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Synthesis of an enantiomerically pure inherently chiral calix[4]arene phosphonic acid and its evaluation as organocatalyst.

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Abstract: A facile method for the preparation of enantiomerically pure inherently chiral calix[4]arene phosphonic acid (*cR,pR*)-**7** in four steps starting from the readily available and previously synthesized (*cS*)-enantiomer of calix[4]arene acetic acid **1** or its methyl ester **2** was developed. The first tests of this unique calixarene Brönsted acid with inherent chirality in organocatalysis of the aza-Diels–Alder reaction of imines with Danishefsky's diene and epoxide ring opening by benzoic acid were performed. The calixarene phosphonic acid (*cR,pR*)-**7** shows good catalytic activities but with low enantioselectivities in these reactions.

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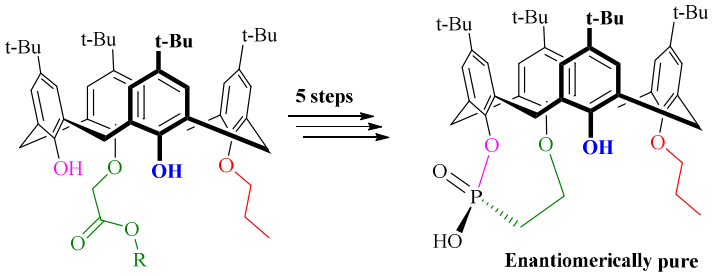


INTRODUCTION

Calixarenes are fascinating cup-shaped macrocyclic molecules synthesized by selective one-pot cyclocondensation of *para*-substituted phenols with formaldehyde and are

ready for easy chemical modification at both the upper and lower rims.[1] This synthetic versatility and their ability to form host-guest supramolecular complexes has raised great interest in recent years for calixarene derivatives which have been used in numerous applications, such as in biomedicine,[2] nanoscience[3] or as sensors.[4] Efficient catalytic systems based on calixarenes have also been developed.[5,6] In particular, many chiral calixarene derivatives containing chiral residues at the upper or lower rims have been synthesized allowing the development of new chiral receptors for asymmetric recognition[7] which proved to be powerful tools to mimic and to obtain stereochemical insights on biochemical systems[8] as well as efficient systems for asymmetric catalysis.[9] Challenging trends in design of chiral receptors is by using of ''inherently''chiral calixarene derivatives possessing asymmetrical disposition of achiral substituents at the three- dimensional macrocyclic platform.[10] During the past three decades, a diversity of inherently chiral calixarenes were synthesized, but only few of them could be obtained as pure enantiomers[6,11] and even less have been used in asymmetric catalysis. [6a,12,13]

We recently developed a novel and efficient gram scale method for the synthesis of enantiomerically pure inherently chiral calix[4]arene carboxylic acids.[11a] In this article, we will present an efficient method for preparation of the inherently chiral calix[4]arene phosphonic acid in high yields and the first tests of this unique calixarene Brönsted acid in organocatalysis. Indeed, chiral organophosphorus Brönsted acids (see Figure 1) are currently used as organocatalysts showing in some cases very good catalytic activities and enantioselectivities (*ee* up to 99%).[14] However, calixarene based organophosphorus Brönsted acids with inherent chirality has not yet been explored in organocatalysis to the best of our knowledge.

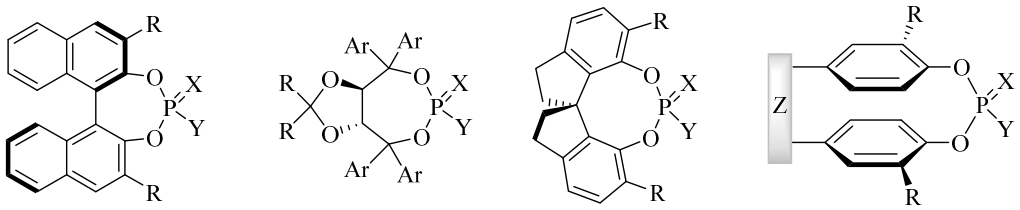


Figure 1: Phosphorus organocatalysts and ligands bearing chiral diol units.

RESULTS AND DISCUSSION

The target enantiopure inherently chiral calixarene phosphonic acid (*cR,pR*)-**7** was obtained in four steps (Scheme 1) from the early synthesized (c*S*)-enantiomer of calix[4]arene acetic acid (*cS*)-**1** or its methyl ester (*cS*)-**2**.[11a] The first step is the reduction of compounds **1, 2** into 2-hydroxyethoxycalixarene (*cS*)-**3** by $LiAlH_4$. Since, there are two phenolic OH groups in the compounds, a 5-fold excess of lithium aluminum hydride was used for acid (*cS*)-**1**. After 1 hour reaction, alcohol (*cS*)-**3** was isolated with practically quantitative yields. In the same conditions, ester (*cS*)-**2** was also easily reduced, but a 4 eq. excess of lithium aluminum hydride was used. ^{13}C NMR resonance peaks of bridged methylene groups ($^{Ar}C\text{-}CH_2\text{-}C^{Ar}$) are in the 33.9 – 34.2 ppm range which are characteristic values for calix[4]arenes in the *cone* conformation.[15] The *cone* conformation of (*cS*)-**3** was confirmed by the X-ray diffraction method (Figure 2). In the crystal packing of (c*S*)-**3**, there are two independent molecules and three CH_3CN solvent molecules by asymmetric unit. Each calix[4]arene molecule contains CH_3CN molecule incorporated inside its cavity whereas the third CH_3CN is located along a two-fold axis. Because of the absence of heavy atoms in the structure of (*cS*)-**3**, the determination of the absolute configuration was not possible unambiguously (Flack'parameter = 0.2(3), see Table S1 in the Supporting Information file). O-H...O or C-H...O hydrogen bonds are described in Table S2.

