# Symmetrical and inherently chiral water-soluble calix[4]arenes bearing dihydroxyphosphoryl groups

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A series of symmetrical and inherently chiral water-soluble calix[4]arenes bearing one, two or four proton-ionisable dihydroxyphosphoryl groups at the narrow rim of the macrocycle has been synthesised by consecutive treatment of appropriate diethoxyphosphoryl derivatives with bromotrimethylsilane and methanol. The calix[4]arene phosphoric acids synthesised possess p$K_a$-values 2.85–3.10 ($CH_3OH$–$H_2O$ 70 : 30) and form salts with L-(−)-α-phenylethylamine or (1*S*,2*R*)-(+)-ephedrine in methanol solution. The salts of the inherently chiral calixarene phosphoric acids with chiral amines are easily separated into diastereomeric forms by the RP HPLC method on Separon SGX C18 or Partisil 5 ODS 3 achiral columns.

## Introduction

Molecular design of the Host systems based on water-soluble calixarenes(CAs)[1] which can mimic enzymes in an aqueous media are a focus of interest and research activity within supramolecular chemistry.[2] After the first reports of Ungaro[3] and Shinkai[4] a variety of new compounds have been obtained and their remarkable binding properties in aqueous media have been demonstrated.[5]

Water-soluble calixarenes have been synthesised by functionalisation of the macrocyclic narrow rim or the wide rim of parent calixarenes with non-ionic glucosides,[6] cyclodextrins,[7] or poly(ethylene glycol)[8] moieties as well as with cationic or anionic groups such as $NR_3^+$,[9] $CO_2^-$,[10] $SO_3^-$,[11] $PO_3^{2-}$.[8,12] These calixarenes form complexes in a water medium with metal cations,[13] fullerenes,[14] choline and acetylcholine,[15] and amino acids,[16] and are used as ligands in dual supramolecular and metallocomplexing catalysis,[17] as sensors in binding of analytes.[18]

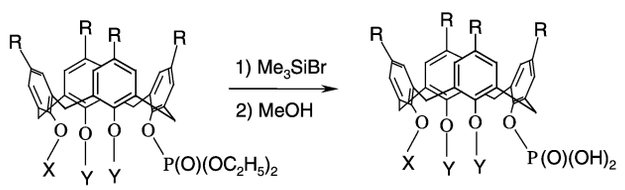
The development of water-soluble calixarenes has led to a resurgence in the study of their biological activities,[19] with patents on their activities as anticoagulants and antithrombotics,[20] antiviral,[21] antimicrobial and antifungal agents.[22]

In the present paper we describe the synthesis, stereochemistry and some binding properties of the new water-soluble calix[4]arenes bearing proton-ionisable dihydroxyphosphoryl groups at the macrocyclic lower rim.[23] The main attention in the article is focused on the inherently chiral[24] derivatives with asymmetrical placement of substituents at the macrocyclic rim of calix[4]arenes.

## Results and discussion

### Symmetrical calix[4]arene phosphoric acids

Calix[4]arenes **5**–**8**, containing one, two and four dihydroxyphosphoryl groups at the lower rim, have been synthesised by consecutive treatmen of easily accessible diethoxyphosphoryl derivatives of calix[4]arenes **1**–**4**[25] with bromotrimethylsilane and methanol. The reaction of ethyl esters **1**–**4** with an excess of bromotrimethylsilane in dry chloroform (24 h; 20 °C) quantitatively leads to corresponding trimethylsilyl esters CA–$P(O)(OSiMe_3)_2$, which are identified by $^{31}P$ NMR spectroscopy ($\delta \approx -22$). Treatment of the trimethylsilyl esters with absolute methanol results in cleavage of the P–O–Si bonds and formation of the corresponding acids **5**–**8** in high yields (Scheme 1).




**1-4** **5-8**

**1** R = H, X = Et, Y = H
**2** R = H, X = P(O)(OEt)$_2$, Y = H
**3** R = t-Bu, X = P(O)(OEt)$_2$, Y = H
**4** R = t-Bu, X = Y = P(O)(OEt)$_2$

**5** R = H, X = Et, Y = H
**6** R = H, X = P(O)(OH)$_2$, Y = H
**7** R = t-Bu, X = P(O)(OH)$_2$, Y = H
**8** R = t-Bu, X = Y = P(O)(OH)$_2$

**Scheme 1**

Calixarene phosphorus acids **5**–**8** in solution possess a *flattened cone* conformation, in which two phosphorylated aromatic rings of the macrocyclic skeleton are nearly perpendicular to the main plane of the macrocycle formed by methylene bridges, and two phenol groups are nearly parallel to this macrocyclic plane. Two doublets of an AX spin system of methylene bridge protons with a difference between their chemical shifts of $\Delta\delta$ 1.1 ppm for calixarene monophosphoric acids or diphosphoric acids **5**–**7**, and 1.5 ppm for calix[4]arene tetraphosphosphoric acid **8**, are observed in their $^1H$ NMR spectra. The chemical shift of the methylene bridge carbon atoms in $^{13}C$ NMR spectra of diphosphoric acid **7** at $\delta$ 32 also testifies to the conformation with the all-*syn* orientation of aromatic rings.[26]

In the case of **8**, similar to most of the lower-rim-tetrasubstituted calix[4]arenes, a fast (over the NMR timescale) exchange between two equally populated *flattened cone* conformations can be realised in solution.[27]

Calix[4]arene phosphoric acids **5**–**8** are white crystalline compounds, easily soluble in the polar organic solvents (methanol, ethanol, DMSO, DMF) as well as in alkaline aqueous solutions. The first p$K_a$-values of calixarene phosphoric acids **6** (2.90 ± 0.10), **7** (3.10 ± 0.10), and **8** (2.90 ± 0.10) obtained by potentiometric titration of the acids with KOH in

