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Synthesis of Geminal Bis- and Tetrakisphosphonate Ester Derivatives and Their Coordination Behavior Towards Ca(II) Ions

Ingo Koehne[a] and Rudolf Pietschnig*[a]

The preparation and thorough characterization of a variety of (arylmethylene)phosphonate ester derivatives (**S1**–**S7**) as well as derived geminal bisphosphonate (BP) ester ligands (**L1**–**L7**) is presented. Subsequent complexation reactions of $CaCl_2$ with selected BPs (**L1**–**L3**) and a known aliphatic tetrakisphosphonate ester (**L8**) yield the respective Ca(II) coordination compounds $[Ca(H_2O)_2(\mathbf{L1}\text{--}\mathbf{L3})_2]Cl_2$ (**C1**--**C3**) and $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**) for potential future application as multi-delivery systems in osteoporosis treatment. Obtained SCXRD and ^{1}H DOSY-NMR data provide a detailed insight into their solid- as well as solution-state structures extending the so far scarcely found X-ray studies on geminal BP-supported Ca(II) complexes.

Introduction

The first bisphosphonates (BP) were prepared as early as in the 19th century, but only in the last 50 years they have been applied in the treatment of calcium metabolism disorders. In the beginning, BPs found primarily application as rust proofers, complexing agents in the textile-, fertilizer-, oil- and mining industries, as well as for a variety of further industrial processes.[1] Geminal BPs share a common P–C–P bridging motif in their backbone, where each P is characterized by a phosphonate moiety. In general, geminal BPs are the P–C–P derivatives of naturally occurring P–O–P-bridged inorganic pyrophosphates but are neither prone to chemical nor enzymatic hydrolysis. The phosphonate groups are crucial for interaction with and binding to the bone tissue, as well as for cell-mediated antiresorptive activity of these compounds.[2] In particular, the average O···O distance of the phosphonate moieties is in a similar range to the Ca–O mean bond length in hydroxyapatite (HA). This promotes an immobilization on the HA surface *via* a multidentate oxygen chelation of calcium ions.[2a] Nowadays, geminal BPs are the leading class of pharmaceuticals for the treatment of numerous bone diseases, like osteoporosis or bone metastases affiliated to breast- and prostate cancer.[3] As a result, BP-based alkaline earth metal-organic frameworks (AEMOFs),[4] group 2 coordination polymers[5] as well as distinct molecular complexes[2b,6] have found a widespread biomedical application. Especially in the context of osteoporosis treatment synergistic and combined delivery systems of clinically relevant geminal BPs (e.g. alendronate, clodronate, etidronate, etc.), and essential bone minerals like calcium are employed.[2,6a] However, further research effort is needed to avoid complications such as "bisphosphonate-induced osteonecrosis of the jaw" (BIOJ) which still is poorly understood.[7] As an advantage to a neat BP medication, BP-supported alkaline earth metal complexes provide a slow drug release via successive complex decomposition under biological conditions avoiding unwanted side effects.[4b,6b] As lined out in the review by Gałęzowska, the amount of single crystal X-ray diffraction (SCXRD) studies on geminal BP-supported Ca(II) complexes is limited.[2b] The first reported BP-based Ca(II) X-ray structure is characterized by an eight-fold coordination mode of the calcium ion forming infinite strands.[8] Moreover, the only known monomeric BP–Ca(II) complex exhibits a seven-fold coordination as reported by Zucchi in 1983.[9] Most common for the majority of the structures is a polymeric, sixfold, all-O octahedral coordination mode (Figure 1).[4b,10] Only a few structures exhibit a polymeric seven-fold, pentagonal-bipyramidal coordination like determined for Ca(II) in HA.[11] So far, solution-state structure elucidations of geminal BP-based Ca(II) complexes have focused on standard NMR spectroscopy, potentiometric titration or isothermal titration calorimetry studies.[12] The results indicate that a variety of pH dependent mono- and dimeric species like Ca_2L, CaL and CaL_2 (L = geminal BP ligand) are formed, and that even polymeric structures like $[CaL]_n$ are retained in solution.[2b]

Herein, we present the preparation and detailed characterization of five symmetrical (**L1**--**L5**; R = R′ = Et) as well as two asymmetrical geminal BP ester ligands (**L6** + **L7**; R = Et, R′ = *i*Pr) starting from their corresponding ethyl- or isopropyl (arylmethylene)phosphonate ester precursors (**S1**–**S7**). Additionally, a known aliphatic tetrakisphosphonate ester (**L8**) is synthesized to even have access to a tetradentate chelate ligand for subsequent Ca(II) ion coordination to evaluate differences in the coordination behavior of di- and polydentate chelators. On

[a] *Dr. I. Koehne, Prof. Dr. R. Pietschnig*
Institute of Chemistry and Center for Interdisciplinary Nanostructure Science and Technology (CINSaT),
University of Kassel
Heinrich-Plett-Str. 40, 34132 Kassel, Germany
E-mail: pietschnig@uni-kassel.de
www.uni-kassel.de/go/hym

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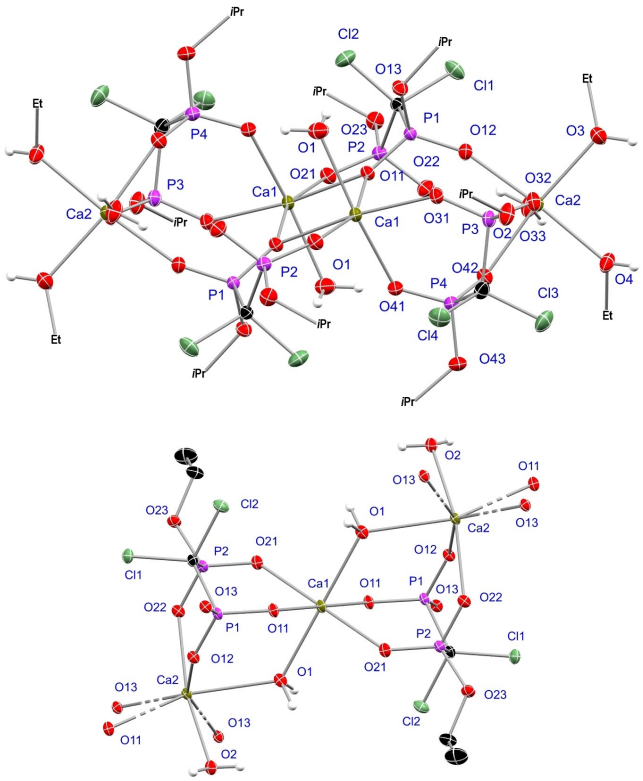
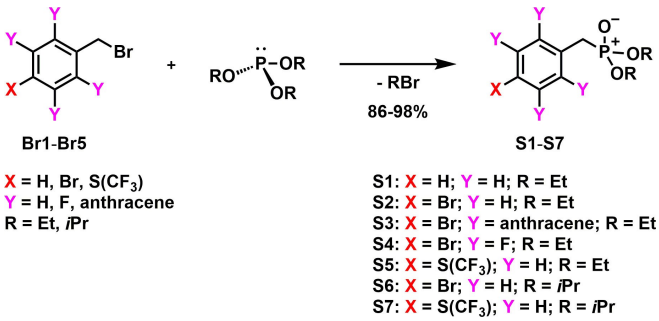


Figure 1. Top: Tetrameric solid-state structure of literature known $[\{Ca_2(Cl_2C(PO_3iPr)_2)_2(EtOH)_2(H_2O)_2\}\cdot H_2O]_2$[10c] (**A**) using a mono isopropyl ester derivative of the geminal BP clodronate. The Ca(II) ions exhibit a distorted octahedral coordination.; Bottom: Two-dimensional polymeric crystal structure of literature known $[\{Ca_{1.5}(Cl_2C(PO_3Et)_2(H_2O)_2\}\cdot 0.5CH_3COCH_3\cdot 4.5H_2O]_n$[10b] (**B**) using a mono ethyl ester clodronate derivative. The Ca(II) ions show a six-fold, distorted octahedral coordination as well as a seven-fold, distorted monocapped trigonal-prismatic geometry. Anisotropic displacement parameters are depicted at the 50% probability level. Lattice solvent molecules are omitted for clarity. Except for H_2O and EtOH ligands, hydrogen atoms are omitted as well.

the way to potential future multi-delivery systems of geminal BPs and calcium for osteoporosis treatment, a complexation with $CaCl_2$ yields derived Ca(II) coordination compounds of the form $[Ca(H_2O)_2(\mathbf{L1}\text{--}\mathbf{L3})_2]Cl_2$ (**C1**--**C3**) or $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**). The



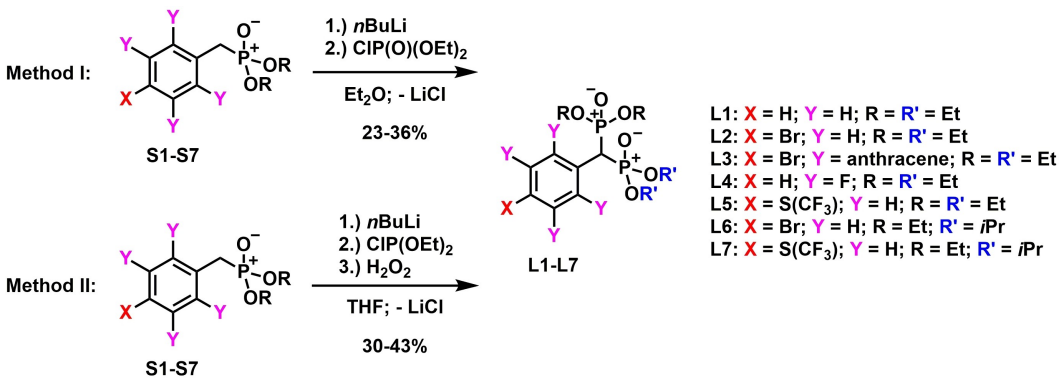
Scheme 1. Synthesis of the monophosphonate ester starting materials **S1**–**S7**.

corresponding solid- as well as solution-state structures of **C1**–**C4** are evaluated and discussed in detail.