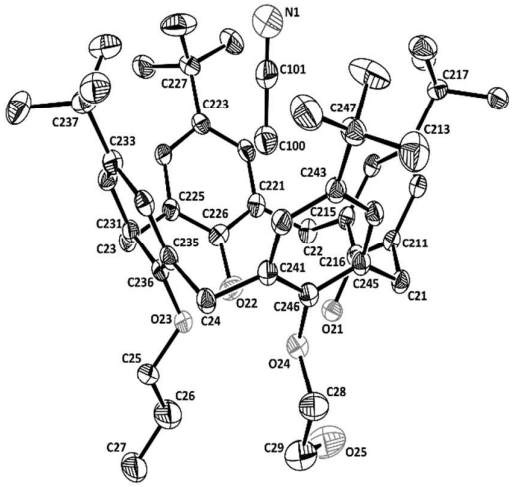
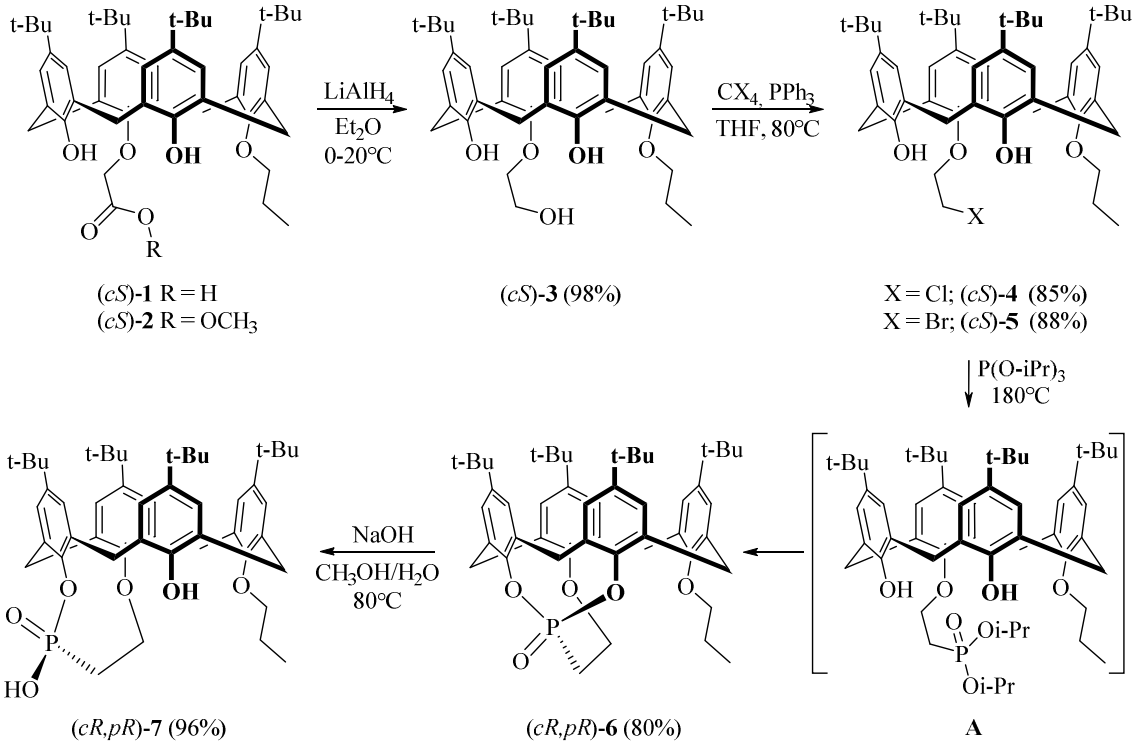


Figure 2: ORTEP view of compound (c*S*)-**3**. Only one of the two independent calixarene molecules complexed with CH_3CN "guest" is represented. Ellipsoids are drawn at the 30% probability level. The solvent CH_3CN molecules and H atoms have been omitted for clarity.

The next step is the substitution of the OH group in 2-hydroxyethyl moiety of (*cS*)-**3** by chlorine or bromine atom. All attempts to synthesise the chloro derivative (*cS*)-**4** by reaction of alcohol (*cS*)-**3** with thionyl chloride failed. After boiling of (*cS*)-**3** with thionyl

chloride in chloroform, no reaction was observed. Boiling in pure thionyl chloride yields a complex mixture of degradation products. However, the Appel reaction of alcohol (*cS*)-**3** in the carbon tetrachloride/THF mixture (1:4 v/v) in presence of triphenylphosphine was successful.[16] After refluxing the mixture for 4-6 hours and purification of the crude products by flash column chromatography, the chloride (*cS*)-**4** was obtained with 88% yield as a white solid. Similarly, bromide (*cS*)-**5** was prepared using carbon tetrabromide with slightly better yields (see Scheme 1). The substitution of the OH group of (*cS*)-**3** could easily followed by ^{13}C NMR on the terminal carbon bearing OH group in (*cS*)-**3** (62.2 ppm) or chlorine atom in (*cS*)-**4** (72.2 ppm) or bromine atom in (*cS*)-**5 (**77.2 ppm). Again, ^{13}C NMR resonance peaks of bridged methylene groups (^{Ar}C-CH$_2$-C^{Ar}) in the 33.8 – 34.3 ppm range for both (*cS*)-**4** and (*cS*)-**5** shows the *cone* conformation is preserves during the substitution.[15]

We used Michaelis–Arbuzov reaction[17] to introduce a phosphoryl group. The reaction of chloride (*cS*)-**4** overnight in refluxing triisopropyl phosphite gives surprisingly not the expected Michaelis–Arbuzov product, namely calixarene diisopropylphosphonate **A**, but the calixarene spiro-phosphonate (*cR,pR*)-**6** in 80% yield, as a single diastereoisomer with full control of the phosphorus atom geometry. We can suppose that, in the hard condition (180 °C), calixarene diisopropylphosphonate **A,** formed in a first step by the classical Michaelis-Arbuzov reaction, immediately undergoes intramolecular transesterification with two neighboring OH groups at the lower rim.[18] The Michaelis–Arbuzov reaction of bromide (*cS*)-**5** in the same condition gave only a complex mixture of not identified products. Peaks of vinyl protons can be found in ^{1}H NMR spectra of the crude mixture at 5.2 – 6.2 ppm indicating the presence of HBr elimination product. Probably, the hard conditions cause elimination of HBr from 2-bromoethoxy moiety followed by different the acid-induced side reactions. Lowering temperature to less than 150 °C gave no reaction.



Scheme 1: Synthesis of enantiomerically pure calix[4]arene phosphonic acid (*cR,pR*)-**7** from chiral (*cS*)-calix[4]arene carboxylic acid (*cS*)-**1** or its ester (*cS*)-**2**.

The transformation of chloride (*cS*)-**4** to spirophosphonate (*cR,pR*)-**6**) dramatically changes chemical shifts of the terminal carbon atoms respectively from 77.2 ppm (CH_2Cl) to 36.6 ppm (CH_2P) in the ^{13}C NMR spectra. . Two carbon atoms ^{Ar}C-O-P in (*cR,pR*)-**6** showed coupling constants $^{2}J_{C-P}$ 10.4 Hz and 10.7 Hz suggesting the cyclic structure of (*cR,pR*)-**6**. Again, ^{13}C resonance peaks of bridged methylene groups (^{Ar}C-CH_2-C^{Ar}) could be found in the 33.4 – 34.4 ppm range showing a *cone* conformation[15] for (*cR,pR*)-**6**. Indeed, the molecular structure of (*cR,pR*)-**6** was fully established by X-ray diffraction method (see Figure 3). Calixarene (*cR,pR*)-**6** absolute configuration (inherent chirality and central chirality on phosphorus) could be determined thanks to the presence of the heavy phosphorus atom in the molecule (Flack'parameter = 0.01, see Table S1 in the Supporting Information file). Two independent molecules appears to be linked though weak C-H···O interactions (C(29)-O(15) and C(26)A-O(15) (see Table S2).

