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Synthetic approaches to mixed ligand chelators on *tert*-butylphenol–formaldehyde oligomer (PFO) platforms

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ABSTRACT

Synthetic approaches to mixed ligand chelators on readily available *tert*-butylphenol–formaldehyde oligomer, PFO, scaffolds were examined. In a promising approach, tris and tetraphenol oligomers were selectively mono or di protected using *tert*-butyldiphenyl silyl chloride. The utility of these protected intermediates to prepare representative mixed PFO chelators, carrying ligands such as hydroxamic acid, 3,2-hydroxypyridinones, and others was then demonstrated. The introduction of the ligand tethers onto the phenolic scaffold can be done sequentially under relatively mild conditions that tolerate the presence of other sensitive ligand groups. The differential reactivity of the disilyl derivative **20b**, allowed stepwise introduction of two different ligands on the internal phenolic positions. This enabled the introduction of three different ligand groups of choice onto the tetraphenol platform.

1. Introduction

The development of selective chelators for a variety of metal ions has been an area of high interest. Metal ion chelators have been shown to have numerous applications that range from therapeutics and diagnostics to separation technology and environmental remediation.[1] A major challenge in this area is to design and synthesize chelators capable of specifically binding the target cation in the desired manner.[2] This requires an understanding of the coordination chemistry, geometry, and ligand preferences that complement the target metal ion. In many applications the resultant complex must also address stability, solubility, and toxicity concerns.[3] The specific attributes of the metal–chelator complexes need to be varied to meet the proposed application. In many cases selective binding of the target cation in the presence of competing cations is desired and the strength of the metal binding (e.g., high binding constant) may be less critical.

A number of reports have appeared on the properties and applications of calix[*n*]arenes, a unique class of macromolecules.[4] Recent reviews document the potential uses of the calixarene scaffold in the development of new drugs[5] and as hosts for a variety of metal ions.[6] A solid phase synthesis of a library of peptidocalix[4]arenes has been recently reported. Some members of this library were shown to be host molecules for guest peptides in aqueous media.[7,8]

Some time ago, we disclosed the syntheses of the 4-*tert*-butylcalix[4]arene derived tetrahydroxamate,[9] **1**, and the 3-hydroxy-2-pyridinone (3,2-HOPO)[10] **2**, metal ion extractants designed for the separation of hard cations such as actinide(IV) using liquid–liquid extractions. In order to ascertain the importance of the calix[4]arene backbone in the selectivity and efficiency of metal ion binding, and to develop a more systematic understanding of the actinide chelation/extraction properties of this class of ligands, we also prepared the corresponding acyclic (phenol–formaldehyde oligomers, PFOs) trihydroxamate **3**, and tetrahydroxamate **4**, and the tetraHOPO **5**. Just like the parent calixarenes **1** and **2**, the PFO extractants **3**, **4**, and **5** were excellent extractants of cations such as iron(III) and thorium(IV) into chloroform from acidic aqueous solutions.[11,12] Our results strongly supported the hypothesis that the rigidity of the calixarene backbone is not imperative to achieve strong metal ion binding and may not offer increased metal ion binding selectivity. Hence, both calixarenes and the corresponding ligand functionalized PFOs are useful templates for separation applications.[13] Compared to calixarenes, development of PFO-based chelators has received minimum attention. Some phenolic oligomers have been functionalized with various ligand groups to prepare receptors for cations[14] and anions.[15] It is also interesting to note that the unfunctionalized PFOs have been shown to form a variety of host–guest complexes with various organic compounds.[16]

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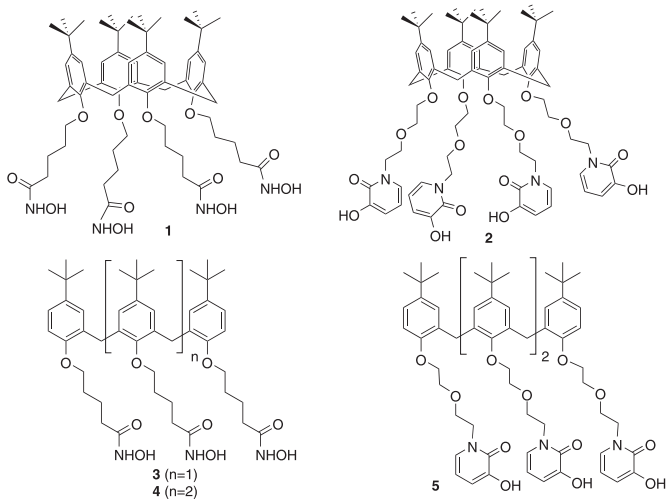


The primary goal of this study was to develop and demonstrate the utility of a flexible synthetic approach to access sets of mixed ligand chelators[17] built on lipophilic PFO platforms that could be screened for the binding of cations of interest. Having access to a related set of metal binding hosts built on PFO platforms, would also provide useful information on the impact of ligand variation on metal ion complexation. This class of chelators has the potential to be useful as diagnostic agents and in selective metal sequestration. More specifically, our goal was to develop synthetic methodology for the preparation of a broad range of trimeric and tetrameric polyphenol chelators, exemplified by **I** and **II** (Fig. 1). The proposed synthetic methodology would allow one to specifically install the ligand of choice (some examples are shown in Fig. 1) on each of the phenol monomer units, leading to a diverse array of unique cation binding hosts.

provide the starting material **III**. Lithiation of **III** and subsequent coupling with an aldehyde, **IV**,[18] carrying L_2 should proceed to give benzylic alcohol, **V**, which could be reduced with triethylsilane and trifluoroacetic acid to give **VI**. The challenge is how to repeat this sequence to add the third phenolic moiety. One might anticipate that selective monoformylation of intermediate **VI** would not be possible since it is not as reactive as the corresponding phenol. Also the highly basic phenol organolithium coupling conditions would only be compatible with the most stable ligands.

In spite of the potential hurdles, it was decided to examine the viability of the key aldehyde coupling step in this approach to PFO platforms by the synthesis of a trimeric host carrying stable polyether ligands. Polyether-type ligands have been prepared and shown to be extractants of alkali metal cations.[19] The arylbromide **6** was prepared by alkylation of 2-bromophenol with 2-(2-methoxyethoxy)ethyl methanesulfonate using Cs_2CO_3 in refluxing acetonitrile (Scheme 1). Formylation of bisphenol **7**[20] was accomplished using paraformaldehyde, $MgCl_2$, and triethylamine in refluxing THF for 3 d.[21] The authors of this paper have proposed that the initially formed salicyl alcohol undergoes a redox reaction with a second equivalent of formaldehyde, to give the corresponding aldehyde and methanol. Two major products, the monoaldehyde **8** and the dialdehyde **9** were isolated in 46 and 20% yields, respectively, after chromatographic purification. Our attempts to selectively obtain the monoaldehyde, **8**, in higher yields were not successful. It is interesting to note that when the formylation reaction of **7** was conducted in a microwave reactor in acetonitrile under pressure at elevated temperature, the dialdehyde **9** was obtained in 95% yield. This is a useful finding as the dialdehyde, **9**, is potentially a useful intermediate for the synthesis of other polyphenol metal binding hosts. The monoaldehyde **8** was then alkylated with 2-(2-methoxyethoxy)ethyl methanesulfonate under similar conditions to give the polyether aldehyde **10** in 52% yield.

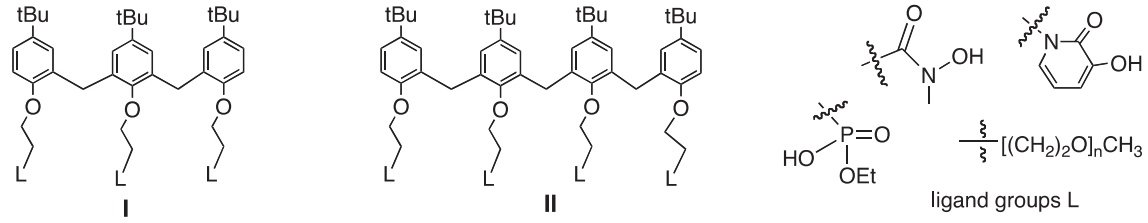


Fig. 1. Potential polyphenol extractants.