Results and Discussion

Ligand Synthesis

Preparation of the ethyl or isopropyl (arylmethylene)phosphonate ester starting materials (**S1**–**S7**) is carried out via Michaelis-Arbuzov[13] reactions commencing from the corresponding benzylic bromides and triethyl- (**S1**–**S5**) or triisopropyl phosphite (**S6** + **S7**) (Scheme 1): Benzyl bromide (**Br1**), 4-bromobenzyl bromide (**Br2**), 9-bromo-10-(bromomethyl)-anthracene (**Br3**),[14a] 1-bromo-4-(bromomethyl)-2,3,5,6-tetrafluoro-benzene (**Br4**)[14a] and (4-(bromomethyl)phenyl)(trifluoromethyl)-sulfane) (**Br5**). Subsequently, two different approaches have been evaluated to obtain the derived BP ester ligands (**L1**–**L7**) (Scheme 2). Method I proceeds via a lithiation of the starting materials **S1**–**S7** followed by a reaction with the phosphorus(V) species diethyl chlorophosphate giving the desired BP ligands in moderate yields between 23–36% after workup. As indicated by unpublished reactions with Me_3SiCl showing a quantitative introduction of a TMS group at the methylene bridge after lithiation, an initial quantitative deprotonation of the CH_2 bridge with *n*BuLi can unequivocally be



Scheme 2. Synthesis of symmetrical (**L1**–**L5**) and asymmetrical geminal BP ester ligands (**L6**–**L7**) *via* a P(V) (**Method I**) and a P(III) (**Method II**) approach.

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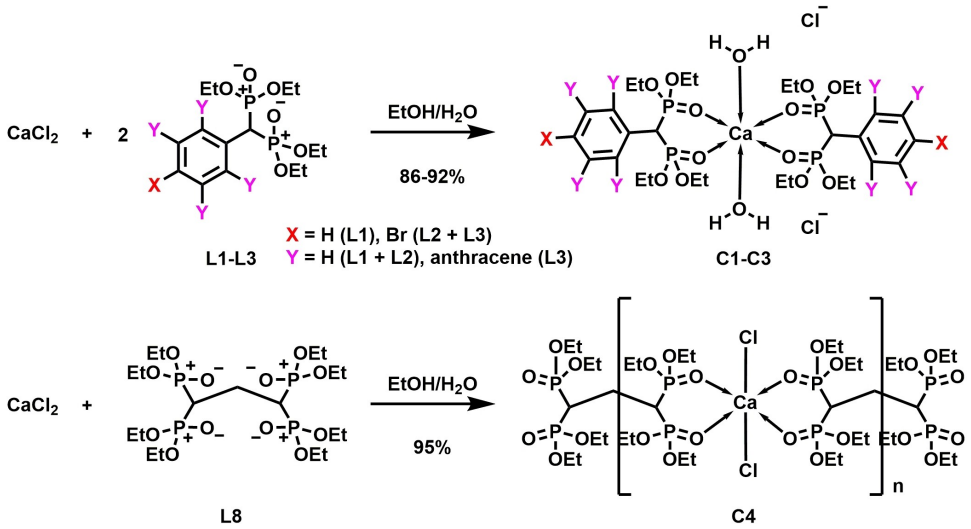

Scheme 3. Top: Synthesis of complexes $[Ca(H_2O)_2(\mathbf{L1}–\mathbf{L3})_2]Cl_2$ (**C1**--**C3**). Bottom: Synthesis of complex $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**).

derived. However, a significant amount of protonated starting material is retrieved from each reaction batch after aqueous workup indicating the introduction of a second bulky phosphonate ester substituent at the methylene bridging moiety to be sterically hindered. To further evaluate this hypothesis, a second approach via method II is carried out using the more reactive phosphorus(III) compound diethyl chlorophosphite and subsequent oxidation with concentrated aqueous H_2O_2 solution. Ligands **L1**--**L7** are isolated only in slightly improved yields between 30–43 % after aqueous workup which again indicates that steric congestion around the CH_2 bridge can be identified as the main issue in the synthesis of BP esters **L1**--**L7**. Additionally, in the reaction of mono phosphonate **S4**, the *para* protonated derivative tetraethyl ((2,3,5,6-tetrafluorophenyl)-methylene)bis(phosphonate) (**L4**) is obtained instead of the expected *para* bromide derivative tetraethyl ((4-bromo-2,3,5,6-tetrafluorophenyl)methylene)bis(phosphonate). Similar behavior was observed to a minor extend for the related compound diisopropyl (4-bromo-2,3,5,6-tetrafluorobenzyl)-phosphonate[15] when introducing an azido substituent at the 4-position of the aryl ring tagging these species to be highly available for modifications at their aromatic periphery. In addition to the above mentioned phosphonic esters, the tetrakisphosphonate ester ligand octaethyl propane-1,1,3,3-tetrayltetrakis(phosphonate) (**L8**) is prepared according to a literature procedure, providing four phosphonate ester units at once (see Scheme 3).[16]

Ligand **L3** is the only solid within the row of the prepared ligands **L1**–**L8**. It crystalizes in the orthorhombic space group *Pbca* containing one molecule in the asymmetric unit. An intramolecular hydrogen bond of 2.398(4) Å between O1 and H14 as well as an intermolecular hydrogen bond interaction between O4 and H6 (2.432(4) Å) of adjacent molecules form a two-dimensional network (SI, Figure S39). Both have to be considered as weak building on electrostatic as well as dispersion force interactions.[17] Moreover, a short intermolecular Br···O distance of only 2.99 Å is observed between the trigonally surrounded O1 of one of the phosphonate moieties and the bromide substituent Br1 of neighboring molecules which remains 0.36 Å under the sum of the v.d. Waals radii of 3.35 Å[18] of both atoms (Figure 2). Halogen bonds are strong, specific, and directional interactions including significant charge transfer.[19] An intrinsic feature of the halogen bond is a nearly linear $[BX]^+\cdots Y^-$ bond vector.[20] The corresponding C–Br···O^- angle in **L3** of 176.7 ° (ϕ_2) obeys to this specification (Figure 2). In contrast, the P^+–O^-···Br angle of 159.0 ° (ϕ_1) deviates significantly from 180 ° but is in a similar range as in comparable literature structures.[14] The observed deviations can be rationalized by crystallographic packing effects enabling the above-mentioned hydrogen bond network and the advantageous zig-zag-structure within the strands. With an intermediate value, the observed interaction cannot be assigned clearly to one of the two classifications of halogen bonds with either $\phi_1 \approx \phi_2$ (type I) or $\phi_1 \approx 90°$ (involving the Lewis basic oxygen atom) with $\phi_2 \approx 180°$ (involving the Lewis acidic halogen) (type

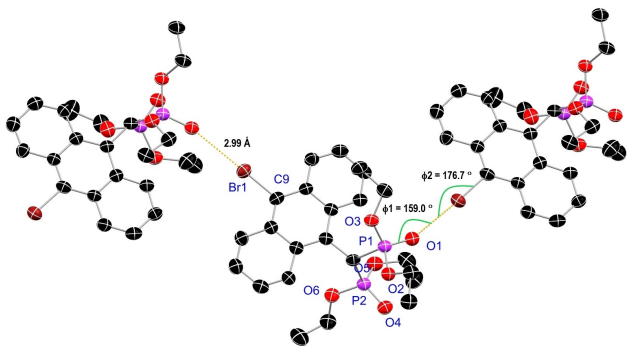

Figure 2. Zig-zag strands with schematic halogen-bonds formed within the solid-state structure of **L3**. Anisotropic displacement parameters are depicted at the 50 % probability level. Hydrogen atoms are omitted for clarity. Selected structural data are given in Table 2.

Research Article
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II).[21] The $^{31}P\{^1H\}$ signals of **L1**–**L8** in solution resonate in a typical range for phosphonate esters ranging from 16.1 ppm in **L4** to 22.9 ppm in **L8** (Table 1). The asymmetrically substituted BP esters (**L6** and **L7**) exhibit two resonances in a ratio of 1:1 with a shift difference of 2 ppm. With respect to literature values, the O*i*Pr substituted phosphorus can be assigned to the high field shifted signal in both cases.[14] The expected triplet ^{1}H-NMR signals of the CH bridging moiety can be found between 3.63 ppm in **L6**, and strongly deshielded 5.48 ppm in **L3** while the respective resonance in **L5** is covered by one of the signals arising from the OEt residues. A triplet of triplet with a chemical shift of 3.40 ppm is recorded for **L8**. Triplet resonances corresponding to the methine bridge in a range of 36.0 ppm (**L4**) to 45.4 ppm (**L1** + **L5**) are found in the $^{13}C\{^1H\}$ spectra of the symmetrical BPs while doublet of doublet signals at 46.0 (**L6**) and 46.3 ppm (**L7**) are observed for the asymmetrically substituted derivatives. Again, the aliphatic tetrakisphosphonate ester ligand **L8** exhibits the most shielded resonance at 34.1 ppm and a triplet of triplet coupling pattern.

Complex Synthesis

Complexation reactions are carried out with the ligand systems available in the highest yields (**L1**--**L3** and **L8**). The calcium complexes **C1**–**C4** are prepared in a mixture of EtOH and water starting from $CaCl_2$ and two equivalents (**L1**–**L3**) or one equivalent (**L8**) of the geminal bis- or tetrakisphosphonate ester ligands (Scheme 3). Coordination compounds represented by the general formulas $[Ca(H_2O)_2(\mathbf{L1}\text{--}\mathbf{L3})_2]Cl_2$ (**C1**--**C3**) or $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**) are obtained in excellent yields between 86–95 %. With exception of **C3**, the $^{31}P\{^1H\}$ resonances of the free ligands **L1**--**L3** and **L8** experience a low-field shift between 0.2 ppm in **C2** over averaged 0.8 ppm in **C4** to 1.2 ppm in **C1** upon calcium ion coordination (Table 1). The observation of two $^{31}P\{^1H\}$ signals in a ratio of 1:1 in **C4** indicates a loss of symmetry within **L8** upon coordination as also reflected by multiplet resonances in the acquired ^{1}H- and $^{13}C\{^1H\}$ NMR spectra. This feature can most likely be rationalized by two of the phosphonate moieties being involved in the formation of intramolecular hydrogen bonds that are retained in solution (Figure 3). The methine bridge protons in **C1**-**C3** seem to be most affected by a coordination to an electronically deficient metal ion. Especially in **C1**, a significant shift of 1.41 ppm to lower field is observed. The corresponding $^{13}C\{^1H\}$ NMR signals all exhibit a high field shift, again most pronounced in **C1**.