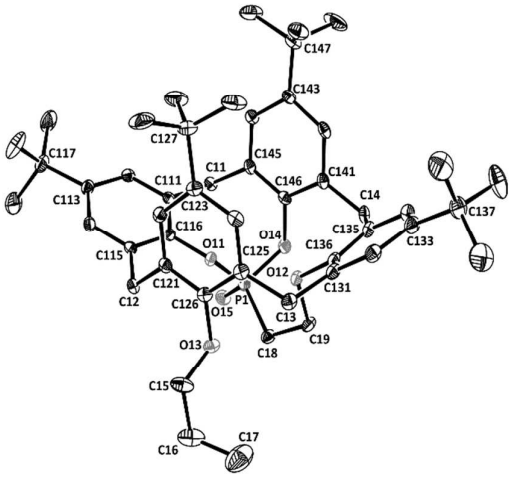


Figure 3: ORTEP view of compound (*cR,pR*)-**6**. Only one of two independent molecules is represented. Ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity.

Finally, stereoselective hydrolysis of one P-O-C^{Ar} bond of the spirophosphonate (*cR,pR*)-**6** in a water-methanol solution of sodium hydroxide gives enantiomerically pure phosphonic acid (*cR,pR*)-**7** with *ABCH* type of substitution on the lower rim. Similar protocol were previously applied by Gloede and coworkers to hydrolyze selectively only one bond of three P-O-C^{Ar} bonds in P-bridged calixarene derivative.[19] Nevertheless, such stereoselective hydrolysis is an unprecedented example to the best of our knowledge. The ^{1}H NMR spectrum of calixarene (*cR,pR*)-**7** shows a set of four AB systems for the methylene bridges at 4.75, 4.43, 4.24 and 4.04 ppm for the axial protons, and at 3.49, 3.29, 3.25 ppm for the equatorial protons with $^{2}J_{H\text{-}H}$ 12.8 Hz, 13.6 Hz, 13.8 Hz and 14.2 Hz. The ^{13}C NMR spectrum shows resonance peaks of bridged methylene groups (^{Ar}C-CH_2-C^{Ar}) in the 33.4– 34.4 ppm range. The ^{1}H and ^{13}C NMR data indicate clearly that (*cR,pR*)-**7** exists in the *cone* conformation with inherent chirality. The *cone* conformation and absolute configuration of (*cR,pR*)-**7** could be fully determined by X-ray diffraction method (see Figure 4): the (Flack'parameter = -0.02, see Table S1 in the Supporting Information file). In the crystal, two independent (*cR,pR*)-**7** molecules are linked through P-O-H···O=P strong hydrogen bonds (see Figure 4 and Table S2). These hydrogen bonds build up a $\mathbf{R_2^2(8)}$ graph set motif.[20,21]

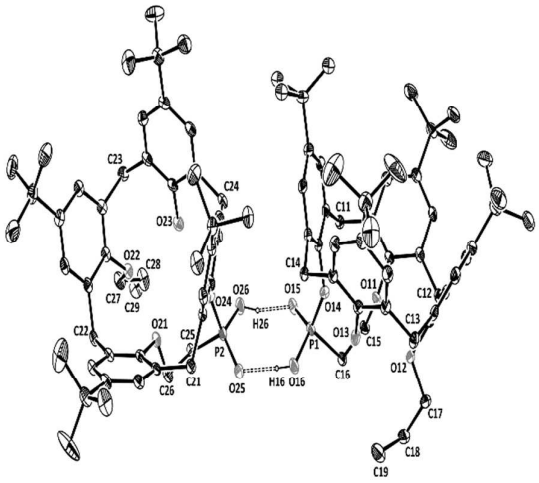


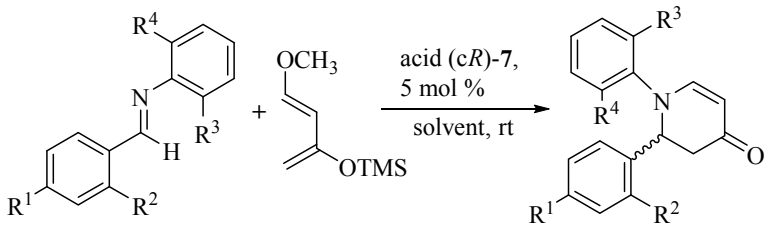
Figure 4: ORTEP view of compound (*cR,pR*)-**7**. The two independent molecules linked by P-O-H···O=P hydrogen bonds are represented. Ellipsoids are drawn at the 30% probability level.

The application of inherently chiral calixarenes as chiral catalysts is a worthy challenge in organic synthesis. However, as already pointed out in the introduction, the reported examples of asymmetric organocatalysis with inherently chiral calixarenes are still quite scarce, essentially in aldol and Michael reactions.[7b,7e,9e,13a-d] Aza-Diels–Alder reaction is an effective tool to synthesize various tetrahydropyridine derivatives. Nitrogen atom may be part of a diene or dienophile. There are a number of successful synthetic developments both in achiral[22] and stereoselective variants of the reaction:[23] tetrahydropyridine derivatives could be obtained with good yields and *ee* in the 3 – 91% range.

Organocatalytic properties of the chiral calixarene phosphonic acid (*cR,pR*)-**7** were examined first in the aza-Diels–Alder reaction of imines possessing electron-withdrawing or electron donor substituents, with E-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (Table 1).

Calixarene (*cR,pR*)-**7** effectively catalyses the reaction (up to 95% yield, Table 1). However, enantioselectivity of the reaction was still moderate (up to 21% *ee*, see entry 6, Table 1). The yields of the reaction in acetonitrile are slightly higher than in toluene. The effects of the substituents of the imine substrates are small as usually observed[24] and more mechanistic insights[25] would be necessary to understand their rather subtle effects.

Table 1. Asymmetric aza-Diels–Alder reactions catalyzed by (*cR,pR*)-**7**.