2. Results and discussion

A straightforward approach, to build PFO hosts of the types **I** and **II**, would involve a stepwise linking of functionalized phenolic monomer units carrying the desired ligands. This approach is illustrated in Fig. 2. Bromination of 4-*tert*-butylphenol followed by its alkylation with the desired first ligand L_1 should

Arylbromide **6** was lithiated with *s*-butyl lithium at −78 °C in THF and then transferred via cannula to a solution of the aldehyde **10** at −78 °C in THF (Scheme 2).[18] The crude benzylic alcohol obtained from the reaction was reduced with trifluoroacetic acid and triethylsilane[22] to give the tris polyether chelator **11** in 45% yield (two steps) after purification. A significant byproduct was the reduced monomeric phenol ether. This suggests that nucleophilic

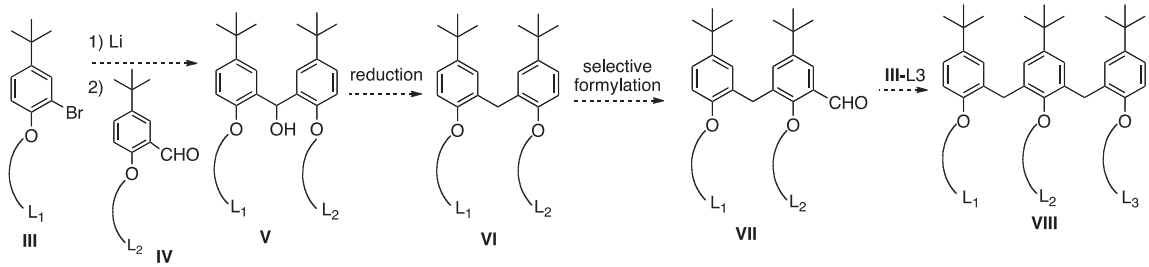
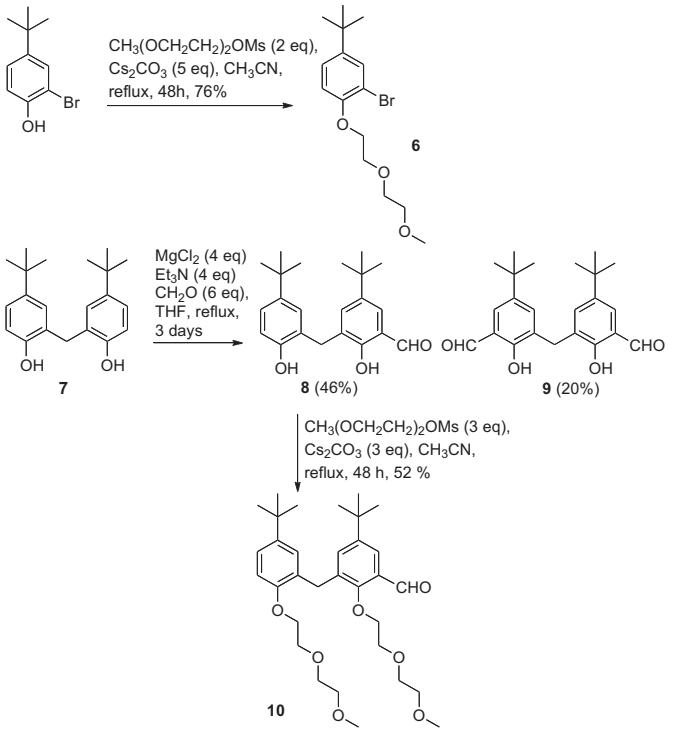
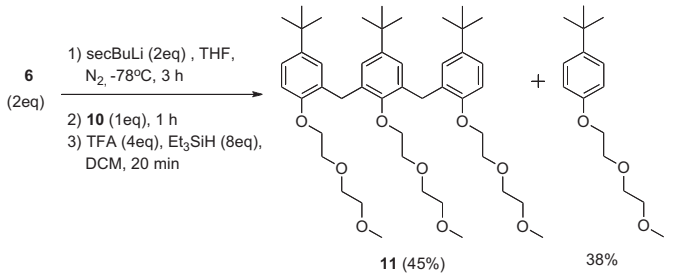


Fig. 2. Proposed synthetic route for synthesis of mixed ligand PFOs.



Scheme 1. Preparation of bromide **6** and aldehyde **10**.



Scheme 2. Synthesis of tris polyether extractant **11**.

addition to the aldehyde competes with proton exchange. It is highly unlikely that such a coupling could proceed in the presence of sensitive ligands or the aldehyde **10**. Although we were successful in the preparation of **11**, this approach does not allow the systematic introduction of phenolic monomer units carrying differing ligand moieties. Further, addition of another phenolic monomer to obtain a tetra PFO chelator is not possible due to the lack of a viable procedure to achieve selective bromination or formylation of **11**.

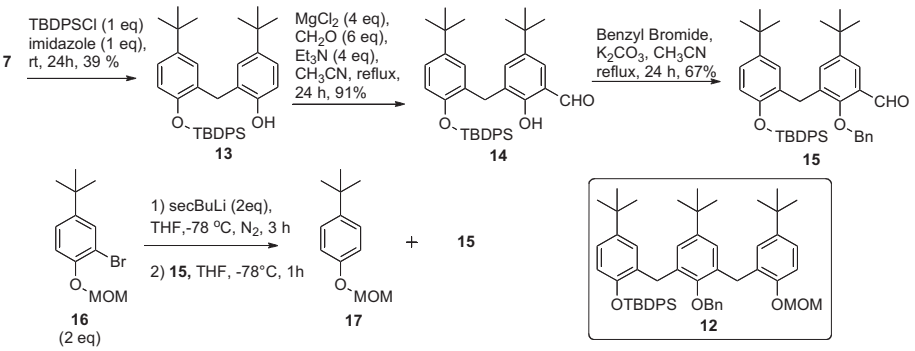
Given the questionable stability of the ligands being considered for this study, it was decided to explore a strategy to prepare differentially protected PFO moieties by phenol coupling reactions. The synthetic approach is depicted by the attempted synthesis of **12** (Scheme 3). The monoprotected *tert*-butyldiphenyl silyl (TBDPS) phenol **13** was prepared in 39% yield by treatment of bisphenol **7** with TBDPSCl (1 equiv) and imidazole (1 equiv) in DMF. As expected, in addition to the desired product **13**, unreacted starting material (25%) and disilylated product (10%) were obtained after purification. The silylphenol **13** was then treated with $MgCl_2$ and formaldehyde in the presence of triethylamine in refluxing acetonitrile to give the differentially monoprotected bisphenol aldehyde **14** in excellent yield.[21] Alkylation with benzyl bromide using standard conditions gave aldehyde **15**.

The methoxymethyl (MOM) protected arylbromide **16** (2 equiv) was treated with *s*-BuLi (2 equiv) in anhydrous THF at −78 °C for 3 h. A solution of aldehyde **15** in anhydrous THF was then added to the aryllithium and the reaction mixture stirred at −78 °C for 1 h.[18] After workup and purification, none of the desired coupling product was obtained. The aldehyde **15** was recovered in near quantitative yield along with the debrominated MOM protected phenyl ether, **17**. This indicated that the desired lithiation of **16** had occurred but the coupling with the aldehyde **15** did not proceed. These aldehydes are not particularly good electrophiles presumably because of electron donation from the alkoxy moiety (vinylogous esters). Proton abstraction successfully competes with the nucleophilic addition of the aryllithium to the aldehyde. Given these observations, this approach was abandoned.

2.1. Selective protection of PFOs

The sequential assembly of substituted phenolic units to prepare the PFO targets, although highly attractive, proved to be experimentally fraught with problems. Although our goal remained to develop methodology for mixed chelators of the types **I** and **II**, it became clear that further studies were required before we could achieve the synthesis of such complex targets. Hence, we decided to explore an alternate approach to the target hosts.

In this approach we begin with the desired PFO template. The key to this approach is the preparation of an intermediate such as **IX** with three orthogonal protecting groups (Fig. 3). The nature of the protecting groups needs to allow selective deprotection at the desired phenolic unit. Subsequently the desired ligand group could be attached to the phenol using standard alkylation conditions.



Scheme 3. Attempted synthesis of an orthogonally protected PFO **12**.