Crystals suitable for SCXRD experiments have been obtained from vapor diffusion of pentanes into saturated solutions of **C1** or **C2** in THF, or from slow evaporation of a $CDCl_3$ solution of **C4** in an NMR tube. No suitable single crystals have been obtained for complex **C3** so far. Compounds **C1** and **C2** are isostructural crystallizing in the triclinic space group $P\bar{1}$ showing one half (**C2**) or two half molecules (**C1**) in the asymmetric unit, respectively (SI, Figures S40 and S41). The symmetry equivalent positions are generated *via* a two-fold rotation axis or an inversion center. In both cases, the Ca(II) ions show an occupation of $^1/_2$. Both complexes exhibit an octahedral all-O coordination around the Ca(II) ion consisting of two bidentate BPs as well as two water molecules residing at the apical positions (Figure 3, left). At the same time, a solvent-separated ion pair is formed, which probably best reflects the presence of dissolved calcium chloride or BP-supported calcium complexes in the human body that are expected to show a solvation by ubiquitous water molecules. Despite of being formally hexadentate chelate ligands, the geminal BP esters of this study show an exclusive bidentate coordination *via* the P^+–O^- oxygen atoms which was already observed for the corresponding monophosphonate ester derivatives.[14,15] Additionally, weak intermolecular hydrogen bonds of 2.490(2) Å are formed in $[Ca(H_2O)_2(\mathbf{L1})_2]Cl_2$ (**C1**) between O6 and the aromatic para hydrogen atom (H20) of adjacent molecules forming infinite hydrogen bonded strands (SI, Figure S40). Complex $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**) crystallizes in the monoclinic space group $P2_1/c$ containing 1.5 molecules of **C4** as well as four co-crystallized lattice $CDCl_3$ molecules in the asymmetric unit. Again, a six-fold, octahedral coordination is adopted around the Ca(II) ions but this time by forming a contact ion pair (Figure 3, right). The coordination sphere is made up by two BP units of different **L8** molecules

Table 1. Selected NMR spectral data [ppm] of **L1**–**L8** and **C1**–**C4** in $CDCl_3$. Multiplicity given in brackets (m).

Compound	$^{31}P\{^1H\}$[a]	^1H[b] (CH_{bridge})	$^{13}C\{^1H\}$[c] (CH_{bridge})
L1	18.5 (s)	3.74 (t)[b]	45.4 (t)
L2	17.9 (s)	3.68 (t)	45.3 (t)
L3	19.4 (s)	5.48 (t)	41.4 (t)
L4	16.1 (s)	4.31 (t)	36.0 (t)
L5	17.7(s)	4.40–3.49 (covert, m)	45.4 (t)
L6	18.1 (s, $P(OEt)_2$ 16.0 (s, $P(OiPr)_2$	3.63 (t)	46.0 (dd)
L7	17.8 (s, $P(OEt)_2$ 15.8 (s, $P(OiPr)_2$	3.72 (t)	46.3 (dd)
L8	22.9 (s)	3.40 (tt)	34.1 (tt)
$[Ca(H_2O)_2(\mathbf{L1})_2]Cl_2$ (**C1**)	19.7 (s)	5.15 (t)	44.1 (t)
$[Ca(H_2O)_2(\mathbf{L2})_2]Cl_2$ (**C2**)	18.1 (s)	3.81 (s_{br})	44.9 (t)
$[Ca(H_2O)_2(\mathbf{L3})_2]Cl_2$ (**C3**)	19.4 (s)	6.00 (t)	41.2 (t)
$[Ca(\mathbf{L8})Cl_2]_n$ (**C4**)	24.0 (s) 23.3 (s)	3.82–3.65 (m)	35.0–32.7 (m)

[a] @ 202 MHz. [b] @ 400 MHz or 500 MHz. [c] @ 100 MHz or 126 MHz.

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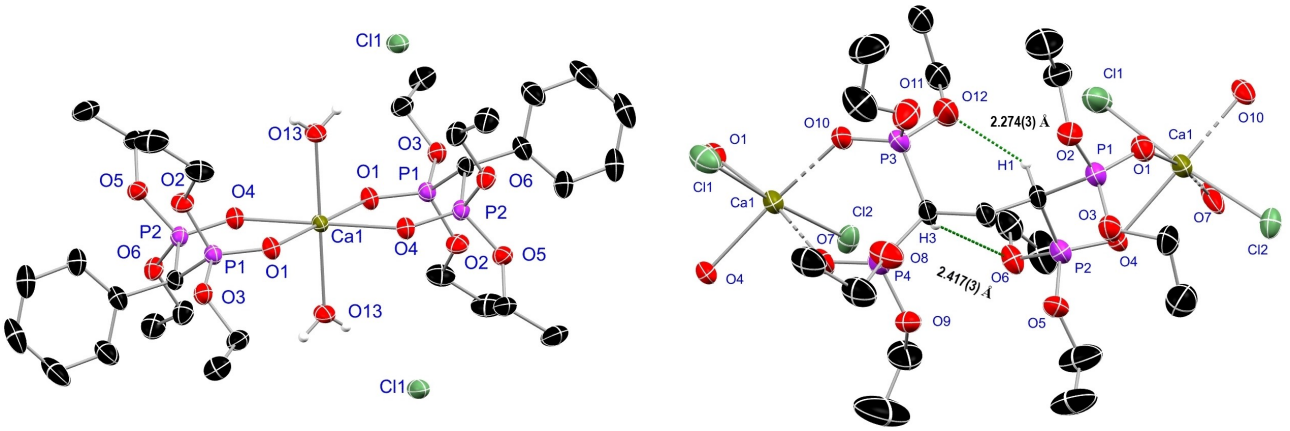

Figure 3. Left: Crystal structure of $[Ca(H_2O)_2(\mathbf{L1})_2]Cl_2$ (**C1**) which is isostructural to $[Ca(H_2O)_2(\mathbf{L2})_2]Cl_2$ (**C2**). Symmetry transformations used to create equivalent atoms: #1: −x+1, −y+1, −z+2; #2: −x, −y, −z+1. Right: Snippet from the polymeric strands formed in the solid-state structure of $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**) also showing two intramolecular hydrogen bonds. Symmetry transformations used to create equivalent atoms: #1: x, −y+3/2, z+1/2; #2: x, −y+3/2, z−1/2. Except for H_2O ligands, H1 and H3, hydrogen atoms are omitted for clarity. Lattice solvent molecules are omitted as well. Anisotropic displacement parameters are depicted at the 50% probability level. Selected structural data are given in Table 2.

and two chloride anions at the apical positions. Hence, the tetrakisphosphonate ester ligand **L8** is bridging adjacent $CaCl_2$ units forming infinite linear strands in the solid-state. Furthermore, weak intramolecular hydrogen bonds[17] of 2.274(3) and 2.417(3) Å are established between O12/H1 and O6/H3, respectively. In the following, **C1**, **C2** and **C4** are compared to the related octahedral coordinated Ca(II) complexes $[\{Ca_2(Cl_2C(PO_3iPr)_2)_2(EtOH)_2(H_2O)_2\}\cdot H_2O]_2$[10c] (**A**), $[\{Ca_{1.5}(Cl_2C(PO_3Et)_2(H_2O)_2\}\cdot 0.5CH_3COCH_3\cdot 4.5H_2O]_n$[10b] (**B**), $[\{Ca((CH_3)(OH)C(HPO_3)_2)_2\}\cdot 2H_2N(CH_3)_2]_n$[10a] (**C**) and $[\{Ca((C_5H_{10}NH_3)(OH)C(HPO_3)_2)_2\}\cdot 3H_2O]_n$[4b] (**D**). The used geminal BP ligands are ethyl- or isopropyl ester derivatives of clodronate (**A** and **B**), the 1-hydroxyethylidene-1,1-diphosphonic acid dianion (**C**) and neridronate (**D**). The Ca–$O_{(P^+-O^-)}$ distances of the prepared complexes are in-between the observed bond lengths for **A**-**D** ranging from 2.314(2) Å in **A** and 2.346(2) Å in **D** (Table 2). In contrast, the corresponding P^+–O^- (1.464(5) to 1.477(2) Å) and P–OR (1.556(5) to 1.557(3) Å) distances are slightly shorter than those determined for the literature structures. Moreover, the O–Ca–O angles are with 80.7(2)° (**C4**) to 81.1(1)° (**C2**) more acute than in the related structures that range from 82.1(2)° in **C** to 86.6(1)° in **D**. The observed P–C–P angles range from 112.2(4)° in **C4** to 112.7(2)° in **C1** and **C2**, and are in good agreement to the values observed for complexes **A** and **B**. In contrast, compound **C** exhibits the widest angle of 114.1(1)° while **D** shows the most acute angle of 110.1(1)° within the considered row of geminal BP-supported Ca(II) complexes.

^{1}H-DOSY-ECC-MW Estimation Study

To explore the aggregation behavior of Ca(II) complexes **C1**–**C4** in solution, structure elucidation has been performed via ^{1}H-DOSY external calibration curve (ECC) molecular weight (*MW*) estimation in donating (DMSO-d_6 or MeCN-d_3) as well as non-donating ($CDCl_3$ or CD_2Cl_2) solvents.[22] Previous studies showed that for most organometallic compounds the dissipated spheres and ellipsoids (DSE) calibration curve is most suitable for an accurate estimation.[23] Hence, only values from the DSE and, for comparison, from the merge calibration curve are considered (Table 3). Although this method is only strongly reliable for molecules up to 600 g/mol, a previous study has shown that still good results are obtained for aggregates up to 1000 g/mol (For detailed DOSY data, see SI).[24] Hypothetical aggregates for **C1**--**C3** in donating or non-donating solvents are $[Ca(H_2O)_n(\mathbf{L1}$--$\mathbf{L3})_2Cl_{2-n}]^{n+}$ (n = 0–2). For **C4**, hypothetical aggregates in $CDCl_3$ are $[Ca_n(\mathbf{L8})_{n-1}Cl_{2n}]$ (n = 4–7) while mono- di- and trimers of the

Table 2. Selected bond lengths [Å] and angles [°] of **L3**, **C1**, **C2**, **C4** and the related compounds **A**–**D**. If there is more than one value for a considered bond length or angle, merged values are given.