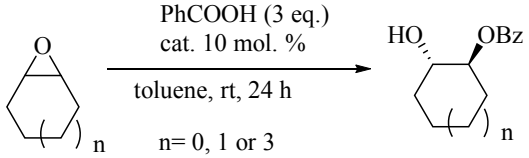


№	*Solvent*	R_1	R_2	R_3	R_4	Isolated yield, %	ee, %
1.	*CH_3CN*	H	H	H	H	83	2
2.	*CH_3CN*	Cl	H	H	H	83	1
3.	*CH_3CN*	NO_2	H	H	H	88	0
4.	*CH_3CN*	OCH_3	H	H	H	85	5
5.	*CH_3CN*	H	OH	H	H	95	9
6.	*Toluene*	H	H	H	H	72	21
7.	*Toluene*	Cl	H	H	H	81	3
8.	*Toluene*	NO_2	H	H	H	74	4
9.	*Toluene*	OCH_3	H	H	H	56	3
10.	*Toluene*	H	OH	H	H	69	11
11.	*Toluene*	H	H	OH	H	76	10

Conditions: imine/diene = 1/2, 5 mol. % of the catalyst, 25°C, 200 h.

Asymmetric epoxide ring opening is another important synthetic transformation[26] and is also applied industrially. The first asymmetric version of the epoxide ring opening with benzoic acid catalyzed by chiral binol-derived phosphoric acids was described by the List group (yields of the opened products were 55 – 86% and *ee* up to 93%).[27] Calixarene phosphonic acid (*cR,pR*)-**7** was examined as chiral organocatalyst for the asymmetric ring opening of several cyclic *meso* epoxides (Table 2). Cyclohexene and cyclopentene oxides were opened by benzoic acid with good yields but low enantiomeric excesses (71% yield, 18% *ee*; and 75% yield, 11% *ee* respectively). Cyclooctene oxide was found to be poorly reactive with conversions of less than 10%.

Table 2. Asymmetric ring opening of epoxides catalyzed by (*cR,pR*)-**7**.



№	*Substrate*	Isolated yield, %	ee, %
1.	cyclopentene oxide (n= 0)	75	11
2.	cyclohexene oxide (n=1)	71	18
3.	cyclooctene oxide (n= 3)	8	-

Conditions: benzoic acid/epoxide = 1.5/1, 10 mol. % of catalyst, 25°C, 24 h.

CONCLUSIONS

In the present study an efficient and straightforward method for preparation of enantiomerically pure inherently chiral calix[4]arene phosphonic acid (*cR,pR*)-**7** in four steps starting from the readily available calix[4]arene acetic acid (*cS*)-**1** or its methyl ester (*cS*)-**2** was developed. The first tests of this unique calix[4]arene Brönsted acid with inherent chirality as organocatalyst in the asymmetric Aza-Diels–Alder reaction of imines with Danishefsky's diene and in the asymmetric ring opening of epoxides by benzoic acid were performed. The calixarene phosphonic acid (*cR,pR*)-**7** demonstrates good catalytic activities but with low enantioselectivities in these reactions. The evaluation of catalytical efficiency of the calixarene phosphonic acid (*cR,pR*)-**7** for other asymmetrical reactions as well as the design of more efficient inherently chiral calixarene catalysts are in progress.

EXPERIMENTAL SECTION

General experimental

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Melting points were determined on the Boetius apparatus and were uncorrected. Solvents were carefully dried by conventional methods and distilled under argon before use. Column chromatography was performed on Carlo Erba silica gel 60, 0.035-0.070 mm. (*cS*)-5,11,17,23-tetra-tert-butyl-25,26-dihydroxy-27-carboxylmethoxy-28-propoxycalix[4]arene (*cS*)-**1** and (*cS*)-5,11,17,23-tetra-tert-butyl-25,26-dihydroxy-27-methoxycarbonylmethoxy-28-propoxycalix[4]arene (*cS*)-**2** were prepared according to literature procedures.[11a] All commercially available chemicals ($LiAlH_4$, powder, 97%, Alfa Aesar; PPh_3, 99%, Sigma Aldrich; $(iPrO)_3P$, 90+%, Alfa Aesar) were used as received. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra of compounds were recorded with a Bruker Avance 400 FT-NMR spectrometer. The

resonances were calibrated relative to the residual solvent peaks and are reported with positive values downfield from TMS. For all characterized compounds, the peak assignments in the ^{1}H and ^{13}C NMR spectra were based on COSY, HSQC and HMBC 2D experiments. HRMS were obtained from dichloromethane solutions with a Xevo G2 Q TOF spectrometer by the electrospray ionization method.

(*cS*)-5,11,17,23-Tetra-tert-butyl-25,26-dihydroxy-27-hydroxyethoxy-28-propoxycalix[4]arene (*cS*)-3.

To lithium aluminum hydride (0.40 g, 10.5 mmol) in a schlenk tube under argon atmosphere absolute diethyl ether (50 mL) was added. The slurry was stirred at room temperature for 0.5 h, cooled to 0 ˚C and small portions (1.72 g, 2.3 mmol) of ((cS)-5,11,17,23-tetra-tert-butyl-25,26-dihydroxy-27-carboxylmethoxy-28-propoxycalix[4]arene) (*cS*)-**1** or corresponding ester ((cS)-5,11,17,23-tetra-tert-butyl-25,26-dihydroxy-27-methoxycarbonylmethoxy-28-propoxycalix[4]arene) (*cS*)-**2** were added. The resulting mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), 5 mL of ethyl acetate was added dropwise and the mixture was stirred for 15-20 min. Then, methanol (10 mL), water (25 mL) and H_2SO_4 (25 mL of 10% water solution) was added in corresponding order. Ether solution was separated, washed twice with 25 mL of distilled water and 25 mL of brine, dried over Na_2SO_4 and evaporated to give the product as a white crystalline solid (1.66 g, 98% yield and 95% purity according to ^{1}H NMR) which was used without further purification. If needed, product can be crystallized from acetonitrile.