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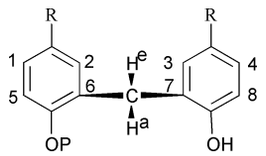
**Table 1** $^{1}H$, $^{31}P$ NMR spectra of calix[4]arene phosphoric acids **6**–**8** and their chiral salts[a]




| No | $\delta(H^{eq}, H^{ax})$ ($^{2}J_{HH}$/Hz) | $\delta^{b}(H^{1}, H^{2})$ ($^{3}J_{HH}$/Hz) | $\delta(H^{3}, H^{4})$ ($^{3}J_{HH}$/Hz) | $\delta_P$/ppm |
|---|---|---|---|---|
| **6** | 3.35, 4.44 (14.0) | 6.65 (6.8) | 7.06 (6.8) | −4.4 |
| **6** + **PEA**[c] (1 : 2.8) | 3.22, 4.53<br>3.24, 4.61 (14.0) | 6.62 (7.2) | 6.92[d] (7.2) | |
| **6** + **PEA**[c] (1 : 3.7) | 3.22, 4.58<br>3.24, 4.70 (14.0) | 6.63 (7.4) | 6.91[d] (7.4) | |
| **6** + **EP**[c] (1 : 2.6) | 3.27, 4.64<br>4.70 | 6.59 (7.4) | 6.95 (7.4) | |
| **6** + **EP**[c] (1 : 3.3) | 3.26, 4.68<br>4.77 (14.0) | 6.55–6.60 (7.5) | 6.94 (7.5) | |
| **7** | 3.31, 4.42 (13.6) | 6.75 | 7.10 | −4.1 |
| **7** + **PEA**[e] (1 : 2.8) | 3.23, 4.58<br>4.66 (13.5) | 6.78 | 6.99,[f] 7.01 | −1.7 |
| **7** + **PEA**[e] (1 : 4.9) | 3.21, 4.59<br>4.77 (13.2) | 6.81,[f] | 6.97,[f] 6.99 | −1.2 |
| **7** + **EP**[e] (1 : 4.7) | 3.21, 4.68<br>4.78 (13.8) | 6.61,[f] 6.63 | 6.98,[f] 7.01 | 0.5 |
| **8** | 3.18, 4.75 (13.4) | 6.89 | | −3.1 |
| **8** + **EP**[e] (1 : 3) | 3.12, 4.98 (12.8) | 6.86 | | |

[a] Deuteromethanol. [b] Assignment on the HETCOR experiment. [c] Concentration of acid – $C$ = 31.7 mM. [d] Doublet of quartets, ABX-system, $^{4}J_{HH}$ = 1.2 Hz. [e] Concentration of an acid – $C$ = 25 mM. [f] Doublet of doublets, $^{4}J_{HH}$ = 2.4 Hz.

70% methanol solution are close to the first p$K_a$-value of the corresponding phenylphosphoric acid (3.30 ± 0.10) determined under the same conditions. As expected, the acidity is sufficiently high to form salts with amines.

The process of acid–amine salt formation was monitored by $^{1}H$, $^{31}P$ NMR titration of calixarenes **6**–**8** with L-(−)-α-phenylethylamine (PEA) or (1*S*,2*R*)-(+)-ephedrine (EP) in deuteromethanol solution. Starting from an amine : acid ratio of 0.7 : 1, signals of enantiotopic equatorial protons of the methylene bridges Ar–$CH_2$–Ar of the macrocyclic skeleton are split (Table 1). Increasing the amine : acid ratio to 2 : 1 leads to further splitting of the signals of the axial Ar–$CH_2$–Ar hydrogen atoms, as well as of aromatic enantiotopic *meta*-hydrogen atoms in the phosphorylated ($H^1H^2$) and *non*-phosphorylated ($H^3H^4$) phenolic fragments (Table 1). As a result of this, the calixarene aromatic protons in the $^{1}H$ NMR spectra show an ABX spin system in the case of calix[4]-arenediphosphate **6** or two AB spin systems in the spectra of *tert*-butylcalix[4]arene diphoshate **7**. A similar doubling of signals of enantiotopic carbon atoms of the methylene bridges,[28] as well as of $C^5C^6$, $C^7C^8$, and $C^3C^4$ carbon atoms of the benzene rings, is observed in $^{13}C$ NMR spectra in the case of an interaction of acid **7** with PEA and EP (Table 2). Further increasing the amine : acid ratio (>2 : 1) leads only to very small changes in the spectra, which is why we suppose the complexes formed have the 2 : 1 stoichiometry. In contrast to diphosphoric acids **6**, **7** ($C_{2v}$ symmetry) the more symmetrical calixarenete traphosphoric acid **8** ($C_{4v}$ symmetry) does not display splitting of the signals in its $^{1}H$, $^{13}C$ NMR spectra in the presence of EP (Table 1).

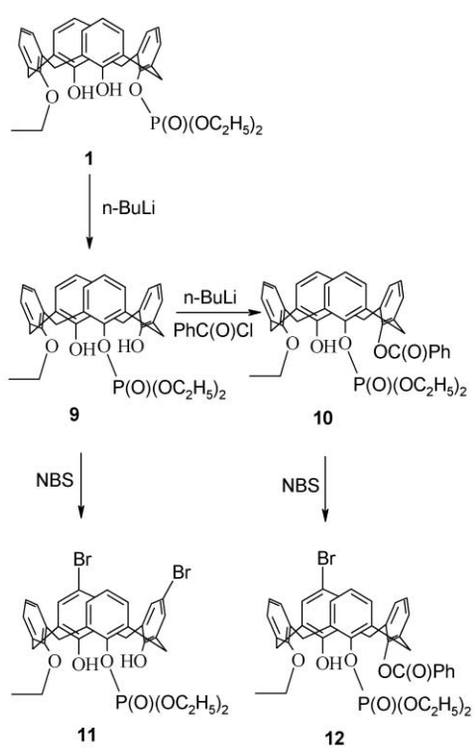
The diastereotopicity observed for the hydrogen and carbon atoms in the $^{1}H$, $^{13}C$ NMR spectra of the chiral salts formed at millimolar concentration specifies that in deuteromethanol solution at room temperature the salts exist as tight ion pairs.[29] However, increasing the temperature to 60 °C or addition of deuterated water leads to appreciable dissociation of the ion pairs. Under these conditions the diastereotopicity of the methylene bridge protons or aromatic rings protons is less expressed and their signals are broad in the $^{1}H$ NMR spectra.