	Ca–$O_{(P^+-O^-)}$	P^+–O^-	P–OR	O–Ca–O	P–C–P
L3	–	1.462(4)	1.569(5)	–	113.7(3)
C1	2.328(2)	1.477(3)	1.557(3)	80.9(1)	112.7(2)
C2	2.316(2)	1.477(2)	1.557(3)	81.1(1)	112.7(2)
C4	2.330(5)	1.464(5)	1.556(5)	80.7(2)	112.2(4)
A[9c]	2.314(2)	1.492(2)	1.579(2)	83.4(5)	112.4(1)
B[9b]	2.337(2)	1.499(2)	1.575(2)	86.6(1)	112.9(1)
C[9a]	2.323(1)	1.505(1)	1.575(1)	82.1(2)	114.1(1)
D[4b]	2.346(2)	1.501(2)	1.584(2)	82.8(1)	110.1(1)

Table 3. ^{1}H-DOSY-ECC-*MW* estimation of **C1**–**C4** in DMSO-d_6[a] or MeCN-d_3[b] (top columns) or CD_2Cl_2[c] or $CDCl_3$[d] (bottom columns), at room temperature.

Complex	$MW_{theo.}$ [g/mol]	MW_{DSE} [g/mol] ($MW_{dif.}$ [%])	MW_{merge} [g/mol] (MW_{dif} [%])
C1:[b] $[Ca(H_2O)_2(\mathbf{L1})_2]^{2+}$	805	771 (4)	909 (−11)
$[Ca(H_2O)(\mathbf{L1})_2Cl]^{+}$	822	771 (7)	909 (−10)
$[Ca(\mathbf{L1})_2Cl_2]$	840	771 (9)	909 (−8)
C2:[a] $[Ca(H_2O)_2(\mathbf{L2})_2]^{2+}$	963	857 (12)	991 (−3)
C3:[b] $[Ca(H_2O)_2(\mathbf{L3})_2]^{2+}$	1163	538 (116)	619 (88)
C4:[b] $[Ca_2(CD_3CN)_4(\mathbf{L8})Cl_4]$	987	963 (2)	1154 (−14)
C1:[c] $[Ca(H_2O)_2(\mathbf{L1})_2]^{2+}$	805	700 (15)	795 (1)
C2:[d] $[Ca(H_2O)_2(\mathbf{L2})_2]^{2+}$	963	78 (1135)	76 (1167)
C3:[c] $[Ca(H_2O)_2(\mathbf{L3})_2]^{2+}$	1163	443 (163)	485 (140)
C4:[d] $[Ca_6(\mathbf{L8})_5Cl_{12}]$	3608	3763 (−4)	4943 (−27)
$[Ca_7(\mathbf{L8})_6Cl_{14}]$	4308	3763 (14)	4943 (−13)

form $[Ca(\mathbf{L8})Cl_2]$, $[Ca_2(CD_3CN)_4(\mathbf{L8})Cl_4]$ or $[Ca_3(CD_3CN)_4(\mathbf{L8})_2Cl_6]$ are considered in MeCN-d_3. Starting with the donating solvents, **C1** exhibits an estimated molecular weight of 717 (DSE) and 909 g/mol (merge) in MeCN-d_3 (Table 3, top columns). Within the error range, these values fit to all three considered aggregates $[Ca(H_2O)_n(\mathbf{L1})_2Cl_{2-n}]^{n+}$ (n = 0–2) indicating that there might be a fast exchange between water and chloride ligands. Thus, it is most likely that a mixture of different contact and solvent separated ion pairs is present in solution. The molecular weight of **C2** in DMSO-d_6 is estimated to 957 (DSE) and 991 g/mol (merge) deviating only by 12% and −3% from the theoretical *MW* of $[Ca(H_2O)_2(\mathbf{L2})_2]^{2+}$. This indicates that an ion pair separation is maintained in solution. A measurement of **C3** in MeCN-d_3 gives a slightly better result but just like for the measurement in CD_2Cl_2 (vide infra) no assignment to chemically feasible complex aggregates could be carried out. This might be due to π-stacking of anthracene units influencing the diffusion of **C3** in solution resulting in a strong underestimation of its molecular weight. Finally, the molecular weight of **C4** in MeCN-d_3 is estimated to 963 (DSE) and 1154 g/mol (merge). Within the error range, these values fit best to the presence of dimeric aggregates of the form $[Ca_2(CD_3CN)_4(\mathbf{L8})Cl_4]$ that are terminated by CD_3CN molecules to suit the coordination sphere of the Ca(II) ions. Continuing with the investigations in non-donating solvents, the molecular weight of **C1** is estimated to 700 (DSE) and 795 g/mol (merge) (Table 3, bottom columns). These values deviate only by 15 and 1% from the theoretical molecular weight of 805 g/mol of a monomeric aggregate $[Ca(H_2O)_2(\mathbf{L1})_2]^{2+}$ again indicating that the solvent separated ion pair is most likely retained in solution. Unfortunately, for **C2** and **C3** no chemically feasible results are obtained showing only *MW*s which strongly deviate from any expected theoretical values. Again, this might be due to π-interaction of aromatic rings disturbing the diffusion rate of **C2** and **C3** in solution. The molecular weight of **C4** in $CDCl_3$ is estimated to 3763 (DSE) and 4943 g/mol (merge) that fit within the error range to both, hexa- ($[Ca_6(\mathbf{L8})_5Cl_{12}]$) as well as to heptameric ($[Ca_7(\mathbf{L8})_6Cl_{14}]$) aggregates. However, the molecular weight in solution may be strongly underestimated in this molecular weight dimension so that the presence of even longer polymeric chains cannot be excluded.

Conclusion

The synthesis and thorough characterization of five symmetrical (**L1**-**L5**; R = R′ = Et) as well as two asymmetrical geminal BP ester ligands (**L6** + **L7**; R = Et, R′ = *i*Pr) starting from the respective ethyl- or isopropyl (arylmethylene)phosphonate ester precursors (**S1**–**S7**) are presented. To pave the way for a potential future application as multi-delivery systems for geminal BPs as well as calcium mineral in osteoporosis treatment, a complexation with $CaCl_2$ provides derived Ca(II) compounds with the general formulas $[Ca(H_2O)_2(\mathbf{L1}–\mathbf{L3})_2]Cl_2$ (**C1**--**C3**) or $[Ca(\mathbf{L8})Cl_2]_n$ (**C4**). A comparison of their SCXRD structures with some of the rarely found X-ray data of related geminal BP-supported Ca(II) complexes like $[\{Ca_2(Cl_2C(PO_3iPr)_2)_2(EtOH)_2(H_2O)_2\}\cdot H_2O]_2$ (**A**), $[\{Ca_{1.5}(Cl_2C(PO_3Et)_2(H_2O)_2\}\cdot 0.5CH_3COCH_3\cdot 4.5H_2O]_n$ (**B**), $[\{Ca((CH_3)(OH)C(HPO_3)_2)_2\}\cdot 2H_2N(CH_3)_2]_n$ (**C**) and $[\{Ca((C_5H_{10}NH_3)(OH)C(HPO_3)_2)_2\}\cdot 3H_2O]_n$ (**D**) reveals the determined bond lengths, angles and the preferred octahedral coordination mode to be in good agreement with the literature data. In contrast to **A**--**D**, the used geminal BP ester ligands in **C1**, **C2** and **C4** show an exclusively bidentate coordination behavior despite being formally hexadentate ligand systems as well. Nonetheless, and just like for most of the previously reported structures, **C4** forms infinite polymeric strands promoted by ligand **L8** bridging adjacent $CaCl_2$ units. By contrast, **C1** and **C2** exhibit a preferred monomeric coordination mode as well as solvent separated ion pairs in the solid-state. A solution-state structure elucidation *via* ^{1}H-DOSY-ECC-*MW* experiments indicates the solvent separated ion pairs in **C1**–**C3** to be maintained in donating as well as non-donating solvents. For **C4**, it is most likely that hexa- or heptameric species are formed in a non-donating solvent like $CDCl_3$ while the presence of dimeric species is indicated in a donating solvent like MeCN-d_3. In summary, the DOSY results nicely support previous solution-state structure investigations of geminal BP-supported Ca(II) complexes *via* standard NMR spectroscopy, potentiometric titration or isothermal titration calorimetry. The previously reported investigations as well propose the presence of mono- and dimeric species like, CaL, CaL_2 and Ca_2L (L = geminal BP ligand), and that even polymeric structures like $[CaL]_n$ might be retained in solution. Additionally, a cytotoxicity study on the herein presented geminal BP esters and the derived Ca(II)

complexes has to be carried out in the future to obtain a comprehensive classification of their impact on the proliferation of living cells in comparison to drugs based on clinically relevant geminal BPs and their derivatives of today.

Experimental Section

General Information. All manipulations involving air- and moisture sensitive compounds were carried out under an argon atmosphere using Schlenk techniques or handled in an argon glovebox. Solvents were dried over Na or K metal or Na/K alloy and were used freshly distilled. Starting materials were purchased commercially and were used as received, unless stated otherwise. The benzylic bromides **Br3** and **Br4** have been prepared according to literature procedures.[14] Ligand **L8** was synthesized according to a modified and improved literature protocol.[16] Filtering of moisture and air sensitive compounds was carried out with self-made filter cannulas assembled from Whatman fiberglass filters (GF/B, 25 mm), which were applied with Teflon tape to Teflon cannulas. Flash chromatography was performed with an Interchim PuriFlash XS 520Plus device using PF-30SIHP-F0020 or -F0040 columns. CV = column volumes. For TLC, pre-coated Macherey-Nagel Alugram Xtra SIL G/UV_{254} plates were used. NMR experiments were performed with Varian 400 or 500 MHz spectrometers, and spectra were processed with MestReNova (v11.0.4-18998, Mestrelab Research S.L.). ^{1}H- and ^{13}C NMR spectra are referenced relative to TMS using the residual solvent signals as internal standards.[25] DOSY-NMR experiments were recorded on a Varian 400 MHz spectrometer. Sample spinning was deactivated during the measurements and the temperature was set and controlled at 298 K. All DOSY experiments were performed using the Dbppste pulse sequence.[26] DOSY transformation and processing was carried out with MestReNova (v11.0.4-18998, Mestrelab Research S.L.). Molecular weight estimation was carried out with the software (v1.3) provided by Bachmann.[22c] IR spectra were recorded with a diamond- or germanium probe ATR IR spectrometer by Bruker. Elemental analyses were performed using a HEKAtech Euro EA-CHNS elemental analyzer. For analyses, samples were prepared in tin cups with V_2O_5 as an additive to ensure complete combustion. ESI mass spectra were recorded on a Finnigan LCQDeca (ThermoQuest) or a MicrOTOF (Bruker Daltonics) device.