^{1}H NMR (δ (ppm), 400MHz, $CDCl_3$): 1.16 (t, 3H, $OCH_2CH_2CH_3$, $^{3}J_{H\text{-}H}$ = 7.4 Hz), 1.17 (s, 9H, t-Bu), 1.20 (s, 9H, t-Bu), 1.23 (s, 9H, t-Bu), 1.31 (s, 9H, t-Bu), 2.08-2.25 (m, 2H, $OCH_2CH_2CH_3$), 3.37 (d, 1H, Ar-CH_2-eq, $^{2}J_{H\text{-}H}$ = 12.8 Hz), 3.43 (d, 1H, Ar-CH_2-eq, $^{2}J_{H\text{-}H}$ = 11.7 Hz), 3.44 (d, 1H, Ar-CH_2-eq, $^{2}J_{H\text{-}H}$ = 14.0 Hz), 3.45 (d, 1H, Ar-CH_2-eq, $^{2}J_{H\text{-}H}$ = 13.8 Hz), 3.86-3.94 (m, 1H, $OCH_2CH_2CH_3$), 3.95-4.01 (m, 1H, OCH_2CH_2OH), 4.02-4.08 (m, 1H, $OCH_2CH_2CH_3$), 4.19 (d, 1H, Ar-CH_2-ax, $^{2}J_{H\text{-}H}$ = 13.8 Hz), 4.18-4.30 (m, 1H, OCH_2CH_2OH, 2H, OCH_2CH_2OH), 4.30 (d, 1H, Ar-CH_2-ax, $^{2}J_{H\text{-}H}$ = 13.7 Hz), 4.50 (d, 1H, Ar-CH_2-ax, $^{2}J_{H\text{-}H}$ = 12.4 Hz), 4.60 (d, 1H, Ar-CH_2-ax, $^{2}J_{H\text{-}H}$ = 12.8 Hz), 5.23-5.21 (s, br, 1H, OCH_2CH_2OH) 6.94 (d, 1H, Ar-*H*, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 6.96 (d, 1H, Ar-*H*, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 7.08 (d, 1H, Ar-*H*, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 7.09-7.11 (m, 2H, Ar-*H*), 7.12 (d, 1H, Ar-*H*, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 7.13-7.15 (m, 2H, Ar-*H*), 9.24 (s, 1H, O*H*), 9.66 (s, 1H, O*H*); $^{13}C\{^{1}H\}$ NMR (δ (ppm), 125MHz, $CDCl_3$): 10.38 (CH_2CH_3), 23.15 (CH_2CH_3), 30.62 (CMe_3), 31.22 ($C(CH_3)_3$), 31.36 ($C(CH_3)_3$), 31.61

(C(CH_3)$_3$), 31.46 (C(CH_3)$_3$), 32.73 (CMe_3), 32.95 (CMe_3), 33.18 (CMe_3), 33.90 (Ar-CH_2-Ar), 34.97 (Ar-CH_2-Ar), 34.12 (Ar-CH_2-Ar), 34.13 (Ar-CH_2-Ar), 62.24 (HOCH_2CH_2O), 77.22 (OCH_2CH_2OH), 78.67 (OCH_2CH_2), 124.97 (CH^{Ar}), 125.46 (CH^{Ar}), 125.46 (CH^{Ar}), 125.60 (CH^{Ar}), 125.80 (CH^{Ar}), 126.08 (CH^{Ar}), 126.46 (CH^{Ar}), 126.59 (CH^{Ar}), 126.94 (C^{Ar}-CH_2-C^{Ar}), 126.95 (C^{Ar}-CH_2-C^{Ar}), 127.97 (C^{Ar}-CH_2-C^{Ar}), 128.08 (C^{Ar}-CH_2-C^{Ar}), 130.11 (C^{Ar}-CH_2-C^{Ar}), 131.70 (C^{Ar}-CH_2-C^{Ar}), 133.87 (C^{Ar}-CH_2-C^{Ar}), 134.04 (C^{Ar}-CH_2-C^{Ar}), 142.70 (C^{Ar}-*t*-Bu), 142.95 (C^{Ar}-*t*-Bu), 146.61 (C^{Ar}-*t*-Bu), 147.16 (C^{Ar}-*t*-Bu), 148.28 (C^{Ar}-OH), 148.94 (C^{Ar}-OH), 150.15 (C^{Ar}-OCH_2), 151.21 (C^{Ar}-OCH_2); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{49}H_{67}O_5$ 735.4989; Found 735.4998; mp 85-89°C; $[\alpha]_D^{20}$ +32.7 (c=1.47, $CHCl_3$).

(*cS*)-5,11,17,23-Tetra-tert-butyl-25,26-dihydroxy-27-chloroethoxy-28-propoxycalix[4]arene (*cS*)-4.

Alcohol (*cS*)-**3** (0.59 g, 0.8 mmol) and triphenylphosphine (0.66 g, 2.5 mmol) were dissolved in a mixture of carbon tetrachloride (4 mL) and THF (15 mL) and refluxed for 5 h. After completion of the reaction (monitored by TLC), mixture was diluted with THF and filtered through celite, solvent was removed in vacuo and crude materials was purified by flash-chromatography on silica, using a EtOAc/hexane mixture (1/3, v/v) as eluent to yield product (0.51 g, yield 84%) as a white crystalline solid.

^{1}H NMR (δ (ppm), 400MHz, $CDCl_3$): 0.99 (s, 9H, t-Bu), 1.06 (t, 3H, $OCH_2CH_2CH_3$, $^3J_{H\text{-}H}$ = 7.4 Hz), 1.17 (s, 9H, t-Bu), 1.21 (s, 18H, t-Bu), 1.98-2.22 (m, 2H, $OCH_2CH_2CH_3$), 3.32 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 12.8 Hz), 3.35 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 14.0 Hz), 3.41 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 14.4 Hz), 3.46 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 14.2 Hz), 3.52-3.63 (m, 1H, OCH_2CH_2Cl), 3.68-3.80 (m, 1H, $OCH_2CH_2CH_3$), 3.80-3.90 (m, 1H, $OCH_2CH_2CH_3$), 4.07-4.17 (m, 5H, 1H OCH_2CH_2Cl, 2H OCH_2CH_2Cl, 2H Ar-CH_2-ax), 4.40 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 13.2 Hz), 4.50 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 12.6 Hz), 6.86 (s, 2H, Ar-*H*), 6.94 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.4 Hz), 6.99 (d, 2H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.0 Hz), 7.03 (m, 2H, Ar-*H*), 7.09 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.4 Hz), 8.31 (s, 1H, O*H*), 8.94 (s, 1H, O*H*); ^{13}C{^{1}H} NMR (δ (ppm), 125MHz, $CDCl_3$): 10.49 ($OCH_2CH_2CH_3$), 23.32 ($OCH_2CH_2CH_3$), 30.84 (CMe_3), 31.30 (C(CH_3)$_3$), 31.44 (C(CH_3)$_3$), 31.70 (C(CH_3)$_3$), 31.62 (C(CH_3)$_3$), 32.65 (CMe_3), 32.72 (CMe_3), 33.77 (CMe_3), 33.97 (Ar-CH_2-Ar), 34.04 (Ar-CH_2-Ar), 34.07 (Ar-CH_2-Ar), 34.27 (Ar-CH_2-Ar), 72.18 ($ClCH_2CH_2O$), 74.70 (OCH_2CH_2Cl), 78.14 ($OCH_2CH_2CH_3$), 124.83 (CH^{Ar}), 125.08 (CH^{Ar}), 125.19 (CH^{Ar}), 125.27 (CH^{Ar}), 125.47 (CH^{Ar}), 125.67 (CH^{Ar}), 126.63 (CH^{Ar}), 126.75