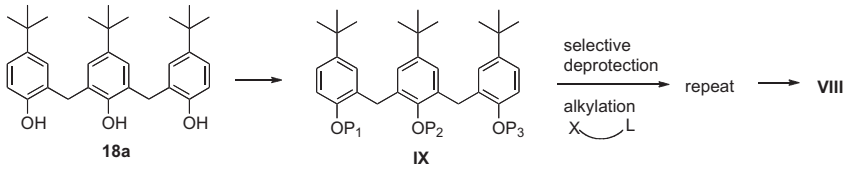


Fig. 3. Selective protection approach to preparation of chelators of type **VIII**.

Repetition of the sequence would allow the synthesis of chelators such as **VIII** using relatively simple chemistry.

In order to develop a method for differential protection of phenols, it was necessary to understand the relative reactivity of the phenols in the PFO structure (internal vs external). It was first decided to study the silylation of the tri and tetraphenols **18a** and **18b** with *tert*-butyldiphenyl silyl chloride, TBDPSCl. This group was chosen because it was stable to the alkylation conditions used to attach the ligand arms. The steric bulk of this group was also expected to affect the relative reactivity of the internal and external phenols of the oligomeric chain.

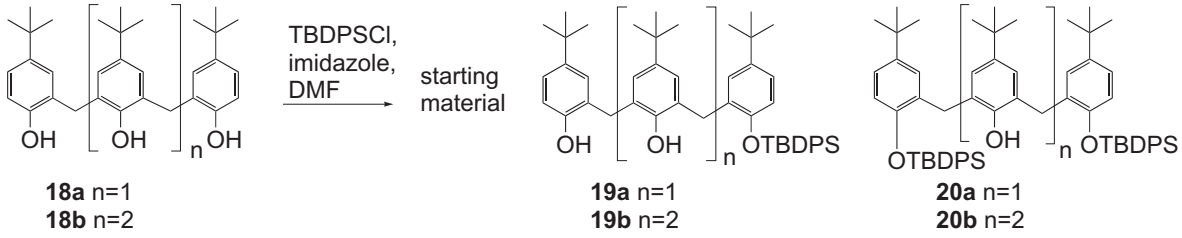
The results of this study are shown in Table 1. Treatment of trisphenol **18a** with TBDPSCl (1 equiv) and imidazole (1 equiv) in DMF gave the monoprotected product **19a** in 53% yield. The result may not be surprising and can be ascribed to favorable steric factors and simple statistics. When the trisphenol was treated with 2 equiv of TBDPSCl under similar conditions, the major product was the symmetric disilylated product, **20a**, along with some mono product, **19a**. The preferred method for preparing the disilyl derivative involved heating the trisphenol **18a** with 3 equiv of TBDPSCl. Under these conditions, the desired the disilylated phenol **20a** was isolated in 65% yield. It is interesting to note that no significant formation of the trisilylated product was observed under these reaction conditions. In the case of the tetraphenol, **18b**, treatment with 1 equiv of TBDPSCl using the conditions described earlier, gave the desired monosilylated product, **19b**, in 42% yield accompanied by the symmetrical disilylated product, **20b**, and unreacted starting material. In comparison to the trisphenol, the tetraphenol could be disilylated in high yield and selectivity with only 2 equiv of TBDPSCl. The symmetry of the disilyl derivatives made structural assignments by ^{1}H NMR and ^{13}C NMR straightforward. The subtle difference in reactivity of the trisphenol and tetraphenol is not readily explained.

2.2. Synthesis of mixed chelators on the trisphenol scaffold

With the mono and disilyl protected intermediates of the trisphenol (**19a** and **20a**) and the tetraphenol (**19b** and **20b**) in hand, the goal was to demonstrate their usefulness in the synthesis of sets of mixed ligand chelators that would permit structure–activity comparisons. Our group has been actively involved in the synthesis of hydroxamates[23] and hydroxypyridinones (HOPO),[24] well-known ligands for iron(III) and actinides. Hence, these ligand systems were chosen for incorporation onto the PFO platform in our studies.

The disilyl derivative **20a** was used to prepare the diHOPO-mono hydroxamate **25** as shown in Scheme 4. Treatment of the

Table 1
Protection of phenol–formaldehyde oligomers, **18**



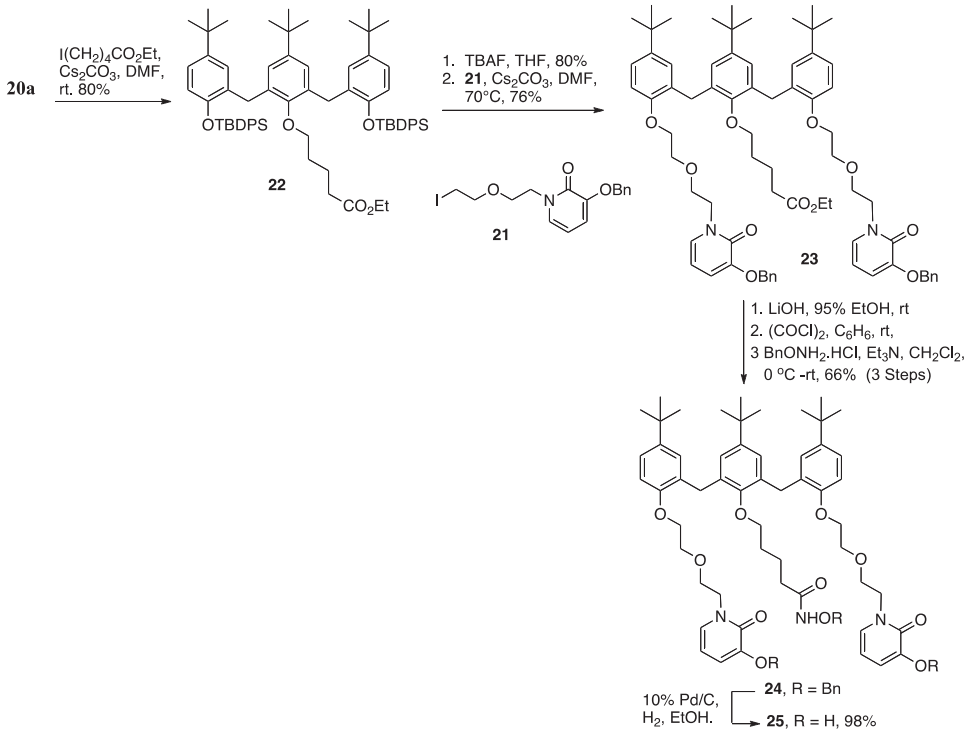
18a n=1
18b n=2

19a n=1
19b n=2

20a n=1
20b n=2

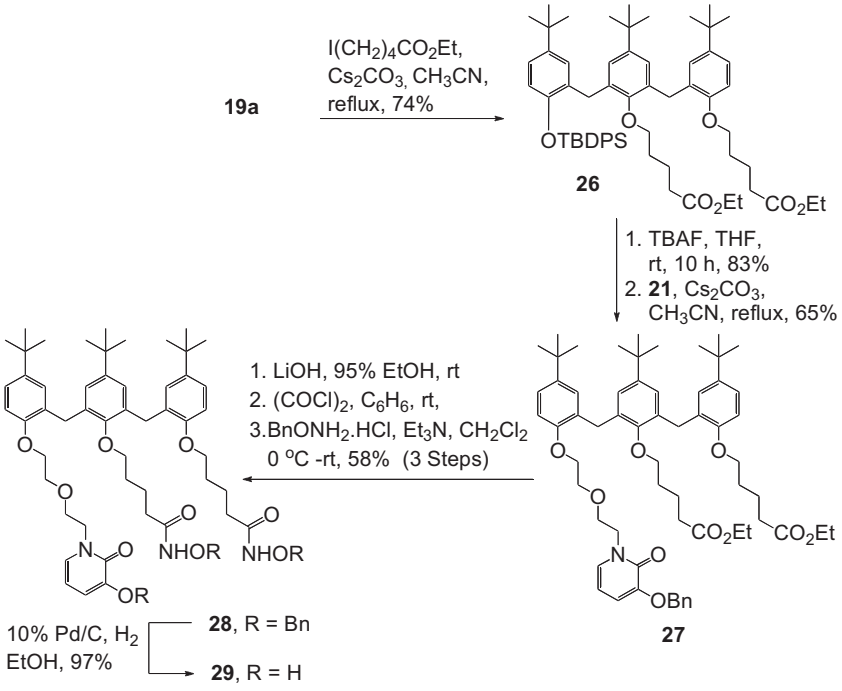
Entry	Phenol–formaldehyde oligomer	*n*	Conditions	Starting material **18** (%)	MonoTBDPS **19** (%)	DiTBDPS **20** (%)
1	**18a**	1	1 equiv TBDPSCl 1 equiv imidazole rt 14 h	19	53	11
2	**18a**	1	2 equiv TBPSCl 4 equiv imidazole rt 24 h	[a]	23	51
3	**18a**	1	3 equiv TBDPSCl 3 equiv imidazole rt 1 d, 50 °C 1 d	[a]	Trace	65
4	**18b**	2	1 equiv TBDPSCl 1.5 equiv imidazole 6 h rt	35	42	14
5	**18b**	2	2 equiv TBDPSCl 3 equiv imidazole 16 h rt	[a]	[a]	96

[a] In these runs, only the major products were isolated.