*Dialkyl (arylmethylene)phosphonate ester starting materials (**S1**–**S7**).* **General procedure for a Michaelis-Arbuzov reaction**. A benzylic bromide derivative: **Br1** (benzyl bromide), **Br2** (4-bromobenzyl bromide), **Br3** (9-bromo-10-(bromomethyl)anthracene), **Br4** (1-bromo-4-(bromomethyl)-2,3,5,6-tetrafluorobenzene) or **Br5** ((4-(bromomethyl)-phenyl)(trifluoromethyl)sulfane) (40.0 mmol, 1.00 eq.) and $P(OEt)_3$ (**S1**-**S5**) or $P(OiPr)_3$ (**S6, S7**) (44.0 mmol, 1.10 eq.) were mixed in a 50 mL round-bottom flask and attached to a distillation bridge with a short Vigreux column. The mixture was slowly heated up to 160 °C and stirred for 2.5 h. The corresponding alkyl bromide side product usually starts to distill off around 115–125 °C and is continuously removed from the reaction flask. The mixture was cooled to 65 °C and detached from the Vigreux column. Excess phosphite and residual alkyl bromide were removed under reduced pressure, and the product was cooled to RT (**S1**, **S2**, **S4**–**S7**) giving colorless to pale-yellow oils. In case of **S3**, the mixture was directly cooled to RT resulting in the formation of a yellow solid. The solid material was ground in a mortar to obtain a yellow powder which was washed with −20 °C pentanes (3× 50 mL), filtered (frit, P3) and dried. Compound **S4** forms a colorless solid after some time that is still contaminated with a small amount of colorless oil which is subsequently removed by washing with −20 °C pentanes (2×20 mL). In case of **S5**, the opaque pale-yellow oil was additionally diluted with pentanes (15 mL), percolated, and the solvent was removed. Compound **S7** also forms a colorless solid after some time. ***Diethyl benzylphosphonate (S1)*** (38.9 mmol, 98 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 4H, H2 + H6; H3 + H5), 7.23–7.18 (m, 1H, H4), 4.01–3.92 (m, 4H, CH_2CH_3), 3.11 (d, 2H, $^2J_{PH}$ = 21.6 Hz, CH_2), 1.20 (t, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 131.6 (d, 1 C, $^2J_{PC}$ = 9.0 Hz, C1), 129.8 (d, 2 C, $^3J_{PC}$ = 6.6 Hz, C2 + C6), 128.5 (d, 2 C, $^4J_{PC}$ = 3.2 Hz, C3 + C5), 126.9 (d, 1 C, $^5J_{PC}$ = 3.7 Hz, C4), 62.1 (d, 2 C $^2J_{PC}$ = 6.7 Hz, CH_2CH_3), 33.8 (d, 1 C, $^1J_{PC}$ = 138 Hz, CH_2), 16.4 (d, 2 C, $^3J_{PC}$ = 6.1 Hz, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 26.4 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1249 (P=O), 1097 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 251.12 (100) $[M+Na^+]^+$, 479.25 (15) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{11}H_{17}O_3P$ (228.23 g/mol): C 57.89, H 7.51; found: C 57.52, H 7.75. ***Diethyl 4-bromobenzylphosphonate (S2)*** (37.9 mmol, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 2H, H3 + H5), 7.17 (dd, 2H, $^3J_{HH}$ = 8.4, $^4J_{PH}$ = 2.5 Hz, H2 + H6), 4.06–3.97 (m, 4H, CH_2CH_3), 3.08 (d, 2H, $^2J_{PH}$ = 21.7 Hz, CH_2), 1.24 (t, 6H, $^3J_{HH}$ = 6.8 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 131.8 (d, 2 C, $^4J_{PC}$ = 3.0 Hz, C3 + C5), 131.6 (d, 2 C, $^3J_{PC}$ = 6.6 Hz, C2 + C6), 130.9 (d, 1 C, $^2J_{PC}$ = 9.1 Hz, C1), 121.0 (d, 1 C, $^5J_{PC}$ = 4.7 Hz, C4), 62.3 (d, 2 C, $^2J_{PC}$ = 6.7 Hz, CH_2CH_3), 33.4 (d, 1 C, $^1J_{PC}$ = 139 Hz, CH_2), 16.5 (d, 2 C, $^3J_{PC}$ = 5.9 Hz, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 25.4 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1247 (P=O), 1092 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 329.09 (100) $[M+Na^+]^+$, 637.11 (60) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{11}H_{16}BrO_3P$ (307.12 g/mol): C 43.02, H 5.25; found: C 42.87, H 5.52. ***Diethyl ((10-bromoanthracen-9-yl)methyl)phosphonate (S3)*** (38.2 mmol, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61–8.54 (m, 2H, H4 + H8), 8.36–8.31 (m, 2H, H5 + H1), 7.62–7.55 (m, 4H, H2 + H6; H3 + H7), 4.17 (d, 2H, $^2J_{PH}$ = 22.4 Hz, CH_2), 3.96–3.76 (m, 4H, CH_2CH_3), 1.08 (t, 6H, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 131.2 (d, 2 C, $^4J_{PC}$ = 6.7 Hz, C13 + C14), 130.4 (d, 1 C, $^5J_{PC}$ = 4.5 Hz, C10), 128.7 (d, 2 C $^6J_{PC}$ = 1.8 Hz, C3 + C7), 126.9 (d, 2 C, $^5J_{PC}$ = 1.9 Hz, C4 + C8), 126.3 (d, 2 C, $^5J_{PC}$ = 2.3 Hz, C2 + C6), 125.6 (d, 2 C, $^4J_{PC}$ = 3.3 Hz, C1 + C5), 124.8 (d, 1 C, $^2J_{PC}$ = 11.1 Hz, C9), 123.7 (d, 2 C, $^3J_{PC}$ = 8.0 Hz, C11 + C12), 62.4 (d, 2 C, $^2J_{PC}$ = 7.0 Hz, CH_2CH_3), 27.5 (d, 1 C, $^1J_{PC}$ = 141 Hz, CH_2), 16.4 (d, 2 C, $^3J_{PC}$ = 5.9 Hz, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 24.7 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1245 (P=O), 1101 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 429.02 (100) $[M+Na^+]^+$, 837.07 (20) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{19}H_{20}BrO_3P$ (407.24 g/mol): C 56.04, H 4.95; found: C 56.38, H 4.96. ***Diethyl 4-bromo-2,3,5,6-tetrafluorobenzylphosphonate (S4)*** (34.5 mmol, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18–4.04 (m, 4H, CH_2CH_3), 3.25 (dt, 2H, $^2J_{PH}$ = 21.5, $^4J_{FH}$ = 1.6 Hz, CH_2), 1.30 (d, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.6–145.9 (m, 2 C, C3 + C5), 144.1–143.4 (m, 2 C, C2 + C6), 111.7 (td, 1 C, $^2J_{FC}$ = 18.3, $^2J_{PC}$ = 10.4 Hz, C1), 99.1–98.3 (m, 1 C, C4), 62.8 (d, 2 C, $^2J_{PC}$ = 6.6 Hz, CH_2CH_3), 21.9 (d, 1 C, $^1J_{PC}$ = 142 Hz, CH_2)), 16.4 (d, 2 C, $^3J_{PC}$ = 6.2 Hz, CH_2CH_3) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = -133.6–133.7 (m, 2F, F3 + F5), −140.2–−140.3 (m, 2F, F2 + F6) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 21.2 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1259 (P=O), 1099 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 402.94 (100) $[M+Na^+]^+$, 780.91 (15) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{11}H_{12}BrF_4O_3P$ (379.09 g/mol): C 34.85, H 3.19; found: C 35.04 H 3.20. ***Diethyl 4-((trifluoromethyl)thio)-benzylphosphonate (S5)*** (36.8 mmol, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 2H, $^3J_{HH}$ = 7.9 Hz, H3 + H5), 7.35 (dd, 2H, $^3J_{HH}$ = 8.3, $^4J_{PH}$ = 2.6 Hz, H2 + H6), 4.06–3.96 (m, 4H, CH_2CH_3), 3.16 (d, 2H, $^2J_{PH}$ = 22.0 Hz, CH_2), 1.22 (t, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 136.4 (d, 2 C, $^4J_{PC}$ = 3.0 Hz, C3 + C5), 135.2 (d, 1 C, $^2J_{PC}$ = 9.2 Hz, C1), 130.9 (d, 2 C, $^3J_{PC}$ = 6.6 Hz, C2 + C6), 129.5 (dq, 1 C, $^1J_{FC}$ = 308, $^7J_{PC}$ = 3.1 Hz, CF_3), 122.8–122.7 (m, 1 C, C4), 62.2 (d, 2 C, $^2J_{PC}$ = 6.8 Hz, CH_2CH_3), 33.7 (d, 1 C, $^1J_{PC}$ = 138 Hz, CH_2), 16.3 (d, 2 C, $^3J_{PC}$ = 6.1 Hz, CH_2CH_3) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = −42.9 (s) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 25.1 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1246 (P=O), 1117 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 351.03 (100) $[M+Na^+]^+$,