(*C*H^{Ar}), 127.88 (*C*^{Ar}-CH$_2$-C^{Ar}), 127.33 (*C*^{Ar}-CH$_2$-C^{Ar}), 128.56 (*C*^{Ar}-CH$_2$-C^{Ar}), 129.57 (*C*^{Ar}-CH$_2$-C^{Ar}), 132.18 (*C*^{Ar}-CH$_2$-C^{Ar}), 133.01 (*C*^{Ar}-CH$_2$-C^{Ar}), 133.03 (*C*^{Ar}-CH$_2$-C^{Ar}), 134.61 (*C*^{Ar}-CH$_2$-C^{Ar}), 141.96 (*C*^{Ar}-*t*-Bu), 142.91 (*C*^{Ar}-*t*-Bu), 145.90 (*C*^{Ar}-*t*-Bu), 147.09 (*C*^{Ar}-*t*-Bu), 148.13 (*C*^{Ar}-OH), 149.69 (*C*^{Ar}-OH), 150.92 (*C*^{Ar}-OCH$_2$), 151.27 (*C*^{Ar}-OCH$_2$); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{49}H_{66}ClO_4$ 753.4649; Found 753.4661; mp 88-89°C; $[\alpha]_D^{20}$ +52.3 (c=1.35, $CHCl_3$).

(*cS*)-5,11,17,23-Tetra-tert-butyl-25,26-dihydroxy-27-bromoethoxy-28-propoxycalix[4]arene (*cS*)-5.

Alcohol (*cS*)-**3** (0.59 g, 0.8 mmol,) CBr_4 (0.40 g, 1.2 mmol) and triphenylphosphine (0.66 g, 2.5 mmol) were dissolved in THF (20 mL) and refluxed for 5 h. After completion of the reaction (monitored by TLC), mixture was diluted with THF and filtered through celite, solvent was removed in vacuo and crude materials was purified by flash-chromatography on silica, using EtOAc/hexane mixture (1/3, v/v) as eluent to yield product (0.56 g, yield 88%) as a white crystalline solid.

^{1}H NMR (δ (ppm), 400MHz, $CDCl_3$): 1.09 (s, 9H, t-Bu), 1.16 (t, 3H, OCH$_2$CH$_2$C*H*$_3$, $^3J_{H\text{-}H}$ = 7.5 Hz), 1.20 (s, 9H, t-Bu), 1.25 (s, 9H, t-Bu), 1.25 (s, 9H, t-Bu), 2.12 (m, 2H, OCH$_2$C*H*$_2$CH$_3$), 3.35 (d, 1H, Ar-C*H*$_2$-eq, $^2J_{H\text{-}H}$ = 12.7 Hz), 3.43 (d, 1H, Ar-C*H*$_2$-eq, $^2J_{H\text{-}H}$ = 13.7 Hz), 3.47 (d, 1H, Ar-C*H*$_2$-eq, $^2J_{H\text{-}H}$ = 14.0 Hz), 3.51 (d, 1H, Ar-C*H*$_2$-eq, $^2J_{H\text{-}H}$ = 13.8 Hz), 3.59 (m, 2H, OCH$_2$C*H*$_2$Br), 3.89 (m, 1H, OC*H*$_2$CH$_2$CH$_3$), 4.14 (m, 3H, 1H OC*H*$_2$CH$_2$CH$_3$ + 2H OC*H*$_2$CH$_2$Br), 4.14 (d, 2H, Ar-C***H*$_2$**-ax, $^2J_{H\text{-}H}$ = 13.9 Hz), 4.41 (d, 1H, Ar-C*H*$_2$-ax, $^2J_{H\text{-}H}$ = 13.2 Hz), 4.50 (d, 1H, Ar-C*H*$_2$-ax, $^2J_{H\text{-}H}$ = 12.7 Hz), 6.91 (s, 2H, Ar-*H*), 6.98 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.4 Hz), 7.02 (m, 2H, Ar-*H*), 7.05 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.4 Hz), 7.06 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.0 Hz), 7.10 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.0 Hz), 8.20 (s, 1H, O*H*), 8.68 (bs, 1H, O*H*); ^{13}C{^{1}H} NMR (δ (ppm), 125MHz, $CDCl_3$): 10.41 (OCH$_2$CH$_2$*C*H$_3$), 23.25 (OCH$_2$*C*H$_2$CH$_3$), 29.15 (*C*Me$_3$), 30.82 (*C*Me$_3$), 31.19 (C(*C*H$_3$)$_3$), 31.30 (C(*C*H$_3$)$_3$), 31.50 (C(*C*H$_3$)$_3$), 31.58 (C(*C*H$_3$)$_3$), 32.48 (*C*Me$_3$), 32.77 (*C*Me$_3$), 33.85 (Ar-*C*H$_2$-Ar), 33.92 (Ar-*C*H$_2$-Ar), 33.96 (Ar-*C*H$_2$-Ar), 34.14 (Ar-*C*H$_2$-Ar), 74.67 (OCH$_2$CH$_2$Br), 77.21 (OCH$_2$*C*H$_2$Br), 78.10 (O*C*H$_2$CH$_2$CH$_3$), 124.92 (*C*H^{Ar}), 125.17 (*C*H^{Ar}), 125.31 (*C*H^{Ar}), 125.40 (*C*H^{Ar}), 125.58 (*C*H^{Ar}), 125.76 (*C*H^{Ar}), 126.42 (*C*H^{Ar}), 126.86 (*C*H^{Ar}), 127.39 (*C*^{Ar}-CH$_2$-C^{Ar}), 127.46 (*C*^{Ar}-CH$_2$-C^{Ar}), 128.68 (*C*^{Ar}-CH$_2$-C^{Ar}), 129.65 (*C*^{Ar}-CH$_2$-C^{Ar}), 132.25 (*C*^{Ar}-CH$_2$-C^{Ar}), 133.16 (*C*^{Ar}-CH$_2$-C^{Ar}), 133.17 (*C*^{Ar}-CH$_2$-C^{Ar}), 134.66 (*C*^{Ar}-CH$_2$-C^{Ar}), 142.17 (*C*^{Ar}-*t*-Bu), 143.10 (*C*^{Ar}-*t*-

Bu), 146.11 (C^{Ar}-*t*-Bu), 147.27 (C^{Ar}-*t*-Bu), 148.29 (C^{Ar}-OH), 149.85 (C^{Ar}-OH), 151.13 (C^{Ar}-OCH_2), 151.42 (C^{Ar}-OCH_2); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{49}H_{66}BrO_4$ 797.4144; Found 797.4152; mp. 95-96°C; $[\alpha]_D^{20}$ +44.4 (c=1.35, $CHCl_3$).

(*cR*)-5,11,17,23-Tetra-tert-butyl-25,26-diphosphonyloxy-27-phosphonylethoxy-28-propoxycalix[4]arene (*cR,pR*)-6.