### Inherently chiral calix[4]arene phosphoric acids

Chiral calixarenes are considered as promising Host molecules for enantiorecognition and enantioseparation of chiral Guest molecules. To the best of our knowledge there are few examples of water-soluble chiral calixarenes known to date.[30]

There are several synthetic approaches towards chiral calixarenes. One approach is based on insertion of chiral groups into the wide, narrow rim or bridges of the macrocycle.[31] The salts of the acids **5**–**8** with chiral amines at the lower rim could be considered as such kinds of chiral calixarenes.

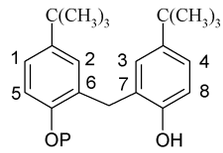
The second approach, based on an asymmetric placement of *achiral* substituents at the macrocyclic rim, leads to inherently chiral calixarenes, first synthesised by Böhmer *et al.* by 1,3-alkylation of calix[4]arenes with two different proximally placed *para*-substituents on the phenolic moieties.[32] Recently we have developed a new approach based on phosphorotropic isomerisation of $C_{2v}$-symmetrical *syn*-1,3-disubstituted calix[4]-arenes into asymmetrical 1,2-regioisomers[33] promoted by strong bases. For example, chiral 25-*O*-ethyl-26-*O*-(diethoxyphosphoryl)calix[4]arene **9** was synthesised by a reaction of $C_s$-symmetric 25-*O*-ethyl-27-*O*-(diethoxyphosphoryl)calix[4]arene **1** with one equivalent of *n*-butyl-lithium (solution in *n*-hexane) (see Scheme 2).




**Scheme 2**

Unexpectedly, further regioselective acylation of calix[4]-arene **9** by benzoyl chloride results in the new chiral calixarene **10**, where the benzoyl group is in a proximal position to the phosphoryl group (structure **A**, Chart 1) but not to the ethyl

**Table 2** $^{13}C$ NMR spectra of *tert*-butylcalix[4]arene diphosphoric acid **7** and salts (deuteromethanol, $c = 25$ mM)




| | $\delta$[C($CH_3$)$_3$] | $\delta$[$CH_2$] | $\delta$[$C$(CH$_3$)$_3$] | $\delta$[C$^1$C$^2$] | $\delta$[C$^3$C$^4$] | $\delta$[C$^5$C$^6$] | $\delta$[C$^7$C$^8$] | $\delta$[C–*t*-Bu] | $\delta$[C–OH] | $\delta$[C–O–P] |
|---|---|---|---|---|---|---|---|---|---|---|
| **7** | 31.43 | 32.93 | 34.73 | 126.81 | 126.36 | 133.45 | 129.74 | 143.46 | 151.34 | 144.38 |
| | 32.15 | | 34.80 | | | | | 148.56 | | |
| **7** + PEA | 31.64 | 33.83 | 34.65 | 126.37 | 125.97 | 134.75 | 130.24 | 142.86 | 151.00 | 146.69 |
| (1 : 5) | 32.15 | 33.94 | 34.71 | | | 134.79 | 130.28 | 146.79 | | |
| **7** + EP | 31.95 | 33.82 | 34.99 | 126.53 | 126.39 | 134.30 | 129.14 | 142.70 | 151.72 | 147.61 |
| (1 : 5) | 32.55 | 34.03 | 35.03 | | 126.43 | 134.57 | | 129.33 | | 143.11 |

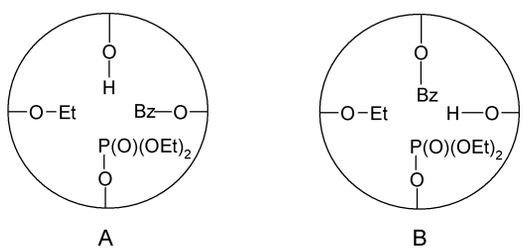
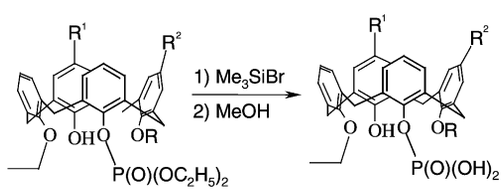



**Chart 1**

one as shown in the structure **B**. This type of substitution is confirmed by the values of the chemical shifts and absorption bands of the OH group in $^1H$ NMR ($\delta = 7.55$, $CDCl_3$) and IR ($\nu = 3280$ cm$^{-1}$) spectra, pointing to the formation of an intramolecular hydrogen bonding O–H ··· O–Et. In the case of isomer **B** with the distal orientation of ethyl and hydroxy groups in which the hydrogen bonds O–H ··· O–Bz or O–H ··· O–P are much more feeble, the chemical shifts and bands of absorption of the OH group should be shifted to high fields ($\delta$) and lower frequencies ($\nu$); as occurs in 25,27-bis-*O*-(diethoxyphosphoryl)calixarene **2** ($\delta$ = 5.60 and $\nu = 3564$ cm$^{-1}$).

Chiral calixarenes **11** and **12** were synthesised by regioselective bromination of non-substituted phenolic fragments of **9**, **10** at the *para*-positions by *N*-bromosuccinimide.

Esters **9**–**12** have been transformed by treatment with bromotrimethylsilane and methanol into chiral calix[4]arene phosphoric acids **13**–**16** (Scheme 3). Acids **13**–**16**, similarly



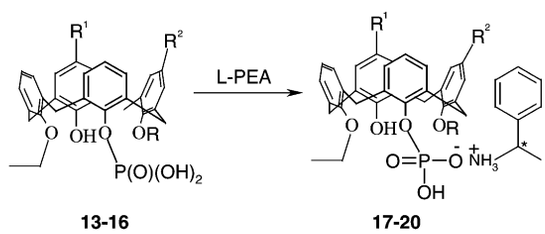

**9-12** **13-16**

**9,13** R = R$^1$ = R$^2$ = H
**10,14** R = C(O)Ph, R$^1$ = R$^2$ = H
**11,15** R = H, R$^1$ = R$^2$ = Br
**12,16** R = C(O)Ph, R$^1$ = Br, R$^2$ = H

**Scheme 3**

to their precursors **9**–**12**, exist as racemic mixtures of two enantiomeric forms.