679.09 (5) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{12}H_{16}F_3O_3PS$ (328.29 g/mol): C 43.90, H 4.91, S 9.77; found: C 42.54, H 5.19, S 8.20. ***Diisopropyl 4-bromobenzylphosphonate (S6)***. For data, see Pietschnig et al.[13] ***Diisopropyl 4-((trifluoromethyl)thio)benzylphosphonate (S7)*** (38.6 mmol, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 2H, $^3J_{HH}$ = 7.8 Hz, H3 + H5), 7.39–7.33 (m, 2H, H2 + H6), 4.69–4.52 (m, 2H, C*H*(CH_3)$_2$), 3.13 (d, 2H, $^2J_{PH}$ = 22.1 Hz, CH_2), 1.27 (d, 6H, $^3J_{HH}$ = 6.2 Hz, CH(C*H*$_3$)$_2$), 1.15 (d, 6H, $^3J_{HH}$ = 6.2 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 136.3 (d, 2 C, $^4J_{PC}$ = 3.0 Hz, C3 + C5), 135.6 (d, 1 C, $^2J_{PC}$ = 9.2 Hz, C1), 131.0 (d, 2 C, $^3J_{PC}$ = 6.4 Hz, C2 + C6), 129.5 (dq, 1 C, $^1J_{FC}$ = 311, $^7J_{PC}$ = 3.1 Hz, CF_3), 122.7–122.5 (m, 1 C, C4), 70.8 (d, 2 C, $^2J_{PC}$ = 6.8 Hz, *C*H(CH$_3$)$_2$), 34.7 (d, 1 C, $^1J_{PC}$ = 139 Hz, CH_2), 24.0 (d, 2 C, $^3J_{PC}$ = 4.0 Hz, CH(*C*H$_3$)$_2$), 23.7 (d, 2 C, $^3J_{PC}$ = 4.9 Hz, CH(*C*H$_3$)$_2$) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = −43.0 (s) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 23.2 (s) ppm; IR (ATR) $\tilde{\nu}$ = 1241 (P=O), 1107 (P–O*i*Pr) cm^{-1}; MS (ESI +) m/z (%): 357.01 (20) [M + H^+]$^+$, 378.98 (100) [M + Na^+]$^+$, 713.01 (20) [2 M + H^+]$^+$, 734.98 (20) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{14}H_{20}F_3O_3PS$ (356.34 g/mol): C 47.19, H 5.66, S 9.00; found: C 47.45, H 5.70, S 8.68.

*Tetraalkyl (arylmethylene)bis(phosphonate) ester ligands **L1**-**L7***. **General procedure A**. A mono-phosphonate ester derivative **S1**-**S7** (5.00 mmol, 1.00 eq.) was dissolved in dry Et_2O (30 mL; **S2**: 50 mL), and cooled to 0 °C. In case of **S3**, dry THF (30 mL) was used. *n*BuLi (2.10 mL, 5.25 mmol, 2.5 M in hexanes, 1.05 eq.) was slowly added dropwise via syringe. The ice-bath was removed, and the mixture was stirred at RT for 1 h. Then, diethyl chlorophosphate (0.76 mL, 5.25 mmol, 1.05 eq.) was added via syringe to the formed suspension, and the subsequently formed solution was stirred at RT for 1 h. Brine (50 mL) was added, and the phases were separated. The organic phase was washed with additional brine (50 mL), and the combined aqueous phases were extracted with Et_2O (2× 25 mL). The combined organic phases were dried over $MgSO_4$, percolated, and the solvent was evaporated. Flash column chromatography (Silica; First, a gradient: DCM/EtOAc (70 : 30 to 30 : 70; 8 CV). Then, EtOH/EtOAc (60 : 40)) gave bisphosphonates **L1**-**L7** as yellow to orange oils. In case of **L3**, a solid formed after some time that was additionally extracted with a mixture of pentane/Et_2O. Yields are between 23 % to 36 %. Crystals of **L3** suitable for SCXRD experiments were obtained by vapor diffusion of pentanes into a saturated solution of **L3** in THF. **General procedure B**. A mono-phosphonate ester derivative **S1**-**S7** (5.00 mmol, 1.00 eq.) was dissolved in dry THF (30 mL) and cooled to 0 °C. *n*BuLi (2.10 mL, 5.25 mmol, 2.5 M in hexanes, 1.05 eq.) was slowly drop wise added via syringe. The ice-bath was removed, and the mixture was stirred at RT for 1 h. Diethyl chlorophosphite (0.75 mL, 5.25 mmol, 1.05 eq.) was added drop wise via syringe, and the mixture was stirred at RT overnight (16 h). The reaction mixture was again cooled to 0 °C, H_2O_2 (conc.) (3.01 mL, 100 mmol, 20.0 eq.) was slowly drop wise added via syringe and again stirred at RT for 1 h. The work-up was carried out as in procedure A. Yields are between 30 % to 43 %. ***Tetraethyl (phenylmethylene)bis(phosphonate) (L1)***. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.43 (m, 2H, H3 + H5), 7.35–7.25 (m, 3H, H2 + H6, H4), 4.16–4.08 (m, 4H, CH_2CH$_3$), 4.07–4.01 (m, 2H, CH_2CH$_3$), 3.97–3.88 (m, 2H, CH_2CH$_3$), 3.74 (t, 1H, $^2J_{PH}$ = 25.1 Hz, CH), 1.27 (t, 6H, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 1.13 (t, 6H, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 130.2 (t, 2 C, $^3J_{PC}$ = 6.6 Hz, C2 + C6), 130.1–129.8 (m, 1 C, C1), 128.3 (s, 2 C, C3 + C5), 127.4 (s, 1 C, C4), 63.3–63.1 (m, 2 C, CH_2CH_3), 62.8–62.6 (m, 2 C, CH_2CH_3), 45.4 (t, 1 C, $^1J_{PC}$ = 133 Hz, CH), 16.2–15.8 (m, 4 C, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 18.5 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1251 (P=O), 1097 (P–OEt) cm^{-1}; MS (ESI +) m/z (%): 387.23 (100) [M + Na^+]$^+$, 751.40 (33) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{15}H_{26}O_6P_2$ (364.32 g/mol): C 49.45, H (7.19); found: C 47.38, H 7.26. ***Tetraethyl ((4-bromophenyl)methylene)bis(phosphonate) (L2)***. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 2H, H3 + H5), 7.37–7.32 (m, 2H, H2 + H6), 4.16–4.05 (m, 6H, CH_2CH$_3$), 4.01–3.92 (m, 2H, CH_2CH$_3$), 3.68 (t, 1H, $^2J_{PH}$ = 25.0 Hz, CH), 1.27 (t, 6H, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 1.17 (t, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 132.1 (t, 2 C, $^3J_{PC}$ = 6.4 Hz, C2 + C6), 131.8 (t, 2 C, $^4J_{PC}$ = 2.0 Hz, C3 + C5), 129.7 (t, 1 C, $^2J_{PC}$ = 7.6 Hz, C1), 122.0 (t, 1 C, $^5J_{PC}$ = 3.3 Hz, C4), 63.7–63.5 (m, 2 C, CH_2CH_3), 63.3–63.1 (m, 2 C, CH_2CH_3), 45.3 (t, 1 C, $^1J_{PC}$ = 133 Hz, CH), 16.5–16.3 (m, 4 C, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 17.9 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1249 (P=O), 1097 (P–OEt) cm^{-1}; MS (ESI +) m/z (%): 451.08 (70) [M + Li^+]$^+$, 893.08 (100) [2 M + Li^+]$^+$; Elemental analysis calcd (%) for $C_{15}H_{25}BrO_6P_2$ (443.21 g/mol): C 40.65, H 5.69; found: C 40.99, H 5.95. ***Tetraethyl ((10-bromoanthracen-9-yl)methylene)bis(phosphonate) (L3)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, 1H, $^3J_{HH}$ = 8.7 Hz, H4), 8.69–8.63 (m, 1H, H1), 8.58 (d, 1H, $^3J_{HH}$ = 8.4 Hz, H8), 8.30–8.24 (m, 1H, H5), 7.67–7.56 (m, 4H, H2 + H6, H3 + H7), 5.48 (t, 1H, $^2J_{PH}$ = 30.8 Hz, CH), 4.20–4.11 (m, 4H, CH_2CH$_3$), 3.86–3.74 (m, 2H, CH_2CH$_3$), 3.66–3.54 (m, 2H, CH_2CH$_3$), 1.26 (t, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 0.80 (t, 6H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 132.2 (t, 1 C, *J* = 4.5 Hz, C_{Ar}), 131.5 (t, 1 C, *J* = 8.5 Hz, C_{Ar}), 130.7–130.5 (m, 1 C, C_{Ar}), 129.3–129.3 (m, 1 C, C_{Ar}), 129.2 (t, 1 C, *J* = 2.1 Hz, C_{Ar}), 127.9 (s, 1 C, C_{Ar}), 127.5 (s, 1 C, C_{Ar}), 127.0 (t, 1 C, *J* = 1.2 Hz, C_{Ar}), 126.6 (s, 1 C, C_{Ar}), 125.9–125.8 (m, 1 C, C_{Ar}), 125.1 (t, 1 C, *J* = 5.3 Hz, C_{Ar}), 124.3 (t, 1 C, *J* = 8.4 Hz, C_{Ar}), 123.9 (t, 1 C, *J* = 1.8 Hz, C_{Ar}), 63.5–63.4 (m, 2 C, CH_2CH_3), 63.3–63.2 (m, 2 C, CH_2CH_3), 41.4 (t, 1 C, $^1J_{PC}$ = 135 Hz, CH), 16.5–16.4 (m, 2 C, CH_2CH_3), 16.0–15.9 (m, 2 C, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 19.4 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1252 (P=O), 1097 (P–OEt) cm^{-1}; MS (ESI +) m/z (%): 487.19 (25) [M–Br + Na^+]$^+$, 565.10 (100) [M + Na^+]$^+$, 1031.24 (15) [2 M–Br + Na^+]$^+$; 1109.14 (85) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{23}H_{29}BrO_6P_2$ (543.33 g/mol): C 50.84, H (5.38); found: C 50.24, H 5.61. ***Tetraethyl ((2,3,5,6-tetrafluorophenyl)methylene)bis(phosphonate) (L4)***. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08–6.97 (m, 1H, H4), 4.31 (t, 1H, $^2J_{PH}$ = 17.4 Hz, CH), 4.26–4.17 (m, 6H, CH_2CH$_3$), 4.13–4.05 (m, 2H, CH_2CH$_3$), 1.35–1.26 (m, 12H, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 147.4–146.4 (m, 1 C, C3), 145.6–144.4 (m, 2 C, C2, C5), 143.8–143.3 (m, 1 C, C6), 112.7–112.4 (m, 1 C, C4), 105.7 (t, 1 C, $^2J_{PC}$ = 22.4 Hz, C1), 63.7 (t, 4 C, $^2J_{PC}$ = 7.7 Hz, CH_2CH_3), 36.0 (t, 1 C, $^1J_{PC}$ = 136 Hz, CH), 16.4 (d, 2 C, $^3J_{PC}$ = 2.3 Hz, CH_2CH_3), 16.36 (d, 2 C, $^3J_{PC}$ = 2.2 Hz, CH_2CH_3) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 16.1 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1248 (P=O), 1098 (P–OEt) cm^{-1}; MS (ESI +) m/z (%): 459.12 (100) [M + Na^+]$^+$, 895.18 (80) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{15}H_{22}F_4O_6P_2$ (436.28 g/mol): C 41.30, H 5.08; found: C 38.35, H 5.08. ***Tetraethyl ((4-((trifluoromethyl)thio)phenyl)methylene)bis(phosphonate) (L5)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.49 (m, 2H, H3 + H5), 7.43–7.03 (m, 2H, H2 + H6), 4.40–3.49 (m, 9H, CH + CH_2CH$_3$), 1.39–0.80 (m, 12H, CH_2CH_3) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 136.5–136.4 (m, 2 C, C3 + C5), 136.3–136.3 (m, 1 C, C1), 131.7–131.5 (m, 2 C, C2 + C6), 129.2 (dq, $^1J_{FC}$ = 228, $^7J_{PC}$ 4.2 Hz, CF_3), 124.0–123.8 (m, 1 C, C4), 63.9–63.7 (m, 2 C, CH_2CH_3), 63.5–63.3 (m, 2 C, CH_2CH_3), 45.4 (t, 1 C, $^1J_{PC}$ = 132 Hz, CH), 16.4–16.1 (m, 4 C, CH_2CH_3) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = −42.8 (s) ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 17.7 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1245 (P=O), 1118 (P–OEt) cm^{-1}; MS (ESI +) m/z (%): 487.13 (85) [M + Na^+]$^+$, 951.20 (100) [2 M + Na^+]$^+$; Elemental analysis calcd (%) for $C_{16}H_{25}F_3O_6P_2S$ (464.37 g/mol): C 41.38, H 5.43, S 6.90; found: C 41.79, H 5.78, S 3.81. ***Diisopropyl ((4-bromophenyl)(diethoxyphosphoryl)-methyl)phosphonate (L6)***. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, 2H, $^3J_{HH}$ = 8.2 Hz, H3 + H5), 7.37–7.30 (m, 2H, H2 + H6), 4.73 (dh, 1H, $^3J_{PH}$ = 12.5, $^3J_{HH}$ = 6.0 Hz, C*H*(CH$_3$)$_2$), 4.58 (dh, 1H, $^3J_{PH}$ = 12.5, $^3J_{HH}$ = 6.5 Hz, C*H*(CH$_3$)$_2$), 4.15–3.96 (m, 4H, CH_2CH$_3$), 3.63 (t, 1H, $^2J_{PH}$ = 25.0 Hz, CH), 1.32–1.23 (m, 12H, CH(CH_3)$_2$ + CH_2CH_3), 1.18 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 1.02 (d, 3H, $^3J_{HH}$ = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 132.3 (t, 2 C, $^3J_{PC}$ = 6.4 Hz, C2 + C6), 131.6 (t, 2 C, $^4J_{PC}$ = 2.1 Hz, C3 + C5), 130.0 (t, 1 C, $^2J_{PC}$ = 7.8 Hz, C1), 121.8 (t, 1 C, $^5J_{PC}$ = 3.3 Hz, C4), 72.6 (d, 1 C, $^2J_{PC}$ = 7.1 Hz, *C*H(CH$_3$)$_2$), 72.0 (d, 1 C, $^2J_{PC}$ = 7.1 Hz, *C*H(CH$_3$)$_2$), 63.5 (d, 1 C, $^2J_{PC}$ = 6.7 Hz,