Calix[4]arene chloride (*cS*)-**4** (98.0 mg, 0.13 mmol) was dissolved in 2 mL of triisopropylphosphite. The solution was then refluxed overnight (T_{bath} = 185°C). After completion of the reaction (monitored by TLC), solvent was removed in vacuo and the crude materials were purified by flash-chromatography on silica, using chloroform ($CHCl_3$) as eluent to yield the product (79.4 mg, yield 80%) as a white crystalline solid.

^{1}H NMR (δ (ppm), 400MHz, $CDCl_3$): 0.58 (s, 9H, t-Bu), 1.00 (s, 9H, t-Bu), 1.11 (t, 3H, $OCH_2CH_2CH_3$, $^3J_{H\text{-}H}$ = 7.4 Hz), 1.34 (s, 9H, t-Bu), 1.36 (s, 9H, t-Bu), 1.80-1.96 (m, 2H, $OCH_2CH_2CH_3$), 2.50-2.71 (m, 1H, OCH_2CH_2PO), 3.19 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 13.4 Hz), 3.24 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 13.4 Hz), 3.36 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 14.0 Hz), 3.48 (d, 1H, Ar-CH_2-eq, $^2J_{H\text{-}H}$ = 15.0 Hz), 3.68-3.89 (m, 3H, 2H $OCH_2CH_2CH_3$, 1H OCH_2CH_2PO), 4.21 (m, 1H, OCH_2CH_2PO), 4.30-4.40 (m, 1H, OCH_2CH_2PO), 4.35 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 13.8 Hz), 4.39 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 13.8 Hz), 4.49 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 13.8 Hz), 4.70 (d, 1H, Ar-CH_2-ax, $^2J_{H\text{-}H}$ = 14.9 Hz), 6.15 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.2 Hz), 6.26 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.0 Hz), 6.75 (d, 1H, Ar-*H*), 6.76 (s, 1H, Ar-*H*), 7.12 (d, 1H, Ar-*H*, $^4J_{H\text{-}H}$ = 2.0 Hz), 7.20 (m, 2H, Ar-*H*), 7.22 (s, 1H, Ar-*H*); $^{13}C\{^1H\}$ NMR (δ (ppm), 125MHz, $CDCl_3$): 11.13 ($OCH_2CH_2CH_3$), 23.60 ($OCH_2CH_2CH_3$), 29.70 (CMe_3), 29.70 (CMe_3), 30.89 ($C(CH_3)_3$), 31.07 ($C(CH_3)_3$), 31.55 ($C(CH_3)_3$), 31.62 ($C(CH_3)_3$), 31.40 (CMe_3), 32.09 (CMe_3), 33.42 (Ar-CH_2-Ar), 33.82 (Ar-CH_2-Ar), 34.22 (Ar-CH_2-Ar), 34.33 (Ar-CH_2-Ar), 36.61 ($OPCH_2CH_2O$), 64.32 (OCH_2CH_2PO), 77.05 ($OCH_2CH_2CH_3$), 124.03 (CH^{Ar}), 124.20 (CH^{Ar}), 125.05 (CH^{Ar}), 125.11 (CH^{Ar}), 125.51 (CH^{Ar}), 125.58 (CH^{Ar}), 125.96 (CH^{Ar}), 126.63 (CH^{Ar}), 128.33 (C^{Ar}-CH_2-C^{Ar}), 130.47 (C^{Ar}-CH_2-C^{Ar}), 130.88 (C^{Ar}-CH_2-C^{Ar}), 131.88 (C^{Ar}-CH_2-C^{Ar}), 132.31 (C^{Ar}-CH_2-C^{Ar}), 133.50 (C^{Ar}-CH_2-C^{Ar}), 135.31 (C^{Ar}-CH_2-C^{Ar}), 136.50 (C^{Ar}-CH_2-C^{Ar}), 144.94 (C^{Ar}-*t*-Bu), 146.57 (C^{Ar}-*t*-Bu), 146.81 (C^{Ar}-*t*-Bu), 147.15 (C^{Ar}-*t*-Bu), 146.28 (d, $^2J_{C\text{-}P}$ = 10.4 Hz, C^{Ar}-OP), 147.15 (d, $^2J_{C\text{-}P}$ = 10.7 Hz, C^{Ar}-OP), 152.32 (C^{Ar}-O-CH_2), 153.21 (C^{Ar}-OCH_2); $^{31}P\{^1H\}$ NMR (δ (ppm), 162MHz, $CDCl_3$): 24.10; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{49}H_{64}O_5P$ 763.4491; Found 763.4496; mp 280-281°C; $[\alpha]_D^{20}$ +8.9 (c=1.7, $CHCl_3$).

(*cR*)-5,11,17,23-Tetra-tert-butyl-25-hydroxy-26-phosphonyloxy-27-phosphonylethoxy-28-propoxycalix[4]arene (*cR,pR*)-7.

Calix[4]arene phosphonate (*cR,pR*)-**6** (40 mg, 0.0524 mmol) was dissolved in methanol (3 mL) at room temperature. Sodium hydroxide (3 mL of a 2 M water solution) was added and the resulting mixture was stirred at T_{bath} = 90°C for 3 h. After cooling back to room temperature, the mixture was quenched with 2 M hydrochloric acid and extracted with dichloromethane, washed twice with 25 mL of distilled water, 25 mL of brine and, finally, dried over Na_2SO_4. Solvent was removed in vacuo to obtain product (39.2 mg, yield 96%) as a white crystalline solid.