The further interaction of acids **13**–**16** with PEA led to diastereomeric salts **17**–**20** (Scheme 4). The diastereomeric nature of the salts was confirmed by the presence of two equally intensive sets of signals for all functional groups in the $^1H$ NMR spectra, and two signals for the phosphorus atom in the $^{31}P$ NMR spectra recorded in $CDCl_3$ or methanol solution (Fig. 1, 2).




**13-16** **17-20**

**13,17** R = R$^1$ = R$^2$ = H
**14,18** R = C(O)Ph, R$^1$ = R$^2$ = H
**15,19** R = H, R$^1$ = R$^2$ = Br
**16,20** R = C(O)Ph, R$^1$=Br, R$^2$ = H

**Scheme 4**

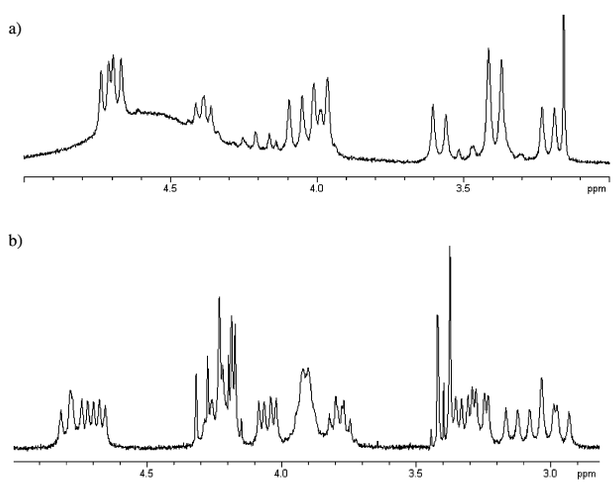



**Fig. 1** $^1H$ NMR spectra of acid **13** (region of the axial and equatorial protons of the methylene links and ArOCH$_2$ group) in DMSO-d$_6$ solution (a), and diastereomeric salt **17** in $CDCl_3$ solution (b).

Usually, enantioseparation of inherently chiral calixarenes is achieved with high performance liquid chromatography (HPLC) on chiral stationary phases, like Chiralpak OP (+),[34a] Sumipax OA-2000,[34b] and Chiralcel ODH.[34c] Recently[35] we have described an optical resolution of inherently chiral calix[4]arenes bearing phosphoryl groups by the additive chiral HPLC method using achiral columns. A number of chiral additives forming diastereomeric associates due to hydrogen bonding or salt bridging with the O–PO(OH)$_2$ group have been examined: D-(−)-tartaric acid, L-(−)-α-phenylethyl amine, (1*S*,2*R*)-(+)-ephedrine hydrochloride, L-(−)-menthol, L-alanine.

Considering the ability of calixarene phosphoric acids **13**–**16** to form weakly dissociated diastereomeric salts **17**–**20** with PEA in polar solvents like methanol, it was interesting to study

**Table 3** Chromatographic characteristics of calixarenes **17**–**20**

| Calixarene | Retention time $t_R$/min | | Capacity factor $k$ | | Selectivity α | Separation coefficient $R_S$ |
|---|---|---|---|---|---|---|
| **17**[a] | 1.20 | 2.33 | 0.19 | 1.31 | 6.94 | 2.5 |
| **18**[b] | 5.75 | 16.33 | 0.55 | 3.67 | 2.49 | 3.0 |
| **19**[c] | 1.33 | 1.65 | 0.32 | 0.63 | 2.03 | 1.23 |
| **20**[d] | 9.83 | 14.75 | 1.81 | 3.21 | 1.49 | 0.91 |

[a] Separon SGX C18 column, MeCN–$H_2O$ (86 : 14); [b] Partisil 5 ODS 3 column, MeOH–$H_2O$ (70 : 30); [c] Separon SGX C18 column, MeOH–MeCN (70 : 30); [d] Partisil 5 ODS 3 column, MeOH–MeCN (60 : 40).