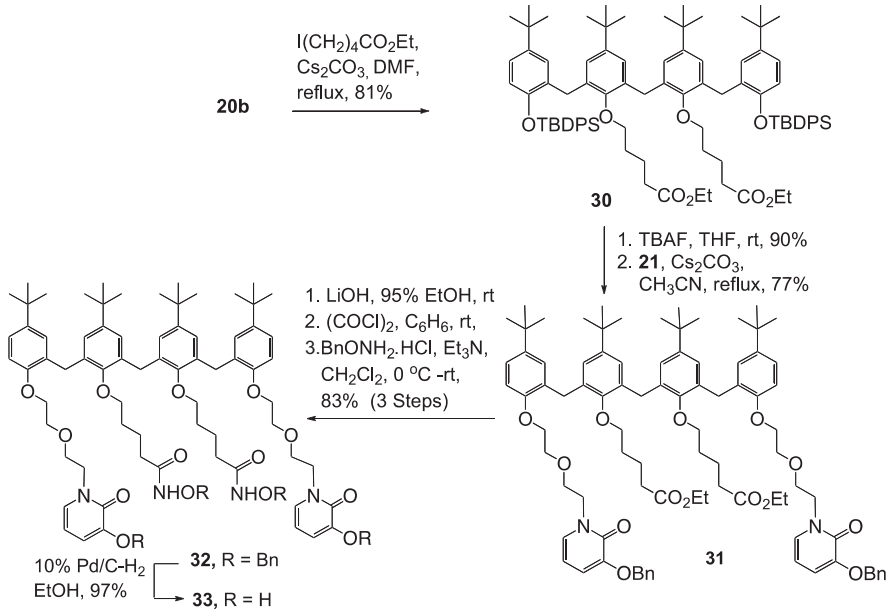


Scheme 4. Synthesis of symmetrical mixed HOPO/hydroxamic acid chelator, **25**.

disilyl phenol **20a** with an excess of ethyl-5-iodovalerate in the presence of Cs_2CO_3 in DMF for 3 d at rt gave the desired ethyl ester **22**, in 80% yield after purification. The TBDPS groups were then removed by treatment with TBAF in THF and the resultant product was alkylated with the known iodo-HOPO derivative[10] **21** to obtain the diHOPO ester **23**. The ethyl ester **23** was saponified with lithium hydroxide in aqueous ethanol and after an acidic workup the corresponding carboxylic acid was isolated in sufficient purity to be used in the next step directly. Treatment of the carboxylic acid with oxalyl chloride gave the corresponding acid chloride, which was then coupled with an excess of *O*-benzylhydroxylamine hydrochloride in the presence of triethylamine in dichloromethane at rt to obtain the amide **24** in 66% (three steps) after purification. Hydrogenolysis of the benzyl protecting groups using 10% Pd/C in ethanol gave the desired target extractant **25** in 98% yield.



Scheme 5. Synthesis of unsymmetrical dihydroxamic acid/HOPO, **29**.



Scheme 6. Synthesis of symmetrical HOPO/hydroxamic acid extractant, **33**.

The synthesis of unsymmetrical HOPO/dihydroxamic acid, shown in Scheme 5, demonstrates the usefulness of the monosilyl derivative. Alkylation of the monosilylated trisphenol **19a** with excess ethyl iodovalerate in refluxing acetonitrile using cesium carbonate as base gave the diester **26** in 74% yield after purification. The silyl protecting group was removed using TBAF and the phenol alkylated with HOPO iodide **21** to give **27**. Conversion of the ethyl esters to the corresponding protected hydroxamic acid by the three-step procedure established previously gave the fully protected chelator **28** in 58% yield for three steps. Removal of the benzyl protecting groups was accomplished using hydrogenolysis to give the unsymmetrical dihydroxamic acid/HOPO chelator **29** in 97% yield.

2.3. Synthesis of mixed chelators on the tetraphenol platform

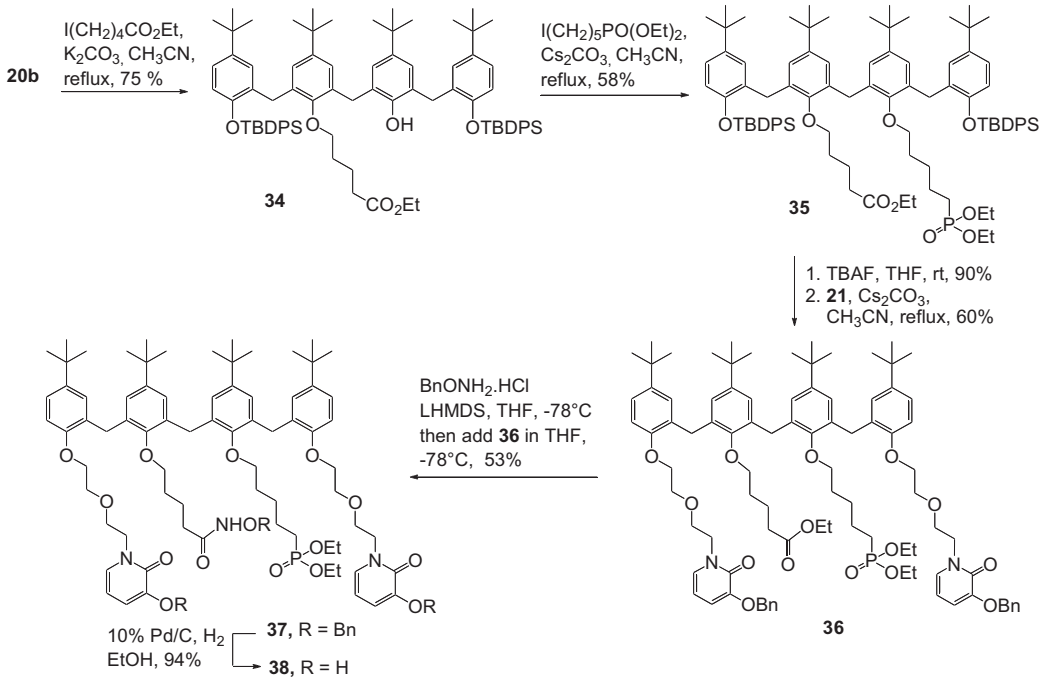
The symmetric disilylated tetraphenol, **20b**, is a useful scaffold for attachment of one set of ligands on the internal phenols and a different ligand system on the external phenol rings. This was demonstrated by the synthesis of chelator **33**, Scheme 6. The two internal phenols of **20b** were alkylated with ethyl iodovalerate (3 equiv) using cesium carbonate in DMF to give the diester **30** in 81% yield after purification. Subsequent removal of the silyl protecting groups and alkylation of the external phenols with HOPO iodide, **21**, gave the diester diHOPO **31** in 66% yield. The ethyl esters were converted to the protected hydroxamic acid, **32**, in three steps and in moderate yield. Finally, cleavage of the benzyl protecting groups gave the organic soluble (chloroform) mixed diHOPO dihydroxamic acid chelator, **33**, in excellent yield. It is pertinent to mention that tetrahydroxamate and tetraHOPO derivatives of calixarenes as well as the corresponding open chain phenol oligomers have been shown to be efficient extractants of actinide(IV) ions. Substrates prepared in this study would be valuable analogs for complexation studies.