CH_2CH_3), 63.1 (d, 1 C, $^2J_{PC}$ = 6.9 Hz, CH_2CH_3), 46.0 (dd, 1 C, $^1J_{PC}$ = 135, 133 Hz, CH), 24.4 (d, 1 C, $^3J_{PC}$ = 2.6 Hz, $CH(CH_3)_2$), 24.2 (d, 1 C, $^3J_{PC}$ = 3.4 Hz, $CH(CH_3)_2$), 23.9 (d, 1 C, $^3J_{PC}$ = 5.9 Hz, $CH(CH_3)_2$), 23.3 (d, 1 C, $^3J_{PC}$ = 6.3 Hz, $CH(CH_3)_2$), 16.5 (d, 1 C, $^3J_{PC}$ = 6.3 Hz, CH_2CH_3), 16.4 (d, 1 C, $^3J_{PC}$ = 6.2 Hz, CH_2CH_3) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 18.1 (s, 1P, P(O)$(OEt)_2$), 16.0 (s, 1P, P(O)$(OiPr)_2$) ppm; IR (ATR) $\tilde{\nu}$ = 1250 (2x P=O), 1102 (P–OEt + P–O*i*Pr) cm^{-1}; MS (ESI+) m/z (%): 495.10 (25) $[M+Na^+]^+$, 965.16 (100) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{17}H_{29}BrO_6P_2$ (471.27 g/mol): C 43.33, H 6.20; found: C 41.12, H 6.26. ***Diisopropyl ((diethoxyphosphoryl)(4-((trifluoromethyl)thio)phenyl)methyl)phosphonate (L7)***. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, 2H, $^3J_{HH}$ = 8.1 Hz, H3 + H5), 7.55–7.49 (m, 2H, H2 + H6), 4.73 (dh, 1H, $^3J_{PH}$ = 12.6, $^3J_{HH}$ = 6.1 Hz, $CH(CH_3)_2$), 4.57 (dh, 1H, $^3J_{PH}$ = 12.3, $^3J_{HH}$ = 5.8 Hz, $CH(CH_3)_2$), 4.16–3.97 (m, 4H, CH_2CH_3), 3.72 (t, 1H, $^2J_{PH}$ = 24.8 Hz, CH), 1.35–1.23 (m, 12H, $CH(CH_3)_2$ + CH_2CH_3), 1.16 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 0.95 (d, 3H, $^3J_{HH}$ = 6.2 Hz, $CH(CH_3)_2$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 136.3–136.2 (m, 2 C, C3 + C5), 134.4 (t, 1 C, $^2J_{PC}$ = 7.7 Hz, C1), 131.5 (t, 2 C, $^3J_{PC}$ = 6.3 Hz, C2 + C6), 129.4 (q, 1 C, $^1J_{FC}$ = 308 Hz, CF_3), 123.6–123.5 (m, 1 C, C4), 72.6 (d, 1 C, $^2J_{PC}$ = 6.9 Hz, $CH(CH_3)_2$), 71.9 (d, 1 C, $^2J_{PC}$ = 7.2 Hz, $CH(CH_3)_2$), 63.4 (d, 1 C, $^2J_{PC}$ = 6.8 Hz, CH_2CH_3), 63.0 (d, 1 C, $^2J_{PC}$ = 6.8 Hz, CH_2CH_3), 46.3 (dd, 1 C, $^1J_{PC}$ = 134, 132 Hz, CH), 24.3 (d, 1 C, $^3J_{PC}$ = 2.5 Hz, $CH(CH_3)_2$), 24.0 (d, 1 C, $^3J_{PC}$ = 3.4 Hz, $CH(CH_3)_2$), 23.7 (d, 1 C, $^3J_{PC}$ = 5.8 Hz, $CH(CH_3)_2$), 22.9 (d, 1 C, $^3J_{PC}$ = 6.5 Hz, $CH(CH_3)_2$), 16.2 (d, 1 C, $^3J_{PC}$ = 6.2 Hz, CH_2CH_3), 16.1 (d, 1 C, $^3J_{PC}$ = 5.9 Hz, CH_2CH_3) ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = -42.9 (s) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 17.8 (s, 1P, P(O)$(OEt)_2$), 15.8 (s, 1P, P(O)$(OiPr)_2$) ppm; IR (ATR) $\tilde{\nu}$ = 1252 (2x P=O), 1118 (P–OEt + P–O*i*Pr) cm^{-1}; MS (ESI+) m/z (%): 515.14 (20) $[M+Na^+]^+$, 1007.23 (100) $[2\,M+Na^+]^+$; Elemental analysis calcd (%) for $C_{18}H_{29}F_3O_6P_2S$ (492.43 g/mol): C 43.90, H 5.94, S 6.51; found: C 43.15, H 6.07, S 4.53.

Octaethyl propane-1,1,3,3-tetrayltetrakis(phosphonate) ester ligand L8. NaH (812 mg, 33.8 mmol, 1.01 eq.) was suspended in dry THF (50 mL) in a 100 mL Schlenk flask. Under vigorous stirring, tetraethyl methylenebis(phosphonate) (8.32 mL, 33.5 mmol, 1.00 eq.) was drop wise added via syringe while the mixture was cooled with a RT water-bath. After the H_2 evolution ceased, tetraethyl ethene-1,1-diylbis(phosphonate) (8.79 mL, 33.5 mmol, 1.00 eq.) was added via syringe and the mixture was stirred at RT for 2 h. The mixture was transferred to a separation funnel, saturated NH_4Cl solution (100 mL) as well as Et_2O (100 mL) were added, and the phases separated. The solvent of the organic phase was removed under reduced pressure. The residue was extracted with DCM, the extract was dried over Na_2SO_4, filtered, and the solvent was again removed. **L8** is obtained as a pale-yellow oil (12.6 g, 21.4 mmol, 64 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.22–4.11 (m, 16H, CH_2CH_3), 3.40 (tt, 2H, $^2J_{PH}$ = 23.8, $^3J_{HH}$ = 6.8 Hz, CH), 2.52–2.39 (m, 2H, CH_2), 1.32 (td, 24H, $^3J_{HH}$ = 7.1, $^4J_{PH}$ = 1.4 Hz, CH_2CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 62.7 (dd, 8 C, $^2J_{PC}$ = 15.9, $^4J_{PC}$ = 6.1 Hz, CH_2CH_3), 34.1 (tt, 2 C, $^1J_{PC}$ = 131.9, $^3J_{PC}$ = 6.9 Hz, CH), 21.9 (p, 1 C, $^2J_{PC}$ = 3.7 Hz, CH_2), 16.5 (dd, 8 C, $^3J_{PC}$ = 5.8, $^5J_{PC}$ = 2.8 Hz, CH_2CH_3). ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 22.9 (s, 4P) ppm; IR (ATR) $\tilde{\nu}$ = 1246 (P=O), 1097 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 589.20 (100) $[M+H^+]^+$; Elemental analysis calcd (%) for $C_{19}H_{44}O_{12}P_4$ (588.44 g/mol): C 38.78, H 7.54; found: C 38.26, H 7.90.