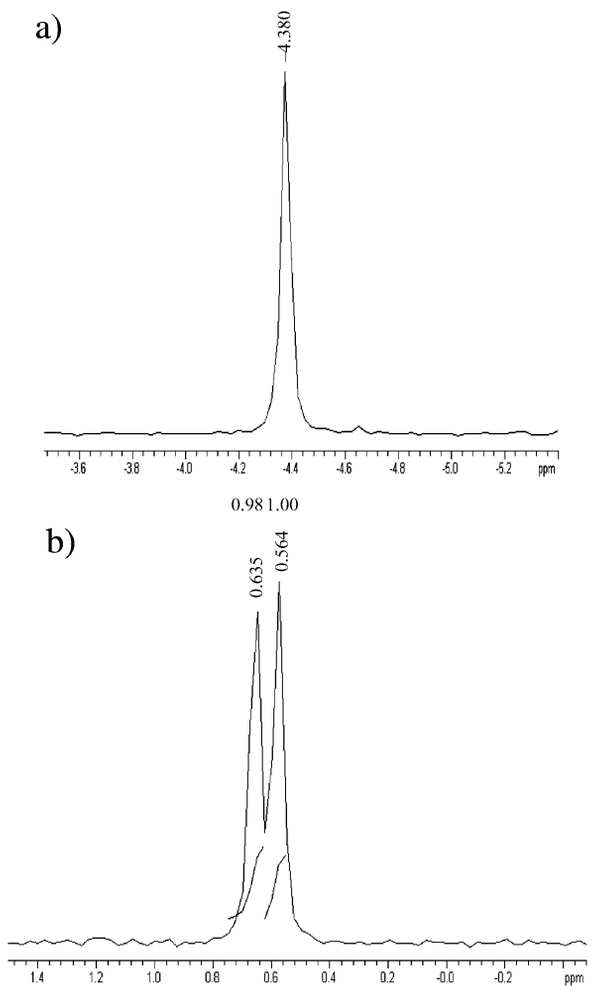



**Fig. 2** $^{31}P$ NMR spectra of acid **13** (a), and diastereomeric salt **17** (b) in methanol solution.

their separation on achiral columns. Standard achiral analytical columns Separon SGX C18 and Partisil 5 ODS 3 with methanol–water, acetonitrile–water or acetonitrile–methanol mixtures as the mobile phases have been examined. The conditions for the separation of salts **17**–**20** are described in the Experimental section, chromatographic characteristics are given in Table 3, and typical chromatograms are presented in Fig. 3. Indeed, chromatograms and the $R_S$-values within the range 0.91–3.0 demonstrate rather effective diastereomeric separation of the salts **17**–**20** under the conditions applied. The best separation has been achieved for trisubstituted calixarene **18** on a Partisil 5 ODS 3 column in methanol–water mobile phase. Preparative separation of the salts and isolation of enantiomerically pure calix[4]arene phosphoric acid is in progress.

### Conclusions

In this article we have described a variety of symmetrical or inherently chiral calix[4]arenes bearing one, two or four

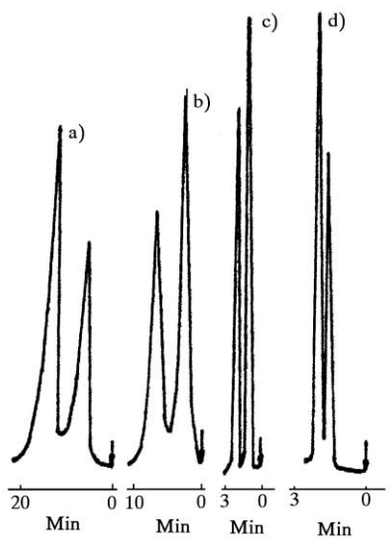



**Fig. 3** RP HPLC separation. a) calixarene **18**; b) calixarene **17**; c) calixarene **19**; d) calixarene **20**.

biologically 'friendly' dihydroxyphosphoryl groups at the narrow rim. We have found that these compounds easily form salts upon reaction with chiral alkylamines, which exist in methanol as weakly dissociated ion pairs. Using HPLC on stationary phases (Separon SGX C18 or Partisil 5 ODS 3) has allowed analytical separation of diastereomeric salts of the inherently chiral calixarene phosphoric acids with L-(−)-α-phenylethyl amine into individual diastereomers.

## Experimental

$^1H$, $^{13}C$ and $^{31}P$ NMR spectra were registered on Varian XL-300 and Bruker WP-200 spectrometers. Tetramethylsilane (internal) and 85% phosphoric acid (external) were used as standards in NMR experiments. Melting points were determined on an Boetius apparatus and are uncorrected.

### Synthesis of diethoxyphosphoryl derivatives of calix[4]arenes

Compounds **1**–**4**,[25,36] **9**,[33b] **11**[33b] were synthesised in accordance with the literature procedures.

**25-*O*-Ethyl-26-*O*-diethoxyphosphoryl-27-*O*-benzoylcalix[4]-arene (10).** *n*-Butyl-lithium (0.054 g, 0.85 mmol) (2.5 M solution in *n*-hexane) was added to a stirred solution of calixarene **9** (0.5 g, 0.85 mmol) in 15 ml of dry THF at room temperature. Benzoyl chloride (0.12 g, 0.85 mmol) was added to a reaction mixture at room temperature. The mixture was stirred for 10 min. THF was evaporated off under reduced pressure. The residue was dissolved in 15 ml of chloroform and washed with distilled water (3 × 10 ml). The organic solution was dried over $Na_2SO_4$ and then evaporated. The solid residue was crystallised from benzene–heptane (1 : 2) to give 0.43 g (86%) of white crystals, mp 159–161 °C; $^1H$ NMR ($CDCl_3$; 300 Mz) $\delta$ 0.99, 1.15 (two t, 6 H, $J$ = 7.2 Hz, $POCH_2CH_3$), 1.76 (t, 3 H, $J$ = 7.0

Hz, $ArOCH_2CH_3$), 3.27, 3.31 (two d, 2 H, $J$ = 13.6 Hz, $ArCH_2Ar$), 3.42, 3.46 (two d, 2 H, $J$ = 13.2 Hz, $ArCH_2Ar$), 3.71–4.39 (m, 8 H, $ArCH_2Ar$, $CH_2CH_3$), 4.59, 4.65 (two d, 2 H, $J$ = 13.7 Hz, $ArCH_2Ar$), 6.64–7.27 (m, 18 H, Ar*H*, ArO*H*); $^{31}$P NMR ($CDCl_3$; 81.026 MHz) $\delta$ −4.19. Calc. for $C_{41}H_{41}O_8P$: C, 71.08; H, 5.97; P, 4.47. Found: C, 71.27; H, 6.12; P, 4.46%.