In our attempts to dialkylate the disilyl protected tetraphenol **20b** with ethyl iodovalerate, an interesting finding was made. We realized that it was possible to obtain the monoalkylated product **34** in 72% yield by using 1 equiv of ethyl iodovalerate (and potassium carbonate) in this reaction (Scheme 7). This suggests that the initially formed monoalkylated phenol, **34**, is more resistant to subsequent alkylation, possibly due to steric factors. This finding enabled the incorporation of two different ligand groups on the internal phenols of **20b**. The unreacted phenol group of **34** was alkylated with diethyl 5-iodopentylphosphonate to give **35** in moderate yield. Deprotection of the silyl groups followed by alkylation with the HOPO iodide, **21**, gave **36** in good yield after purification. The final transformation of the ester to the desired benzyl protected hydroxamic acid was accomplished using a one-pot procedure. Treatment of *O*-benzylhydroxylamine hydrochloride (5 equiv) with LHMDS (1 M in THF, 10 equiv) at −78 °C for 15 min followed by addition of the ester **36**, gave the benzyl protected hydroxamate derivative **37** in 53% yield after workup and purification.[25] Finally, the benzyl protecting groups were removed by hydrogenolysis to give the chelator **38**, having three different ligand moieties in its scaffold. This route is straightforward and flexible and clearly holds much promise for the incorporation of three different ligand groups onto the tetraphenol backbone.

3. Conclusions

The goal of developing a practical route to mixed ligand systems of types **I** and **II** built on PFO platforms, although conceptually simple and easily stated, has presented an interesting synthetic challenge. The first approach was to develop methodology that would allow the sequential addition of phenolic units carrying the desired ligands, to build the oligomeric chain. To some extent this approach was successful as demonstrated by the synthesis of the polyether ligand **11**. However, this approach has limited scope. Further, the extension of this methodology to yield potentially useful orthogonally protected PFOs, such as **12**, was not possible. The coupling of the organolithium derived from **16** with aldehyde **15** did not yield the desired product. Better strategies to achieve the desired coupling reaction need to be developed to make this a viable approach.

The second approach to mixed PFO ligands system uses existing PFO oligomers, which are readily available. The availability of orthogonally protected tris and tetraphenols would allow selective deprotection and introduction of a desired ligand group at a specific site, providing positional control on the ligand being introduced. Once again the challenge is the preparation of these intermediates.



Scheme 7. Synthesis of mixed ligand extractant, **38**.

We have made significant progress to demonstrate the simplicity and viability of this approach. The phenolic moieties of the tris and tetra PFOs can be differentiated by selective silylation with TBDPS chloride. Using this strategy, we have prepared the monosilyl derivatives **19a** and **19b** and the disilyl derivatives **20a** and **20b**. The value of these protected intermediates has been demonstrated by the preparation of some mixed ligand systems, the most complex being the synthesis of **38**, which has three different ligands (two HOPO, a phosphonate, and a hydroxamate) on the tetraphenol backbone. It is noteworthy that the disilyl derivative of the tetraphenol **20b** can be monoalkylated in good yields. This allows the introduction of a two different ligands in the middle of the oligomeric chain. Symmetric and asymmetric mixed hydroxamate/HOPO ligand systems such as **25**, **29**, and **33** were readily prepared using this methodology. The introduction of the ligand tethers onto the phenolic scaffold can be done sequentially under mild conditions that tolerate the presence of other sensitive ligand groups. The alkylating agent is not limited to ligand arms but can be tuned to the application in mind such as development of catalysts and sensors.

Our studies have shown that the selective protection of the phenolic groups in PFOs and subsequent chemistry will provide an attractive pathway for the preparation of sets of mixed ligand chelators. While significant progress has been made, much remains to be done in realizing the goal of developing a convenient route to mixed ligand chelators of types **I** and **II**. It is important to point out that the results of this study are also relevant to the search to increase ligand diversity in other phenolic host systems such as calixarenes.

4. Experimental

4.1. General methods

Melting points were obtained on an *Electrothermal*® melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) were obtained on a Varian Gemini 200. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were obtained on a Varian Unity 400 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were obtained on a 300 MHz Varian NMR system. NMR spectral samples were prepared in $CDCl_3$. All chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (TMS) reference. Elemental analyses were performed by Desert Analytics, Tucson, Arizona. HRMS analyses were performed by the University of California Riverside Mass Spectrometry Facility. Flash chromatography was performed on an Isco CombiFlash system using prepackaged columns. Radial chromatography was performed on a Chromatotron using plates prepared from silica gel 60 containing gypsum. Reagents were normally obtained from Sigma–Aldrich or Alfa Aesar and were used as received unless otherwise noted. Tetrahydrofuran was freshly collected from a GlassContour™ solvent purification system. Other anhydrous solvents (DMF, methylene chloride, acetonitrile, etc.) were obtained from Sigma–Aldrich. Solvents used for chromatography were reagent grade. Tetrabutylammonium fluoride was obtained as a 1 M solution in THF. The bisphenol (**7**), trisphenol (**18a**), tetraphenol (**18b**),[20] and iodo-HOPO (**21**)[10] were prepared according to literature procedures.

4.2. Representative procedure for TBDPS protection of *tert*-butylphenol–formaldehyde oligomers

*4.2.1. 2-(5-tert-Butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-4-tert-butylphenol (**13**).* Imidazole (108 mg, 1.59 mmol) and TBDPSCl (413 μL, 1.59 mmol) were added to a solution of bisphenol (**7**) (500 mg, 1.59 mmol) in DMF (3 mL) under N_2. After stirring at rt for 24 h, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (150 mL), washed with 1 N HCl (25 mL), saturated $NaHCO_3$ (25 mL), brine (25 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. Purification of the crude product by Combiflash on silica gel gave **13** (0.345 g, 39%) as a clear oil. IR (neat) 3437, 3072, 3051, 2962, 2903, 2860, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.69 (m, 4H), 7.47–7.32 (m, 6H), 7.22–7.09 (m, 3H),

6.81–6.72 (m, 2H), 6.40 (d, *J*=8.5 Hz, 1H), 5.84 (s, 1H), 4.12 (s, 2H), 1.29 (s, 9H), 1.14 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 149.9, 144.2, 143.2, 135.5, 132.5, 130.0, 128.3, 127.8, 127.4, 127.3, 126.0, 124.4, 123.9, 118.5, 115.2, 34.0, 31.6, 31.3, 31.2, 26.7, 19.5. Analysis Calcd for $C_{37}H_{46}O_2Si\cdot 0.5H_2O$: C, 79.38; H, 8.46. Found: C, 79.08; H, 8.29.

*4.2.2. 4-tert-Butyl-2-(5-tert-butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-6-(5-tert-butyl-2-hydroxybenzyl)phenol (**19a**).* The representative procedure for TBDPS protection was followed using **18a** (100 mg, 0.21 mmol) to give **19a** (79 mg, 53%) along with **20a** (22 mg, 11%) and **18a** (19 mg, 19%). Compound **19a**: oil; IR (neat) 3368, 2960, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 (m, 6H), 7.44–7.35 (m, 2H), 7.27 (d, *J*=2.3 Hz, 1H), 7.19 (d, *J*=2.3 Hz, 1H), 7.09–7.09 (m, 4H), 6.81 (s, 1H), 6.75 (d, *J*=1.8 Hz, 1H), 6.73 (d, *J*=1.8 Hz, 1H), 6.40 (d, *J*=8.51 Hz, 1H), 4.06 (s, 2H), 3.88 (s, 2H), 1.27 (s, 9H), 1.26 (s, 9H), 1.12 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 149.6, 148.3, 144.5, 143.7, 143.2, 135.5, 132.3, 130.0, 128.1, 127.9, 127.4, 126.6, 126.4, 125.7, 125.5, 124.5, 124.1, 118.7, 116.0, 34.0, 31.6, 31.5, 31.5, 26.6, 19.5. Anal. Calcd for $C_{62}H_{84}O_7Si\cdot CHCl_3$: C, 69.50; H, 7.87. Found: C, 69.88; H, 7.67.

