.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{46}O_5P$: 565.3077; found: 565.3055.

(7*S*,7′*S*,15*S*,15′*S*)-22,22′-{[Propane-1,3-diylbis(oxy)]bis(4,1-phenylene)}bis(7,15-dimethyl-7,9,10,12,13,15,16,22-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecine) [(*S*,*S*,*S*,*S*)-7]

Bisphosphine (*S*,*S*,*S*,*S*)-**7** was prepared from bisphosphine oxide (*S*,*S*,*S*,*S*)-**31** (180 mg, 0.17 mmol) using trimethoxysilane. The eluent was CH_2Cl_2/MeOH (100:1). Bisphosphine (*S*,*S*,*S*,*S*)-**7** (103 mg, 59%) was obtained as a pale yellow oil; R_f = 0.56 (CH_2Cl_2/MeOH 40:1); $[\alpha]_D^{27}$ +149.8 (*c* 1.0 CH_2Cl_2).

IR (neat): 3063, 2968, 2929, 2863, 1591, 1582, 1571, 1497, 1470, 1437, 1275, 1235, 1176, 1157, 1130, 1095, 1068, 1026, 957, 826, 751, 730, 603, 554, 521, 481, 473, 419 cm^{-1}.

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.04–1.11 (m, 12 H, CH_3), 2.29 (pent, *J* = 6.1 Hz, 2 H, CH_2), 3.43–3.52 (m, 2 H), 3.56–3.99 (m, 24 H), 4.06–4.22 (m, 6 H, OCH, OCH_2), 6.62–6.67 (m, 2 H, ArH), 6.74–6.94 (m, 14 H, ArH), 7.23–7.34 (m, 8 H, ArH).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 16.55, 17.32 (CH_3), 29.28 (CH_2), 64.33, 69.02, 69.06, 69.98, 70.05, 70.08, 70.11, 71.00, 71.02, 72.65, 73.99, 74.35, 74.51 (OCH, OCH_2), 110.70 (d, *J* = 1.2 Hz, ArC), 110.99 (d, *J* = 1.9 Hz, ArC), 114.51 (d, *J* = 8.4 Hz, ArC), 120.76 (d, *J* = 24.2 Hz, ArC), 126.38 (d, *J* = 13.5 Hz, ArC), 126.74 (d, *J* = 15.4 Hz, ArC), 127.33 (d, *J* = 10.4 Hz, ArC), 129.68 (d, *J* = 3.9 Hz, ArC), 132.87 (d, *J* = 1.2 Hz, ArC), 133.58, 133.59 (ArC), 136.04 (d, *J* = 23.4 Hz, ArC), 159.64 (ArC), 160.35 (d, *J* = 8.9 Hz, ArC), 160.58 (d, *J* = 10.3 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –29.67.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{59}H_{71}O_{12}P_2$: 1033.4415; found: 1033.4371.

(7*S*,7′*S*,15*S*,15′*S*)-22,22′-{[Butane-1,4-diylbis(oxy)]bis(4,1-phenylene)}bis(7,15-dimethyl-7,9,10,12,13,15,16,22-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecine) [(*S*,*S*,*S*,*S*)-8]

Bisphosphine (*S*,*S*,*S*,*S*)-**8** was prepared from bisphosphine oxide (*S*,*S*,*S*,*S*)-**32** (210 mg, 0.19 mmol) using trimethoxysilane. The eluent was CH_2Cl_2/MeOH (80:1). Bisphosphine (*S*,*S*,*S*,*S*)-**8** was obtained (126 mg, 62%) as a colorless oil; R_f = 0.60 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{27}$ +127.8 (*c* 0.22, CH_2Cl_2).

IR (neat): 3059, 2968, 2928, 2867, 1593, 1583, 1572, 1497, 1472, 1438, 1374, 1278, 1239, 1177, 1158, 1132, 1097, 1069, 1027, 827, 753, 603, 531, 483 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 6.5 Hz, 3 H, CH_3), 1.09 (t, *J* = 6.4 Hz, 3 H, CH_3), 1.97–1.99 (m, 4 H), 3.42–3.48 (m, 2 H), 3.60–3.80 (m, 20 H), 3.83–3.87 (m, 2 H), 3.96–4.04 (m, 6 H), 4.14–4.20 (m, 2 H, OCH, OCH_2), 6.60–6.62 (m, 2 H, ArH), 6.74–6.86 (m, 14 H, ArH), 7.21–7.27 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.94, 17.64 (CH_3), 26.13 (CH_2), 67.36, 69.15, 70.15, 70.18, 71.19, 72.91, 73.92, 74.51, 74.76 (OCH, OCH_2), 110.71 (d, *J* = 1.3 Hz, ArC), 110.92 (d, *J* = 1.8 Hz, ArC), 114.52 (d, *J* = 8.4 Hz, ArC), 120.61 (d, *J* = 0.7 Hz, ArC), 121.09 (d, *J* = 1.1 Hz, ArC), 129.63 (d, *J* = 7.5 Hz, ArC), 133.32 (d, *J* = 101 Hz, ArC), 135.99 (d, *J* = 1.2 Hz, ArC), 136.17 (d, *J* = 0.7 Hz, ArC), 159.63 (d, *J* = 1.8 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –28.52.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{60}H_{73}O_{12}P_2$: 1047.4572; found: 1047.4528.