^{1}H NMR (δ (ppm), 400MHz, $CDCl_3$): 0.82 (s, 9H, t-Bu), 0.99 (s, 9H, t-Bu), 1.13 (t, $^3J_{H-H}$ = 7.4 Hz, C*H*$_3$), 1.36 (s, 9H, t-Bu), 1.37 (s, 9H, t-Bu), 1.97 (m, 2H, $OCH_2CH_2CH_3$), 2.30 (m, 1H, OCH_2CH_2PO), 2.65 (m, 1H, OCH_2CH_2PO), 3.25 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar-C*H*$_2$-Ar), 3.29 (d, 1H, $^2J_{H-H}$ = 14.5 Hz, Ar-C*H*$_2$-Ar), 3.49 (d, 1H, $^2J_{H-H}$ = 14.0 Hz, Ar-C*H*$_2$-Ar), 3.85 (t, 2H, $^3J_{H-H}$ = 6.9 Hz, $OCH_2CH_2CH_3$), 4.04 (d, 1H, $^2J_{H-H}$ = 13.6 Hz, Ar-C*H*$_2$-Ar), 4.04 (m, 1H, OCH_2CH_2PO), 4.24 (d, 1H, $^2J_{H-H}$ = 12.8 Hz, Ar-C*H*$_2$-Ar), 4.43 (d, 1H, $^2J_{H-H}$ = 13.8 Hz, Ar-C*H*$_2$-Ar), 4.59 (m, 1H, OCH_2CH_2PO), 4.75 (d, 1H, $^2J_{H-H}$ = 14.2 Hz, Ar-C*H*$_2$-Ar), 6.27 (bs, 2H, O*H*), 6.43 (d, 1H, $^4J_{H-H}$ = 2.6 Hz, Ar-*H*), 6.53 (d, 1H, $^4J_{H-H}$ = 2.5 Hz, Ar-*H*), 6.72 (d, 1H, $^4J_{H-H}$ = 2.4 Hz, Ar-*H*), 6.79 (d, 1H, $^4J_{H-H}$ = 2.5 Hz, Ar-*H*), 7.07 (d, 1H, $^4J_{H-H}$ = 2.4 Hz, Ar-*H*), 7.10 (bs, 3H, Ar-*H*); $^{13}C\{^1H\}$ NMR (δ (ppm), 125MHz, $CDCl_3$): 10.7 ($OCH_2CH_2CH_3$), 23.6 ($OCH_2CH_2CH_3$), 29.7 (CMe_3), 30.9 (CMe_3), 31.0 ($C(CH_3)_3$), 31.1 ($C(CH_3)_3$), 31.6 ($C(CH_3)_3$), 31.7 (d, J^1_{C-P} = 39.1 Hz, OCH_2CH_2PO), 31.8 ($C(CH_3)_3$), 33.0 (CMe_3), 33.5 (Ar-CH_2-Ar), 33.6 (CMe_3), 33.9 (Ar-CH_2-Ar), 34.0 (Ar-CH_2-Ar), 34.2 (Ar-CH_2-Ar), 66.5 (d, J^2_{C-P} = 10.0 Hz, OCH_2CH_2PO), 78.0 ($OCH_2CH_2CH_3$), 124.8 (CH^{Ar}), 125.3 (CH^{Ar}), 125.55 (CH^{Ar}), 125.60 (CH^{Ar}), 125.62 (CH^{Ar}), 125.70 (CH^{Ar}), 125.74 (CH^{Ar}), 126.5 (CH^{Ar}), 126.9 (C^{Ar}-CH_2-C^{Ar}), 129.1 (C^{Ar}-CH_2-C^{Ar}), 129.6 (C^{Ar}-CH_2-C^{Ar}), 130.8 (d, $^4J_{C-P}$ = 5.0 Hz, C^{Ar}-OCH_2CH_2PO), 131.4 (C^{Ar}-CH_2-C^{Ar}), 132.9 (C^{Ar}-CH_2-C^{Ar}), 134.8 (C^{Ar}-CH_2-C^{Ar}), 136.6 (C^{Ar}-CH_2-C^{Ar}), 141.7 (C^{Ar}-t-Bu), 144.6 (C^{Ar}-t-Bu), 146.03 (d, $^2J_{C-P}$ = 11.1 Hz, C^{Ar}-OP), 146.7 (C^{Ar}-t-Bu), 146.9 (C^{Ar}-t-Bu), 150.5 (C^{Ar}-OCH_2), 150.6 (C^{Ar}-CH_2-C^{Ar}), 153.3 (C^{Ar}-OH); $^{31}P\{^1H\}$ NMR (δ (ppm), 162MHz, $CDCl_3$): 23.04; HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd. for $C_{49}H_{64}O_6P$ 779.4441; Found 779.4433; mp 116-117˚C; $[\alpha]_D^{20}$ +20.6 (c=0.27, $CHCl_3$).

X-ray structural analyses. Single crystal of each compound was mounted under inert perfluoropolyether at the tip of glass fiber and cooled in the cryostream of a Nonius CAD4 fitted with a Bruker APEXII CCD. The structures were solved by using the integrated space-group and crystal structure determination SHELXt software[28] and refined by least-squares procedures on F^2 using SHELXL-2014.[29] All H atoms attached to carbon or oxygen atoms were introduced in calculation in idealised positions and treated as riding models. In all compounds disorders were observed affecting some isopropyl group in compound (c*S*)**-3** and (c*R,pR*)**-7** or propyl chain in (*cS*)**-3** and (c*R,pR*)**-6** . These disordered parts were treated with the tools available in SHELX-2014. In (c*R,pR*)**-7** there are large voids within the unit cell containing some solvent molecules which were difficult to characterize and modelize. So we use the SQUEEZE option within PLATON[30] to remove the contribution of the disordered solvent molecules. The absolute configuration for compounds (c*R,pR*)**-6** and (c*R,pR*)**-7** has been determined by refining the Flack's parameter.[31] The drawing of the molecules was realised with the help of ORTEP32.[32,33] Crystal data and refinement parameters are shown in Table S1.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1572943-1572945. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Aza Diels–Alder reaction procedure.

In a well dried vial under inert atmosphere, a solution of benzimine (0.25 mmol) and catalyst (*cR,pR*)**-7** (9.8 mg, 0.0125 mmol) in dry CH_3CN (3.0 mL) was stirred at room temperature for 30 min. After diene (0.50 mmol) adddition, the mixture was further stirred at room temperature for 24 h. The resulting mixture was quenched with 2 M HCl aqueous solution, diluted with saturated water solution of $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase washed twice with 5 mL of distilled water and 5 mL of brine, dried over Na_2SO_4. The solution was concentrated under reduced pressure to give pale yellow oil, which was further purified by flash chromatography using hexane/ethylacetate (3/2, v/v) as eluting mixture to give the product as a yellow solid. The enantiomeric excess value was determined

by supercritical fluid chromatography (SFC)-HPLC [Chiralcel OJ column; CO_2/iPrOH, 9:1; flow rate: 5 mL min^{-1}].

Asymmetric epoxide ring opening reaction procedure.

In a well dried vial under inert atmosphere, a solution of benzoic acid (0.75 mmol) and catalyst (*cR,pR*)-**7** (39.2 mg, 0.05 mmol) in dry toluene (3.0 mL) was stirred at room temperature for 30 min. After epoxide (0.50 mmol) was added, the mixture was further stirred at room temperature for 24 h. The resulting mixture was quenched with 2M water HCl, diluted with $NaHCO_3$ saturated water solution and then extracted with CH_2Cl_2. The organic phase washed twice with 5 mL of distilled water and 5 mL of brine, dried over Na_2SO_4. The solution was concentrated under reduced pressure to give pale yellow oil, which was further purified by flash chromatography using hexane/MTBE (3/2, v/v) as eluting mixture to give the product as a white solid. Enantiomeric excesses were determined by (SFC)-HPLC [Chiralpak IA column; CO_2/iPrOH, 9:1; flow rate: 2 mL min^{-1}].

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publication website at DOI:

Copies of ^{1}H, ^{13}C, ^{31}P NMR and crystallographic data.

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