*4.2.3. 2-(3-(5-tert-Butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-5-tert-butyl-2-hydroxybenzyl)-6-(5-tert-butyl-2-hydroxybenzyl)-4-tert-butylphenol (**19b**).* The representative procedure for TBDPS protection was followed using **18b** (0.500 g, 0.785 mmol), imidazole (0.080 g, 1.17 mmol) and TBDPSCl (0.204 mL, 0.785 mmol) to give **19b** (0.289 g, 42.1%) along with **20b** (0.127 g, 14.5%) and **18b** (0.174 g, 34.8%). Compound **19b**: white solid. Mp 133–136 °C; IR (KBr) 3271, 2961, 1503 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.76–7.69 (m, 3H), 7.60 (s, 1H), 7.48–7.35 (m, 5H), 7.31–7.27 (m, 2H), 7.21–7.02 (m, 5H), 6.76 (dd, *J*=2.3, 8.5 Hz, 1H), 6.70 (d, *J*=8.2 Hz, 1H), 6.46 (d, *J*=8.5 Hz, 1H), 4.06 (s, 2H), 3.86 (s, 4H), 1.26 (s, 9H), 1.26 (s, 9H), 1.24 (s, 9H), 1.13 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.5, 147.9, 147.4, 144.7, 144.1, 144.0, 143.1, 135.5, 132.2, 130.1, 128.2, 127.9, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7, 126.5, 125.8, 125.7, 125.6, 124.5, 124.2, 118.8, 116.0, 34.0, 33.98, 33.96, 33.95, 31.9, 31.6, 31.5, 31.4, 31.3, 26.7, 19.5. Anal. Calcd for $C_{59}H_{74}O_4Si\cdot 2CH_2Cl_2$: C, 71.10; H, 7.52. Found: C, 69.71; H, 7.48.

*4.2.4. 2,6-Bis(5-tert-butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-4-tert-butylphenol (**20a**).* The representative procedure for TBDPS protection was followed using **18a** (1.0 g, 2.1 mmol), imidazole (0.48 g, 7.0 mmol), and TBDPSCl (1.86 g, 6.8 mmol). The reaction mixture was stirred at rt for 24 h and then heated at 50 °C for 24 h to give **20a** (1.3 g, 65%). White solid. Mp 106–110 °C; IR (KBr) 3431, 2960, 2860, 1606, 1502 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.67 (m, 8H), 7.45–7.27 (m, 12H), 7.12 (d, *J*=2.6 Hz, 2H), 7.03 (s, 2H), 6.73 (dd, *J*=2.6, 8.5 Hz, 2H), 6.45 (s, 1H), 6.34 (d, *J*=8.5 Hz, 2H), 4.15 (s, 4H), 1.24 (s, 9H), 1.10 (s, 18H), 0.99 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 143.7, 142.2, 135.5, 132.7, 129.8, 129.1, 127.8, 127.7, 126.3, 125.0, 123.5, 118.2, 34.0, 33.9, 31.6, 31.6, 31.4, 31.2, 26.5, 22.6, 19.4, 14.1. Anal. Calcd for $C_{64}H_{78}O_3Si_2$: C, 80.79; H, 8.26. Found: C, 80.47; H, 8.03.

*4.2.5. 2-(3-(5-tert-butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-5-tert-butyl-2-hydroxybenzyl)-6-(5-tert-butyl-2-(tert-butyldiphenylsilyloxy)benzyl)-4-tert-butylphenol (**20b**).* The representative procedure for TBDPS protection was followed using **18b** (1.0 g, 1.7 mmol), imidazole (0.34 g, 5.0 mmol), and TBDPSCl (0.94 g, 3.4 mmol) to give **20b** (1.7 g, 96.9%) as a white solid. Mp 110–114 °C; IR (KBr) 3401, 2961, 1501 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.68 (m, 8H), 7.42–7.33 (m, 10H), 7.33–7.30 (m, 2H), 7.18 (d, *J*=2.3 Hz, 2H), 7.13 (d, *J*=2.4 Hz, 2H), 6.97 (d, *J*=2.9 Hz, 2H), 6.75 (dd, *J*=2.7, 8.5 Hz, 2H), 6.37 (d, *J*=8.5 Hz, 2H), 4.10 (s, 4H), 3.92 (s, 2H), 1.23 (s, 18H), 1.13 (s, 18H), 0.97 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 148.9, 144.0, 142.9, 135.5, 132.6, 129.9, 128.9, 127.8, 126.9, 126.6, 125.5, 125.2, 123.7, 118.3, 34.0, 31.6, 31.4, 26.5, 19.4. Anal. Calcd for $C_{75}H_{92}O_4Si_2$: C, 80.88; H, 8.33. Found: C, 80.48; H, 8.47.

4.3. Ethyl 5-(4-*tert*-butyl-2-(5-*tert*-butyl-2-(*tert*-butyldiphenylsilyloxy)benzyl)-6-(5-*tert*-butyl-3-(5-*tert*-butyl-2-(*tert*-butyldiphenylsilyloxy)benzyl)-2-hydroxybenzyl)phenoxy)pentanoate (34)

A mixture of **20b** (0.80 g, 0.76 mmol), ethyl iodovalerate (0.224 g, 0.86 mmol), and K_2CO_3 (0.16 g, 1.1 mmol) in anhydrous CH_3CN (15 mL) was heated at reflux for 9 h. The reaction mixture was cooled and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with water (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography to yield **34** (0.701 g, 75%) as an oil. IR (neat) 3420, 2960, 2860, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.65 (m, 8H), 7.43–7.31 (m, 12H), 7.19 (d, *J*=2.6 Hz, 1H), 7.15 (d, *J*=2.6 Hz, 1H), 7.12 (d, *J*=2.6 Hz, 1H), 7.01 (d, *J*=2.3 Hz, 2H), 6.91 (d, *J*=2.3 Hz, 1H), 6.86 (d, *J*=2.3 Hz, 1H), 6.81–6.70 (m, 2H), 6.38 (d, *J*=8.5 Hz, 1H), 6.30 (d, *J*=8.5 Hz, 1H), 4.21 (s, 2H), 4.13 (s, 2H), 4.08 (q, *J*=7.3 Hz, 2H), 3.98–3.94 (m, 4H), 2.31 (t, *J*=7.3 Hz, 2H), 1.98–1.91 (m, 2H), 1.86–1.78 (m, 2H), 1.21 (t, *J*=7.0 Hz, 3H), 1.20 (s, 9H), 1.15 (s, 18H), 1.30 (s, 9H), 0.97 (s, 9H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 151.4, 151.0, 150.7, 150.0, 147.3, 143.3, 143.1, 142.0, 135.5, 135.4, 133.1, 133.0, 132.9, 132.4, 129.8, 129.6, 129.6, 129.2, 128.2, 127.7, 127.6, 127.5, 126.2, 126.1, 125.5, 124.9, 124.7, 123.4, 123.1, 117.8, 74.3, 60.2, 34.2, 34.0, 33.9, 32.0, 31.6, 31.4, 31.4, 31.3, 31.0, 30.0, 29.5, 26.4, 26.4, 21.5, 19.4, 19.3, 19.2. Anal. Calcd for $C_{82}H_{104}O_6Si_2$: C, 79.31; H, 8.44. Found: C, 79.61; H, 8.31.

4.4. Ethyl 5-(4-*tert*-butyl-2-(5-*tert*-butyl-2-(*tert*-butyldiphenylsilyloxy)benzyl)-6-(5-*tert*-butyl-3-(5-*tert*-butyl-2-(*tert*-butyldiphenylsilyloxy)benzyl)-2-(5-(diethoxyphosphoryl)pentyloxy)benzyl)phenoxy)pentanoate (35)

A mixture of **34** (0.80 g, 0.65 mmol), diethyl 5-iodopentylphosphonate (0.54 g, 1.6 mmol), and Cs_2CO_3 (0.31 mg, 1.6 mmol) in anhydrous CH_3CN (14 mL) was heated at reflux for 48 h. The reaction mixture was cooled and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with water (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography to yield **35** (540 mg, 58%). IR (neat) 2962, 2868, 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.70 (m, 8H), 7.42–7.32 (m, 12H), 7.04 (m, 2H), 6.94–6.93 (m, 4H), 6.78 (dd, *J*=2.3, 8.5 Hz, 2H), 6.36 (d, *J*=8.5 Hz, 2H), 4.25 (s, 4H), 4.14–4.01 (m, 8H), 3.73–3.84 (m, 4H), 2.31–2.21 (m, 2H), 1.76–1.48 (m, 12H), 1.27 (t, *J*=7.0 Hz, 6H), 1.19 (t, *J*=7.0 Hz, 3H), 1.14 (s, 18H), 1.13 (s, 9H), 1.13 (s, 9H), 1.30 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 153.73, 153.66, 151.0, 145.97, 145.93, 143.1, 135.4, 133.09, 133.05, 133.02, 132.6, 129.91, 129.87, 129.7, 127.7, 127.54, 127.51, 125.8, 125.7, 125.43, 125.37, 123.14, 123.10, 117.7, 72.9, 72.7, 61.3(d, J_{PC}=6 Hz), 60.1, 34.2, 34.0, 33.9, 31.41, 31.37, 30.43, 30.36, 30.1, 29.9, 29.4, 27.5, 27.2, 26.6, 25.6 (d, J_{PC}=132 Hz) , 22.6, 22.5, 21.7, 19.5, 16.4(d, J_{PC}=6 Hz), 14.2. Anal. Calcd for $C_{91}H_{123}O_9PSi_2$: C, 75.48; H, 8.56. Found: C, 75.34; H, 8.81.