Bis(2-hydroxyphenyl)phenyl-λ^5-phosphine (14)

Phosphine **14**[15] was prepared from phosphine oxide **13** (200 mg, 0.64 mmol) using trimethoxysilane. The eluent was CH_2Cl_2/MeOH (80:1). Phosphine **14** (120 mg, 63%) was obtained as a white powder; mp 161–163 °C; R_f = 0.28 (CH_2Cl_2/MeOH 80:1).

IR (KBr): 3500, 3405, 3230, 3064, 2945, 2839, 2699, 1911, 1619, 1588, 1577, 1482, 1441, 1348, 1317, 1284, 1216, 1159, 1120, 1065, 1034, 827, 752, 698, 503, 475 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 6.60–6.63 (m, 2 H, ArH), 6.71–6.74 (m, 2 H, ArH), 6.79–6.82 (m, 2 H, ArH), 7.17–7.20 (m, 2 H, ArH), 7.24–7.28 (m, 2 H, ArH), 7.30–7.34 (m, 3 H, ArH).

^{13}C NMR (75 MHz, CD_3OD): δ = 114.20 (d, *J* = 2.0 Hz, ArC), 119.39 (d, *J* = 1.2 Hz, ArC), 122.06 (d, *J* = 9.2 Hz, ArC), 127.82 (d, *J* = 7.3 Hz, ArC), 128.02 (ArC), 129.78 (ArC), 133.42 (ArC), 133.53 (d, *J* = 12.8 Hz, ArC), 136.37 (d, *J* = 8.2 Hz, ArC), 159.28 (d, *J* = 17.0 Hz, ArC).

^{31}P NMR (121.5 MHz, CD_3OD): δ = –30.59.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}O_2P$: 295.0882; found: 295.0874.

(7*S*,15*S*)-7,15-Dimethyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-9]

$LiAlH_4$ (61 mg, 1.60 mmol) and anhyd and pure Et_2O (5 mL) were placed under argon in a three-necked flask fitted with a stirring bar and a dropping funnel. The vigorously stirred mixture was cooled to 0 °C, and the macrocycle (*S*,*S*)-**28** (300 mg, 0.64 mmol) dissolved in toluene (5 mL) was added dropwise. The mixture was warmed up to 40 °C and stirred for 4 h. The mixture was cooled to 0 °C, and H_2O was added dropwise to destroy the excess $LiAlH_4$. H_2O (30 mL), Et_2O (20 mL), and Me_4NHSO_4 were added to the mixture to facilitate the separation of the phases. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by PLC on silica gel using MeOH/CH_2Cl_2 (1:30) as eluent to give (*S*,*S*)-**9** (114 mg, 42%) as an off-white powder; mp 146–148 °C; R_f = 0.34 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{25}$ +1.6 (c 0.7 CH_2Cl_2).

IR (KBr): 3070, 2967, 2955, 2932, 2896, 2871, 1590, 1578, 1480, 1467, 1442, 1375, 1345, 1330, 1281, 1243, 1178, 1161, 1144, 1122, 1102, 1075, 1024, 996, 982, 952, 929, 777, 768, 725, 706, 602, 556, 492, 482, 433 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.18 (d, *J* = 6.2 Hz, 3 H, CH_3), 3.40–3.47 (m, 2 H), 3.57–3.68 (m, 5 H), 3.76–3.79 (m, 2 H), 3.87–3.94 (m, 2 H), 3.98–4.10 (m, 3 H), 6.86–6.96 (m, 3 H, ArH), 7.09–7.17 (m, 2 H, ArH), 7.44–7.47 (m, 1 H, ArH), 7.53–7.56 (m, 1 H, ArH), 7.90–7.94 (m, 1 H, ArH), 8.60 [d, *J* = 537 Hz, 1 H, P(O)H].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.43 (s, CH_3), 16.98 (s, CH_3), 68.89, 70.69, 70.96, 71.11, 72.34, 73.58, 74.02, 74.45 (OCH, OCH_2), 111.27 (d, *J* = 6.0 Hz, ArC), 111.35 (d, *J* = 5.9 Hz, ArC), 117.54 (d, *J* = 103 Hz, ArC), 120.14 (d, *J* = 3.5 Hz, ArC), 120.56 (d, *J* = 12.4 Hz, ArC), 120.98 (d, *J* = 3.4 Hz, ArC), 121.24 (d, *J* = 11.8 Hz, ArC), 132.31 (d, *J* = 8.1 Hz, ArC), 134.46 (d, *J* = 18.4 Hz, ArC), 134.40 (d, *J* = 5.7 Hz, ArC), 160.04 (d, *J* = 3.7 Hz, ArC), 162.82 (d, *J* = 2.8 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 5.96.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{30}O_6P$: 421.1775; found: 421.1759.