**5-Bromo-25-*O*-ethyl-26-*O*-diethoxyphosphoryl-27-*O*-benzoylcalix[4]arene (12).** A solution of bromosuccinimide (0.12 g, 0.67 mmol) in acetone (10 ml) was added to a solution of calixarene **10** (0.35 g, 0.45 mmol) in acetone (10 ml) and the mixture was stirred at room temperature for 24 h. Acetone was evaporated off under reduced pressure. The residue was washed with hot water (3 × 15 ml) and was crystallised from aqueous methanol to give 0.33 g (85%) of white crystals, mp 125–126 °C; $^1$H NMR ($CDCl_3$; 300 MHz) $\delta$ 0.98, 1.13 (two t, 6 H, $J$ = 6.9 Hz, $POCH_2CH_3$), 1.75 (t, 3 H, $J$ = 7.0 Hz, $ArOCH_2CH_3$), 3.17–3.51 (m, 4 H, $ArCH_2Ar$), 3.86–4.39 (m, 8 H, $ArCH_2Ar$, $CH_2CH_3$), 4.58 (d, 1 H, $J$ = 13.6 Hz, $ArCH_2Ar$), 4.86 (d, 1 H, $J$ = 12.9 Hz, $ArCH_2Ar$), 6.64–7.27 (m, 12 H, Ar*H*, ArO*H*), 7.53 (t, 2 H, $J$ = 7.1 Hz, Ar*H*), 7.67 (t, 1 H, $J$ = 7.2 Hz, Ar*H*), 8.64 (d, 2 H, $J$ = 6.9 Hz, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.38. Calc. for $C_{41}H_{40}BrO_8P$: C, 63.82; H, 5.23; Br, 10.36; P, 4.01. Found: C, 63.71; H, 5.41; Br, 9.57; P, 3.95%.

### General procedure for the preparation of calixarene phosphoric acids (5–8, 13–16)

Bromotrimethylsilane (20 mmol for every diethoxyphosphoryl group) was added to a solution of a mono-, di-, or tetrakis-*O*-(diethoxyphosphoryl)calix[4]arene **1**–**4**, **9**–**12** (2 mmol in 20 ml of dry chloroform). The reaction mixture was stirred at room temperature for 24 h and was then evaporated under reduced pressure. An excess of absolute methanol was added to the residue. The methanolic solution was boiled for 2 h and then evaporated. The solid residue was dried *in vacuum* (0.05 mm) for 2 h. Further details are given for the individual compounds.

**25-*O*-Ethyl-27-*O*-(dihydroxyphosphoryl)calix[4]arene (5).** Yield 0.8 g (88%) of white crystals, mp 196–198 °C; $^1$H NMR ($CD_3OD$; 300 MHz) $\delta$ 1.48 (t, 3 H, $J$ = 7.1 Hz, $CH_2CH_3$), 3.28, 3.31 (two d, 4 H, $J$ = 13.4 Hz, $ArCH_2Ar$), 4.02 (q, 2 H, $J$ = 13.2 Hz, $CH_2CH_3$), 4.04 (d, 4 H, $J$ = 13.5 Hz, $ArCH_2Ar$), 6.43 (t, 1 H, $J$ = 7.5 Hz, Ar*H*), 6.56 (t, 1 H, $J$ = 7.2 Hz, Ar*H*), 6.58 (t, 2 H, $J$ = 7.3 Hz, Ar*H*), 6.59 (d, 2 H, $J$ = 7.8 Hz, Ar*H*), 6.74 (d, 2 H, $J$ = 7.6 Hz, Ar*H*), 6.99 (d, 2 H, $J$ = 7.4 Hz, Ar*H*), 7.01 (d, 2 H, $J$ = 7.6 Hz, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.4; Calc. for $C_{30}H_{29}O_7P$: C, 67.66; H, 5.49; P, 5.82. Found: C, 67.86; H, 5.36; P, 5.23%.

**25,27-Bis-*O*-(dihydroxyphosphoryl)calix[4]arene (6).** Yield 2.18 g (93%) of colorless crystals after precipitation by hexane from diethyl ether solution. Mp 186–188 °C; $^1$H NMR ($CD_3OD$; 200 MHz) $\delta$ 3.35, 4.42 (two d, 8 H, $J$ = 14 Hz, $ArCH_2Ar$), 6.40–7.0 (m, 12 H, Ar*H*); $^{31}$P NMR ($CD_3OD$; 81 MHz) $\delta$ −4.4. Calc. for $C_{28}H_{26}O_{10}P_2\cdot 2H_2O$: C, 54.20; H, 4.87; P, 10.60. Found: C, 54.03; H, 4.90; P, 10.70%.

**25,27-Bis-*O*-(dihydroxyphosphoryl)-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (7).** Yield 1.3 g (80%) of colorless crystals after precipitation by hexane from diethyl ether solution. Mp 186–191 °C; $^1$H NMR ($CD_3OD$; 200 MHz) $\delta$ 0.86 (s, 18 H, $C(CH_3)_3$), 1.25 (s, 18 H, $C(CH_3)_3$), 3.31, 4.42 (two d, 8 H, $J$ = 14 Hz, $ArCH_2Ar$), 6.75 (s, 4 H, Ar*H*), 7.10 (s, 4 H, Ar*H*); $^{31}$P NMR ($CD_3OD$; 81 MHz) $\delta$ −4.1. Calc. for $C_{44}H_{58}O_{10}P_2\cdot H_2O$: C, 63.91; H, 7.26; P, 7.50. Found: C, 63.79; H, 7.21; P, 6.88%.

**25,26,27,28-Tetrakis-*O*-(dihydroxyphosphoryl)-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (8).** Yield 1.8 g (95%) of white crystals after precipitation by hexane from diethyl ether solution. Mp 213–216 °C; $^1$H NMR ($CD_3OD$; 200 MHz) $\delta$ 1.01 (s, 36 H, $C(CH_3)$), 3.18, 4.75 (two d, 8 H, $ArCH_2Ar$, $J$ = 14 Hz), 6.89 (s, 8 H, Ar*H*); $^{31}$P NMR ($CD_3OD$; 81 MHz) $\delta$ −3.1. Calc. for $C_{44}H_{60}O_{16}P_4\cdot 2H_2O$: C, 52.59; H, 6.41; P, 12.33. Found: C, 52.52; H, 6.56; P, 12.57%.