4.5. Ethyl 5-(2-(2-(2-(2-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)-5-*tert*-butylbenzyl)-6-(3-(2-(2-(2-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)-5-*tert*-butylbenzyl)-5-*tert*-butyl-2-(5-(diethoxyphosphoryl)pentyloxy)benzyl)-4-*tert*-butylphenoxy)pentanoate (36)

To a solution of **35** (122 mg, 0.084 mmol) in anhydrous THF (10 mL) was added TBAF (130 mg, 0.5 mmol) and stirred at rt for

12 h. Water (20 mL) was added to the reaction mixture and the crude product extracted into ethyl acetate (3×40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The silyl byproducts were removed by radial chromatography to provide the phenol (80 mg, 99%) as an oil. IR (neat) 3366, 2962, 1736, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.47 (s, 1H), 7.15 (d, J=2.3 Hz, 1H), 7.10 (m, 2H), 7.07 (d, J=2.3 Hz, 1H), 7.01 (m, 2H), 6.85 (d, J=2.6 Hz, 1H), 6.80 (d, J=2.6 Hz, 1H), 6.66 (dd, J=2.0, 8.2 Hz, 2H), 4.09–3.99 (m, 6H), 3.96 (s, 2H), 3.83–3.78 (m, 6H), 3.67 (t, J=7.0 Hz, 2H), 2.27 (t, J=7.0 Hz, 2H), 1.85–1.38 (m, 12H), 1.24 (t, J=7.0 Hz, 6H), 1.21 (s, 9H), 1.19 (s, 9H), 1.17 (t, J=7.0 Hz, 3H), 1.11 (s, 9H), 1.08 (s, 9H). A mixture of the phenol (72 mg, 0.072 mmol), HOPO iodide **21** (86 mg, 0.21 mmol), and Cs_2CO_3 (41 mg, 0.21 mmol) in anhydrous CH_3CN (5 mL) was heated at reflux for 3 d. The reaction mixture was cooled and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (40 mL) and washed with water (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography to yield **36** (66 mg, 60%). IR (neat) 2955, 2868, 1733, 1655, 1608, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4H), 7.29–7.18 (m, 6H), 7.05 (dd, J=2.6, 8.5 Hz, 2H), 6.95–6.84 (m, 8H), 6.70 (d, J=8.5 Hz, 2H), 6.52 (dd, J=1.5, 7.3 Hz, 2H), 5.80 (t, J=7.0, 2H), 4.98 (s, 4H), 4.09–4.05 (m, 4H), 4.00–3.94 (m, 12H), 3.92 (s, 4H), 3.80–3.72 (m, 4H), 3.72–3.64 (m, 4H), 3.64–3.54 (m, 4H), 2.17–2.10 (m, 2H), 1.69–1.57 (m, 8H), 1.43–1.32 (m, 4H), 1.20 (t, J=7.0 Hz, 6H), 1.11 (s, 18H), 1.11 (t, J=7.0 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 158.1, 154.37, 154.35, 153.7, 153.67, 148.6, 145.88, 145.84, 143.15, 143.12, 136.3, 133.01, 132.95, 132.37, 132.32, 130.52, 130.51, 129.41, 129.37, 128.48, 128.43, 127.89, 127.83, 127.4, 127.3, 127.2, 126.08, 125.96, 125.7, 123.2, 115.7, 110.93, 110.89, 104.1, 103.9, 73.0, 72.7, 72.3, 70.6, 69.8, 69.1, 67.6, 67.5, 61.6, 61.3 (d, J_{PC}=7 Hz), 60.0, 49.6, 34.1, 34.0, 33.9, 31.41, 31.35, 30.0, 29.8, 29.6, 29.5, 27.3, 27.1, 25.6 (d, J_{PC}=140 Hz), 22.5, 22.4, 21.5, 16.4 (d, J_{PC}=6 Hz), 14.2. Anal. Calcd for $C_{91}H_{121}N_2O_{15}P$: C, 72.20; H, 8.06; N, 1.85. Found: C, 72.57; H, 7.79; N, 1.94.

4.6. Diethyl 5-(2-(2-(2-(2-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)-5-*tert*-butylbenzyl)-6-(3-(2-(2-(2-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)-5-*tert*-butylbenzyl)-2-(5-(benzyloxyamino)-5-oxopentyloxy)-5-*tert*-butylbenzyl)-4-*tert*-butylphenoxy)pentylphosphonate (37)

Lithium bis(trimethylsilylamide) (1 M in THF, 0.8 mL, 0.8 mmol) was added to a suspension of *O*-benzylhydroxylamine hydrochloride (66 mg, 0.41 mmol) in anhydrous THF (5 mL) at −78 °C under N_2. After 15 min, a solution of the ester **36** (125 mg, 0.083 mmol) in anhydrous THF (2 mL) was added and reaction mixture was stirred for 30 min. The reaction was quenched with saturated NH_4Cl (10 mL) at −78 °C. The product was extracted into ethyl acetate (3×25 mL) and dried (Na_2SO_4). The crude product was purified by radial chromatography to give **37** (69 mg, 53%) as an oil. IR (neat) 3428, 3196, 3034, 2959, 2868, 1651, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.1 (s, 1H, NH), 7.42–7.23 (m, 15H), 7.13(m, 2H), 7.05 (d, J=2.6 Hz, 1H), 6.99–6.90 (m, 7H), 6.74 (t, J=7.2 Hz, 2H), 6.60–6.57(m, 2H), 5.90 (m, 2H), 5.04 (s, 4H), 5.01 (s, 2H), 4.83 (s, 2H), 4.11–3.86 (m, 16H), 3.79–3.47 (m, 10H), 2.03 (m, 2H), 1.76–1.61 (m, 10H), 1.49–1.39 (m, 2H), 1.26 (t, J=7.0 Hz, 6H), 1.20 (s, 9H), 1.18 (s, 9H), 1.14 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 154.4, 154.3, 153.6, 153.3, 148.59, 148.56, 145.9, 143.3, 143.2, 136.31, 136.27, 133.0, 132.7, 132.5, 132.3, 130.5, 129.3, 129.2, 129.0, 128.5, 128.2, 127.9, 127.6, 127.3, 126.1, 125.9, 125.8, 125.6, 123.34, 123.26, 115.7, 111.1, 110.9, 104.2, 104.1, 77.2, 73.1, 70.7, 70.6, 69.90, 69.87, 69.2, 69.1, 68.0, 67.8, 61.4 (d, J_{PC}=7 Hz), 49.8, 49.7, 34.19, 34.18, 34.0, 31.53, 31.46, 31.44, 31.39, 31.36, 29.9, 29.7, 29.6, 27.3, 27.0, 25.5 (d, J_{PC}=139 Hz), 22.5, 22.4, 16.5 (d, J_{PC}=6 Hz). Anal. Calcd for $C_{96}H_{124}N_3O_{15}P$: C, 72.47; H, 7.86; N, 2.64. Found: C, 72.13; H, 7.53; N, 2.55.