*Bis- and Tetrakisphosphonate Ester Supported Calcium Complexes **C1-C4***. **General procedure for C1-C3**. $CaCl_2$ (111 mg, 1.00 mmol, 1.00 eq.) was dissolved in a mixture of EtOH (20 mL) and H_2O (0.5 mL) in a 50 mL round-bottom flask. A solution of bisphosphonate ester ligands **L1** or **L2** in EtOH (4.76 mL, 0.42 M, 2.00 mmol, 2.00 eq.) or a solution of **L3** (1.09 g, 2.00 mmol, 2.00 eq.) in EtOH (10 mL) was added via syringe and the mixture was stirred at RT overnight (16 h). The solvent was removed under reduced pressure yielding off white (**L1**), colorless (**L2**) or yellow (**L3**) waxes. Extraction with pentanes (3 x 10 mL) and drying gave the corresponding solids. Yields are between 86 to 92 %. Recrystallization by vapor diffusion of pentanes into saturated THF solutions of **C1** and **C2** at RT yielded crystals suitable for SCXRD experiments. ***[Ca(H$_2$O)$_2$(L1)$_2$]Cl$_2$ (C1)***. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, 4H, $^3J_{HH}$ = 6.2 Hz, H3 + H5), 7.34–7.27 (m, 6H, H2 + H6, H4), 5.15 (t, 2H, $^2J_{PH}$ = 25.8 Hz, CH), 4.34–4.19 (m, 16H, CH_2CH_3), 4.09 (s_{br}, 4H, H_2O), 1.30 (t, 12H, $^3J_{HH}$ = 6.7 Hz, CH_2CH_3), 1.18 (t, 12H, $^3J_{HH}$ = 6.8 Hz, CH_2CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 130.4 (t, 4 C, $^3J_{PC}$ = 6.2 Hz, C2 + C6), 129.4 (t, 2 C, $^2J_{PC}$ = 8.2 Hz, C1), 128.8–128.7 (m, 4 C, C3 + C5), 128.0 (t, 2 C, $^5J_{PC}$ = 2.3 Hz, C4), 64.6–64.5 (m, 4 C, CH_2CH_3), 64.4–64.3 (m, 4 C, CH_2CH_3), 44.1 (t, 2 C, $^1J_{PC}$ = 129 Hz, CH), 16.5–16.3 (m, 4 C, CH_2CH_3), 16.3–16.1 (m, 4 C, CH_2CH_3) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 19.7 (s, 4P) ppm; IR (ATR) $\tilde{\nu}$ = 3319 (OH), 3230 (OH), 1240 (P=O), 1100 (P–OEt) cm^{-1}; MS (ESI+) m/z (%): 803.20 (100) $[M–Cl^-]^+$, 439.07 (10) $[M–L–Cl^-]^+$, 387.12 (80) $[L+Na^+]^+$; Elemental analysis calcd (%) for $C_{30}H_{56}CaCl_2O_{14}P_4$ (875.64 g/mol): C 41.15, H 6.45; found: C 40.73, H 6.50. ***[Ca(H$_2$O)$_2$(L2)$_2$]Cl$_2$ (C2)***. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.34 (m, 8H, H3 + H5; H2 + H6), 4.22–3.98 (m, 16H, CH_2CH_3), 3.97–3.64 (m, 6H, CH + H_2O), 3.81 (s_{br}, 2H, CH), 1.29–1.17 (m, 21H, CH_2CH_3), 1.02 (s_{br}, 3H, CH_2CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 132.2 (t, 4 C, $^3J_{PC}$ = 6.4 Hz, C2 + C6), 131.8 (t, 4 C, $^4J_{PC}$ = 1.9 Hz, C3 + C5), 129.5 (t, 2 C, $^2J_{PC}$ = 7.9 Hz, C1), 122.0 (t, 2 C, $^5J_{PC}$ = 3.3 Hz, C4), 63.8–63.6 (m, 4 C, CH_2CH_3), 63.5–63.4 (m, 4 C, CH_2CH_3), 44.9 (t, 2 C, $^1J_{PC}$ = 132 Hz, CH), 16.5–16.2 (m, 8 C, CH_2CH_3) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 18.1 (s, 4P) ppm; IR (ATR) $\tilde{\nu}$ = 3386 (OH), 1233 (P=O), 1101 (P–OEt) cm^{-1}; Elemental analysis calcd (%) for $C_{30}H_{54}Br_2CaCl_2O_{14}P_4$ (1033.43 g/mol): C 34.87, H 5.27; found: C 35.06, H 4.82. ***[Ca(H$_2$O)$_2$(L3)$_2$]Cl$_2$ (C3)***. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.12 (d, 2H, $^3J_{HH}$ = 8.9 Hz, H4), 8.78–8.69 (m, 2H, H1), 8.66 (d, 2H, $^3J_{HH}$ = 8.8 Hz, H8), 8.59 (d, 2H, $^3J_{HH}$ = 8.9 Hz, H5), 7.72–7.64 (m, 4H, H2 + H6), 7.63–7.57 (m, 4H, H3 + H7), 6.00 (t, 2H, $^2J_{PH}$ = 32.1 Hz, CH), 4.26–3.91 (m, 20H, CH_2CH_3 + H_2O), 1.28–1.24 (m, 3H, CH_2CH_3), 1.10–0.97 (m, 21H, CH_2CH_3) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 132.0–131.8 (m, 4 C, C_{Ar}), 130.7 (t, 2 C, J = 2.5 Hz, C_{Ar}), 130.5 (t, 2 C, J = 3.4 Hz C_{Ar}), 129.2 (s, 2 C, C_{Ar}), 129.0–128.9 (m, 2 C, C_{Ar}), 128.0 (s, 2 C, C_{Ar}), 127.4 (s, 2 C, C_{Ar}), 127.3 (s, 2 C, C_{Ar}), 126.8 (s, 2 C, C_{Ar}), 125.8–125.7 (m, 2 C, C_{Ar}), 125.5 (t, 2 C, J = 5.4 Hz, C_{Ar}), 124.8–124.6 (m, 2 C, C_{Ar}), 124.0 (t, 2 C, J = 8.7 Hz, C_{Ar}), 64.5–64.0 (m, 8 C, CH_2CH_3), 41.2 (t, 2 C, $^1J_{PC}$ = 134 Hz, CH), 16.3–16.0 (m, 8 C, CH_2CH_3) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 19.4 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 3375 (OH), 1227 (P=O), 1097 (P–OEt) cm^{-1}; Elemental analysis calcd (%) for $C_{46}H_{62}Br_2CaCl_2O_{14}P_4$ (1233.67 g/mol): C 44.79, H 5.07; found: C 45.15, H 5.04. **General procedure for C4**. $CaCl_2$ (222 mg, 2.00 mmol, 1.00 eq.) was dissolved in a mixture of EtOH (15 mL) and H_2O (0.5 mL) in a 50 mL round-bottom flask. A solution of **L8** (1.18 g, 2.00 mmol, 1.00 eq.) in EtOH (10 mL) was added via syringe and the mixture was stirred at RT for 3 h. The solvent was removed under reduced pressure yielding a white solid that was washed with pentanes (2 × 15 mL) and dried (1.33 g, 1.90 mmol, 95 %). Crystals suitable for SCXRD experiments were obtained from a saturated solution of **C4** in $CDCl_3$ in an NMR tube at RT. ***[Ca(L8)Cl$_2$]$_n$ (C4)***. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.63–4.42 (m, 6H, CH_2CH_3), 4.32–4.14 (m, 10H, CH_2CH_3), 3.82–3.65 (m, 2H, CH), 2.35–2.20 (m, 2H, CH_2), 1.34–1.25 (m, 24H, CH_2CH_3) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 64.9–64.5 (m, 4 C, CH_2CH_3), 64.1–63.7 (m, 4 C, CH_2CH_3), 35.0–32.7 (m, 2 C, CH), 21.0–20.7 (m, 1 C, CH_2), 17.1–16.3 (m, 8 C, CH_2CH_3) ppm; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 24.0 (s, 2P), 23.2 (s, 2P) ppm; IR (ATR) $\tilde{\nu}$ = 1236 (P=O), 1097 (P–OEt) cm^{-1}; Elemental analysis calcd (%) for $C_{19}H_{44}CaCl_2O_{12}P_4$ (699.42 g/mol): C 32.63, H 6.34; found: C 32.00, H 6.36.

Crystallographic Details. X-ray diffraction experiments were performed with either a STOE IPDS 2 with an image plate (Ø34 cm) using a Mo-GENIX source (λ = 0.71073 nm) or a STOE StadiVari instrument with DECTRIS PILATUS 200 K using a Cu-GENIX source (λ = 1.54186 nm). All structures were solved using direct methods (SHELXT)[27] and refined against F^2 using the full-matrix least-squares

methods of SHELXL[28] within the SHELXLE GUI[29] or with OLEX2.[30] Additional programs used for structural analysis include Mercury[31] and Platon.[32]

Deposition Numbers 2152127 (**L3**), 2152128 (**C1**), 2152129 (**C2**), and 2152130 (**C4**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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