(7*S*,15*S*)-7,15-Diisobutyl-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*][1,4,7,10,13,16]pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-10] and (7*S*,15*S*)-7,15-Diisobutyl-22-hydroxy-6,7,9,10,12,13,15,16-octahydro-22*H*-22λ^5-dibenzo[*n*,*q*]-[1,4,7,10,13,16]-pentaoxaphosphacyclooctadecin-22-one [(*S*,*S*)-33]

Macrocycle (*S*,*S*)-**10** was prepared in the same way as described above for (*S*,*S*)-**9** starting from macrocycle (*S*,*S*)-**27** (300 mg, 0.55 mmol). The crude product was purified by PLC on silica gel using MeOH/CH_2Cl_2 (1:30) as eluent to give (*S*,*S*)-**10** (66 mg, 24%) as a pale yellow oil, and (*S*,*S*)-**33** (88 mg, 31%) as a pale yellow powder.

(*S*,*S*)-10

R_f = 0.55 (CH_2Cl_2/MeOH 15:1); $[\alpha]_D^{25}$ +18.2 (*c* 1.0 CH_2Cl_2).

IR (neat): 3348, 2952, 2929, 1590, 1578, 1478, 1467, 1441, 1386, 1367, 1348, 1280, 1244, 1136, 1090, 1074, 1042, 1022, 925, 838, 814, 755, 728, 708 680, 619, 554, 482, 443 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81–0.98 (m, 12 H, CH_3), 1.06–1.27 (m, 2 H, CH_2), 1.36–1.87 (m, 4 H, CH, CH_2), 3.17–3.23 (m, 1 H), 3.46–3.82 (m, 10 H), 3.89–4.11 (m, 3 H, OCH, OCH_2), 6.88–6.99 (m, 3 H, ArH), 7.10–7.21 (m, 2 H, ArH), 7.45–7.60 (m, 2 H, ArH), 7.93–8.01 (m, 1 H, ArH), 8.65 [d, *J* = 532 Hz, 1 H, P(O)H].

^{13}C NMR (75 MHz, CD_3OD): δ = 22.53, 22.78, 23.22, 23.64 (CH_3), 24.71, 24.76 (CH), 40.80, 41.49 (CH_2), 70.20, 71.03, 71.14, 72.12, 72.46, 73.48, 76.83 (OCH, OCH_2), 111.32 (d, *J* = 6.1 Hz, ArC), 111.41 (d, *J* = 6.1 Hz, ArC), 120.65 (d, *J* = 12.4 Hz, ArC), 121.44 (d, *J* = 11.6 Hz, ArC), 132.40 (d, *J* = 8.3 Hz, ArC), 134.16 (d, *J* = 19.0 Hz, ArC), 134.75 (d, *J* = 5.5 Hz, ArC), 160.28 (d, *J* = 3.9 Hz, ArC), 161.12 (d, *J* = 2.5 Hz, ArC).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 5.30.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}O_6P$: 505.2714; found: 505.2696.

(*S*,*S*)-33

Mp 120–123 °C; R_f = 0.10 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{25}$ +32.6 (*c* 0.9 CH_2Cl_2).

IR (KBr): 3330, 3064, 2955, 2928, 2869, 2067, 1916, 1590, 1576, 1474, 1440, 1386, 1367, 1275, 1239, 1137, 1097, 1029, 950, 832, 755, 706, 679, 668, 649, 620, 570, 518 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.90 (m, 12 H, CH_3), 1.13–1.22 (m, 2 H, CH_2), 1.35–1.44 (m, 2 H, CH_2), 1.55–1.64 (m, 2 H, CH), 3.35–3.56 (m, 10 H), 3.95–4.08 (m, 4 H, OCH, OCH_2), 6.96–7.04 (m, 4 H, ArH), 7.38–7.43 (m, 2 H, ArH), 7.66 (br s, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.80, 22.03 (CH_3), 24.56 (CH), 39.75 (CH_2), 68.94, 69.95, 71.29, 77.75 (OCH_2, OCH), 112.7 (d, *J* = 3.5 Hz, ArC), 120.41 (d, *J* = 11.6 Hz, ArC), 127.39 (d, *J* = 135 Hz, ArC), 131.69, 133.06 (d, *J* = 6.7 Hz, ArC), 160.12 (d, *J* = 0.9 Hz, ArC).

^{31}P NMR (121.5 MHz, CD_3OD): δ = 16.63.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}O_7P$: 521.2663; found: 521.2643.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707854.

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