4.7. Diethyl 5-(4-*tert*-butyl-2-(5-*tert*-butyl-2-(2-(2-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)benzyl)-6-(5-*tert*-butyl-3-(5-*tert*-butyl-2-(2-(2-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)ethoxy)ethoxy)benzyl)-2-(5-(hydroxyamino)-5-oxopentyloxy)benzyl)phenoxy)pentylphosphonate (38)

Palladium on carbon (10%, 10 mg) was added to a solution of **37** (60 mg, 0.038 mmol) in absolute ethanol (3 mL) and the reaction mixture stirred under H_2 balloon at rt for 24 h. The reaction mixture was diluted with ethanol (20 mL) and filtered through a pad of celite on a sintered glass filter. The solvent was removed in vacuo to afford chelator **38** as thick oil (47 mg, 94%). IR (neat) 3226, 2960, 1652, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.05 (m, 3H), 7.01–6.95 (m, 2H), 6.91–6.89 (m, 2H), 6.88–6.78 (m, 4H), 6.70 (m, 3H), 5.99–5.92 (m, 2H), 4.08–3.90 (m, 16H), 3.78–3.72 (m, 4H), 3.69–3.60 (m, 8H), 3.46 (m, 2H), 2.01 (m, 2H), 1.70–1.50 (m, 9H), 1.46–1.36 (m, 3H), 1.21 (t, J=7.0 Hz, 6H), 1.13 (s, 9H), 1.14 (s, 18H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 158.6, 154.4, 154.2, 153.5, 153.2, 146.4, 145.9, 143.3, 143.2, 133.0, 132.4, 132.4, 129.9, 129.0, 128.4, 127.6, 127.2, 126.2, 126.1, 125.7, 125.3, 123.4, 123.3, 114.6, 114.4, 111.0, 110.9, 106.3, 73.0, 72.5, 69.9, 69.2, 69.2, 68.1, 68.0, 61.7, 61.6, 49.8, 49.7, 34.2, 34.2, 34.0, 34.0, 32.6, 31.5, 31.4, 31.4, 31.3, 29.9, 29.8, 29.6, 29.5, 27.2, 27.0, 25.3 (d, J_{PC}=140 Hz), 22.4, 22.3, 16.4, 16.3. Anal. Calcd for $C_{75}H_{106}N_3O_{15}P\cdot 2H_2O$: C, 66.40; H, 8.17; N, 3.10. Found: C, 66.21; H, 7.90; N, 2.96.

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Supplementary data

Full experimental details for compounds **6**–**12**, **14**, **15**, and **22**–**33**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Crisponi, G.; Remelli. *Coord. Chem. Rev.* **2008**, *252*, 1225–1240; (b) Kalinowski, D. S.; Richardson, D. R. *Pharmacol. Rev.* **2005**, *57*, 547–583; (c) Gorden, A. E. V.; Xu, J.; Raymond, K. N. *Chem. Rev.* **2003**, *103*, 4207–4282; (d) Raymond, K. N.; Garrett, T. M. *Pure Appl. Chem.* **1988**, *60*, 1807–1816.
2. Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875–1914.
3. (a) d'Hardemare, A. M.; Torelli, S.; Serratrice, G.; Pierre, J.-L. *BioMetals* **2006**, *19*, 349–366; (b) Liu, Z. D.; Hider, R. C. *Coord. Chem. Rev.* **2002**, *232*, 151–176.
4. (a) Gutsche, C. D. *Calixarenes*, 2nd ed.; Royal Society of Chemistry: Cambridge, 2008; (b) Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Soc. Rev.* **2007**, *36*, 254–266; (c) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734; (d) Casnati, A. *Gazz. Chim. Ital.* **1997**, *127*, 637–649.
5. de Fátima, A.; Fernandes, S. A.; Sabino, A. A. *Cur. Drug Discov. Technol.* **2009**, *6*, 151–170.
6. (a) Yang, Y.; Arora, G.; Fernandez, F. A.; Crawford, J. D.; Surowiec, K.; Lee, E. K.; Bartsch, R. A. *Tetrahedron* **2011**, *67*, 1389–1397; (b) Ohto, K. *Solvent Extraction Research and Development, Japan* **2010**, *17*, 1–18; (c) Sliwa, W.; Girek, T. *J. Inclusion Phenom. Macrocycl. Chem.* **2010**, *66*, 15–41; (d) Siddiqui, S.; Cragg, P. J. *Mini-Rev. Org. Chem.* **2009**, *6*, 283–299; (e) Agrawal, Y. K.; Pancholi, J. P.; Vyas, J. M. *Journal of Scientific & Industrial Research* **2009**, *68*, 745–768; (f) Arora, V.; Chawla, H. M.; Singh, S. P. *Arkivoc* **2007**, *ii*, 172–200; (g) Jose, P.; Shobana, M. Bioinorganic Chemistry and Applications; Bioinorganic Chemistry and Applications **2007**, *2007*, 1–16.
7. Kubo, M.; Nashimoto, E.; Tokiyo, T.; Morisaki, Y.; Kodama, M.; Hioki, H. *Tetrahedron Lett.* **2006**, *47*, 1927–1931.
8. Hioki, H.; Nishimoto, R.; Kawaguchi, K.; Kubo, M.; Harada, K.; Fukuyama, Y. *Chem. Commun.* **2009**, 7194–7196.
9. Dasaradhi, L.; Stark, P. C.; Huber, V. J.; Smith, P. H.; Jarvinen, G. D.; Gopalan, A. S. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1187–1192.

10. Lambert, T. N.; Dasaradhi, L.; Huber, V. J.; Gopalan, A. S. *J. Org. Chem.* **1999**, *64*, 6097–6101.
11. Lambert, T. N.; Tallant, M. D.; Jarvinen, G. D.; Gopalan, A. S. Metal Ion Complexation and Extraction Behavior of some Acyclic Analogs of *tert*-Butyl-calix[4] arene Hydroxamate Extractants In *Calixarenes for Separations*; Lumetta, G., Rogers, R., Gopalan, A., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 2000; Vol. 757, pp 208–222.
12. Lambert, T. N. Ph.D. Dissertation, New Mexico State University, 2001.
13. Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Jakobi, R. A.; Kraft, D.; Mauprivez, O.; Rouquette, H.; Schwing-Weill, M.-J.; Simon, N.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1175–1182.
14. (a) Bychenkov, D. V.; Reznik, A. M.; Semenov, S. A. *Russ. J. Inorg. Chem.* **2010**, *55*, 798–803; (b) Morohashi, N.; Nagata, K.; Tanaka, S.; Ohba, Y.; Hattori, T. *Chem. Lett.* **2008**, *37*, 1228–1229; (c) Iki, N.; Morohashi, N.; Yamane, Y.; Miyano, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1763–1768; (d) Ito, K.; Takasawa, T.; Ohba, Y. *Synth. Commun.* **2002**, *32*, 3839–3849.
15. Ito, K.; Ito, T.; Takasawa, T.; Ohba, Y. *Lett. Org. Chem.* **2006**, *3*, 260–266.
16. Sone, T.; Ohba, Y.; Yamazaki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1111–1116.
17. For some syntheses of mixed ligand systems see: (a) Gama, S.; Dron, P.; Chaves, S.; Farkas, E.; Santos, M. A. *Dalton Trans.* **2009**, 6141–6150; (b) Schobert, R.; Stangl, A.; Hannamann, K. *Tetrahedron* **2008**, *64*, 1711–1720; (c) Abergel, R. J.; Raymond, K. N. *J. Biol. Inorg. Chem.* **2008**, *13*, 229–240; (d) Jurchen, K. M. C.; Raymond, K. M. *Inorg. Chem.* **2006**, *45*, 1078–1090; (e) Abergel, R. J.; Raymond, K. M. *Inorg. Chem.* **2006**, *45*, 3622–3631; (f) Bailly, T.; Burgada, R.; Prangé, T.; Lecouvey, M. *Tetrahedron Lett.* **2003**, *44*, 189.
18. Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1655–1660.
19. Valente, M.; Sousa, S. F.; Magalhães, A. L.; Freire, C. *J. Solution Chem.* **2010**, *39*, 1230–1242.
20. Kim, S.; No, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 315–318.
21. Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258–262.
22. Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758–761.
23. (a) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron* **2011**, *67*, 2206–2214; (b) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *J. Org. Chem.* **2009**, *74*, 782–788.
24. (a) Arumugam, J.; Brown, H. A.; Jacobs, H. K.; Gopalan, A. S. *Synthesis* **2011**, 57–64; (b) Harrington, J. M.; Chittamuru, S.; Dhungana, S.; Jacobs, H. K.; Gopalan, A. S.; Crumbliss, A. L. *Inorg. Chem.* **2010**, *49*, 8208–8221; (c) Chittamuru, S.; Lambert, T. N.; Martinez, G.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett.* **2007**, *48*, 567–571.
25. Gissot, A.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 6925–6928.