**25-*O*-Ethyl-26-*O*-(dihydroxyphosphoryl)calix[4]arene (13).** Yield 0.8 g (88%) of white crystals after precipitation by water from methanol solution. Mp 181–183 °C; $^1$H NMR (DMSO-$d_6$; 300 MHz) $\delta$ 1.71 (t, 3 H, $J$ = 7.0 Hz, $CH_2CH_3$), 3.23 (d, 1 H, $J$ = 13.2 Hz, $ArCH_2Ar$), 3.34, 3.39 (two d, 2 H, $J$ = 13.1 Hz, $ArCH_2Ar$), 3.57 (d, 1 H, $J$ = 13.2 Hz, $ArCH_2Ar$), 4.04, 4.08 (two d, 2 H, $J$ = 13.2 Hz, $ArCH_2Ar$), 4.22 (q, 2 H, $J$ = 7.2 Hz, $CH_2CH_3$), 4.50 (broad s, 4 H, ArO*H*, PO*H*), 4.69, 4.74 (two d, 2 H, $J$ = 13.3 Hz, $ArCH_2Ar$), 6.50–7.53 (m, 12 H, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.38. Calc. for $C_{30}H_{29}O_7P$: C, 67.66; H, 5.49; P, 5.82. Found: C, 67.89; H, 5.36; P, 5.23%.

**25-*O*-Ethyl-26-*O*-dihydroxyphosphoryl-27-*O*-benzoylcalix[4]-arene (14).** Yield 0.83 g (90%) of colorless crystals. Mp 211–213 °C; $^1$H NMR ($CDCl_3$; 300 MHz) $\delta$ 1.45 (t, 3 H, $J$ = 7.0 Hz, $CH_2CH_3$), 3.13, 3.18 (two d, 2 H, $J$ = 12.9 Hz, $ArCH_2Ar$), 3.24, 3.27 (two d, 2 H, $J$ = 13.5 Hz, $ArCH_2Ar$), 3.91 (m, 2 H, $ArCH_2Ar$), 4.27 (q, 2 H, $J$ = 7.1 Hz, $CH_2CH_3$), 4.58 (two d, 2 H, $J$ = 13.1 Hz, $ArCH_2Ar$), 5.62–6.34 (broad s, 3 H, ArO*H*, PO*H*), 6.42–8.40 (m, 17 H, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.25. Calc. for $C_{37}H_{33}O_8P$: C, 69.80; H, 5.23; P, 4.87. Found: C, 69.45; H, 4.76; P, 4.63%.

**5,11-Dibromo-25-*O*-ethyl-26-*O*-(dihydroxyphosphoryl)calix-[4]arene (15).** Yield 0.88 g (95%) of colorless crystals. Mp 227–229 °C; $^1$H NMR (DMSO-$d_6$; 300 MHz) $\delta$ 1.68 (t, 3 H, $J$ = 6.9 Hz, $CH_2CH_3$), 3.29 (d, 1 H, $J$ = 12.6 Hz, $ArCH_2Ar$), 3.39, 3.43 (two d, 2 H, $J$ = 13.5 Hz, $ArCH_2Ar$), 3.63 (d, 1 H, $J$ = 12.9 Hz, $ArCH_2Ar$), 3.96 (m, 2 H, $ArCH_2Ar$ and 1 H, $CH_2CH_3$), 4.36 (q, 1 H, $J$ = 7.2 Hz, $CH_2CH_3$), 4.63, 4.66 (two d, 2 H, $J$ = 12.9 Hz, $ArCH_2Ar$), 5.40–6.10 (broad s, 4 H, ArO*H*, PO*H*), 6.71 (t, 1 H, $J$ = 7.5 Hz, Ar*H*), 7.07 (d, 1 H, $J$ = 7.5 Hz, Ar*H*), 6.50–7.53 (m, 8 H, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.38. Calc. for $C_{30}H_{27}Br_2O_7P$: C, 52.19; H, 3.94; Br, 23.15; P, 4.49. Found: C, 52.35; H, 4.10; Br, 22.68; P, 4.25%.

**5-Bromo-25-*O*-ethyl-26-*O*-dihydroxyphosphoryl-27-*O*-benzoylcalix[4]arene (16).** Yield 0.86 g (93%) of white crystals. Mp 241–243 °C; $^1$H NMR (DMSO-$d_6$; 300 MHz) $\delta$ 1.69 (t, 3 H, $J$ = 7.0 Hz, $CH_2CH_3$), 3.43, 3.47 (two d, 2 H, $J$ = 13.4 Hz, $ArCH_2Ar$), 3.56 (d, 2 H, $J$ = 12.8 Hz, $ArCH_2Ar$), 4.13 (m, 1 H, $ArCH_2Ar$ and 2 H, $CH_2CH_3$), 4.42 (m, 1 H, $ArCH_2Ar$) 4.63 (d, 1 H, $J$ = 13.1 Hz, $ArCH_2Ar$), 4.83 (d, 1 H, $J$ = 13.4 Hz, $ArCH_2Ar$), 5.60–6.40 (broad s, 3 H, ArO*H*, PO*H*), 6.83–8.62 (m, 16 H, Ar*H*); $^{31}$P NMR (DMSO-$d_6$; 81 MHz) $\delta$ −4.15. Calc. for $C_{37}H_{32}BrO_8P$: C, 62.11; H, 4.51; Br, 11.17; P, 4.33. Found: C, 61.89; H, 4.37; Br, 10.86; P, 4.29%.

### General procedure for the preparation of calixarene phosphoric acid – L-(−)-α-phenylethylamine diastereomeric salts (17–20)

L-(−)-α-Phenylethylamine (0.11 g, 0.9 mmol) was added to a solution of a dihydroxyphosphorylcalix[4]arene **13**–**16** (0.9 mmol) in $CH_3OH$ (5 ml), and the reaction mixture was stirred for 10 min. Methanol was evaporated off under reduced pressure and the residue was dried *in vacuum* (0.05 mm Hq). Further details are given for the individual compounds.

**25-*O*-Ethyl-26-*O*-(dihydroxyphosphoryl)calix[4]arene L-(−)-α-phenylethylamine (17).** Yield 0.61 g (100%) of white powder, mp 162–165 °C; $^1$H NMR ($CDCl_3$; 300 MHz), $\delta$ 1.28 (broad d, 6 H, $J$ = 6.9 Hz, $CHCH_3$), 1.50 (t, 3 H, $J$ = 7.1 Hz, $CH_2CH_3$), 1.52 (t, 3 H, $J$ = 7.2 Hz, $CH_2CH_3$), 2.98, 3.04 (two d, 2 H, $J$ = 13.5 Hz, $ArCH_2Ar$), 3.11, 3.15 (two d, 2 H, $J$ = 13.4 Hz,

ArC$H_2$Ar), 3.24, 3.30 (two d, 2 H, $J$ = 13.5 Hz, ArC$H_2$Ar), 3.35, 3.39 (two d, 2 H, $J$ = 13.3 Hz, ArC$H_2$Ar), 3.78 (q, 2 H, $J$ = 7.0 Hz, ArOC$H_2$CH$_3$), 3.74–4.32 (m, 8 H, ArC$H_2$Ar, C$H$CH$_3$), 4.67, 4.72 (two d, 2 H, $J$ = 13.5 Hz, ArC$H_2$Ar), 4.74, 4.79 (two d, 2 H, $J$ = 13.7 Hz, ArC$H_2$Ar), 6.45–7.39 (m, 46 H, Ar$H$, ArO$H$, N$H_2$, PO$H$); $^{31}$P NMR (CD$_3$OD; 81 MHz) $\delta$ 0.55 and 0.48.

**25-*O*-Ethyl-26-*O*-dihydroxyphosphoryl-27-*O*-benzoylcalix[4]-arene L-(−)-α-phenylethylamine (18).** Yield 0.6 g (100%) of white powder, mp 163–166 °C; $^1$H NMR (CDCl$_3$; 300 MHz) $\delta$ 1.20–1.29 (m, 6 H, CH$_2$C$H_3$ and 3 H, CHC$H_3$), 1.65–1.73 (m, 3 H, CHC$H_3$), 3.21–3.45 (m, 8 H, ArC$H_2$Ar), 3.82–4.81 (m, 8 H, ArC$H_2$Ar and 4 H, C$H_2$CH$_3$), 5.15–5.36 (m, 2 H, C$H$CH$_3$), 6.25–7.57 (m, 54 H, Ar$H$, ArO$H$, N$H_2$, PO$H$); $^{31}$P NMR (CDCl$_3$; 81 MHz) $\delta$ −5.76 and −5.82.

**5,11-Dibromo-25-*O*-ethyl-26-*O*-(dihydroxyphosphoryl)calix-[4]arene L-(−)-α-phenylethylamine (19).** Yield 0.59 g (100%) of white powder, $^1$H NMR (CDCl$_3$; 300 MHz) $\delta$ 1.19–1.26 (m, 6 H, CH$_2$C$H_3$ and 3 H, CHC$H_3$), 1.64–1.75 (m, 3 H, CHC$H_3$), 3.18–3.43 (m, 8 H, ArC$H_2$Ar), 3.75–4.82 (m, 8 H, ArC$H_2$Ar and 4 H, C$H_2$CH$_3$), 5.16–5.35 (m, 2 H, C$H$CH$_3$), 6.46–7.48 (m, 42 H, Ar$H$, ArO$H$, N$H_2$, PO$H$); $^{31}$P NMR (CDCl$_3$; 81 MHz) $\delta$ −2.01 and −2.18.

**5-Bromo-25-*O*-ethyl-26-*O*-dihydroxyphosphoryl-27-*O*-benzoylcalix[4]arene L-(−)-α-phenylethylamine (20).** Yield 0.58 g (100%) of white powder, $^1$H NMR (CDCl$_3$; 300 MHz) $\delta$ 1.24–1.38 (m, 6 H, CH$_2$C$H_3$ and 3 H, CHC$H_3$), 1.46–1.57 (m, 3 H, CHC$H_3$), 2.89–3.38 (m, 8 H, ArC$H_2$Ar), 3.80–4.42 (m, 6 H, ArC$H_2$Ar and 4 H, C$H_2$CH$_3$), 4.82–4.95 (m, 2 H, ArC$H_2$Ar and 2 H, C$H$CH$_3$), 6.84–7.40 (m, 52 H, Ar$H$, ArO$H$, N$H_2$, PO$H$); $^{31}$P NMR (CDCl$_3$; 81 MHz) $\delta$ −4.56 and −4.71.

### RP HPLC analysis

The HPLC system consisted of (1) a high-pressure pump Model HPP 4001 (Laboratorni Pristroje, Praha, Czech Republic) connected to a Rheodyne Model sample 7120 injector (20 µl, Rheodyne Inc., Berkeley, CA) and UV–visible detector Model LCD 2563 (Laboratorni Pristroje, Praha, Czech Republic) working at a wavelength of 254 nm. The column (150 × 3.3 mm id) was packed with Separon SGX C18 (Lachema Brno, Czech Republic); (2) a high-pressure pump Model 303 (Gilson Medical Electronics, Inc., Worthington, OH) connected to a Rheodyne Model sample 7120 injector (20 µl, Rheodyne Inc., Berkeley, CA) and UV–visible detector Model 116 (Gilson Medical Electronics, Inc.) working at a wavelength of 300 nm. The column (250 × 4.6 mm id) was packed with Partisil 5 ODS 3. The flow rate of the mobile phase was 0.4 mL min$^{-1}$ (system 1) and 1.0 mL min$^{-1}$ (system 2). The analysis was carried out at an ambient temperature. Samples for the chromatographic analysis were prepared by dissolving the salts in the mobile phase.

### Potentiometry

All potentiometric equilibrium measurements were conducted in a water-jacketed vessel at 25.0 (± 0.1 °C). A solution of the acid in 70% methanol ($c$ = 5 × 10$^{-3}$ M) was titrated with 0.1 M potassium hydroxide. After each addition of the alkali the pH was determined by means of an EV-74 pH-meter in conjugation with a glass electrode and saturated Cl$^-$/Ag electrode as a reference. The first p$K_a$-values were calculated by standard methods.[37]

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