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Selective O-functionalization of phenolic α-amino acids with crown ethers bearing cyclophosphazene sub-units☆

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ABSTRACT

Cyclophosphazenes (CyP) containing a crown ether and an α-amino acid unit have been prepared starting from diphosphaza[16]crown-6 (PNP16C6). Nucleophilic substitution of one (or both) residual ansa-chlorine atom(s) of bis-spiro substituted PNP16C6 by α-arylsulfonamido esters containing a phenolic function leads to the target compounds. These new polyfunctionalized CyP are lariat ethers, potentially useful as starting materials for the preparation of 'pH-controlled active ion carriers' in liquid membranes.

1. Introduction

1.1. Cyclophosphazenes. General

Cyclophosphazenes (CyP) and polyorganophosphazenes (POP), the latter obtained by thermal polymerization and functionalization with organic molecules of the former, have stimulated an increasing interest both as innovative plastic materials and, in supramolecular technology, for the study of biomimetic systems.[1] Since the sixties, a number of POP with different physicochemical characteristics have been synthesized by nucleophilic mono- or poly-substitution of the chlorine atoms of hexachlorocyclophosphazene (**1**).[2,3] In particular, the full substitution with polyether chains affords CyP polypodands, a new class of 'octopus molecules' (**2**).[4] These many-armed ligands, due to the 'cooperative effect' of all the polyether chains, are powerful complexing agents of alkali metal salts even in low polarity media and hence very efficient phase transfer catalysts.[5] An analogous cooperative effect was found with multisite receptors **3** (Fig. 1) containing a certain number of crown moieties linked to the same CyP central unit.[6] With these polymacrocycles the binding of cations slightly exceeding the size of the cavity afforded sandwich-complexes (2:1) instead of 1:1 complexes. These compounds are of great potential interest since they may allow new insights into the possibility of organized systems ('molecular stacking') for the formation of nanotubes in the design of artificial ionic channels.[6]

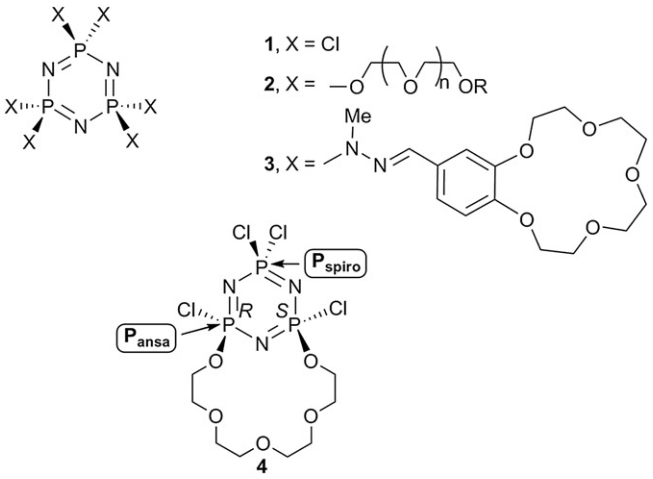

Fig. 1. 'CyP' multisite receptors **2**–**4** derived from hexachlorophosphazene **1**.

☆ In memory of Krystyna Brandt.

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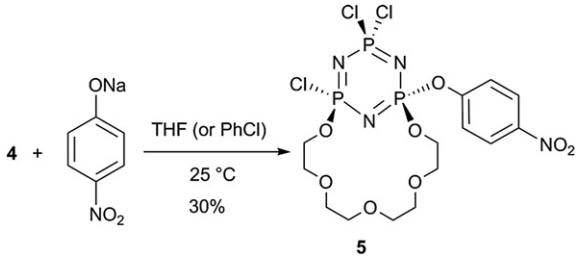
In recent years, much attention has been paid to the synthesis of functional crown ethers that can be regarded as enzyme models because their reactivity is remarkably affected by the cation complexed inside the macrocyclic cavity and the catalytic activity depends on the size fit of the host–guest complex with the substrate. Both are typical properties of the enzyme chemistry.[7] In this line, functional crowns, like diphosphaza[16]crown-6 (PNP16C6) **4**, synthesized by incorporating the Cyp **1** sub-unit into the polyether backbone (Fig. 1), are particularly promising ligands.[8] They combine, in fact, the versatile reactivity of **1**[2,3] with the complexing ability of crown ethers,[9] and hence can be regarded as potential anion activators in nucleophilic substitution reactions. In previous studies, we have revealed the crucial role that the metal ion plays in determining the product distribution in the nucleophilic substitution reactions of **4** with a series of alkali and alkaline-earth metal 4-nitrophenates.[10,11] In particular, in apparent contrast with the rules of classical phosphazene chemistry, we found that lithium, sodium, and calcium salts gave exclusively the product of mono-substitution at one of the 'P_{ansa}' atoms, such as **5** (Scheme 1), in the position geminal to the macrocycle.[12]



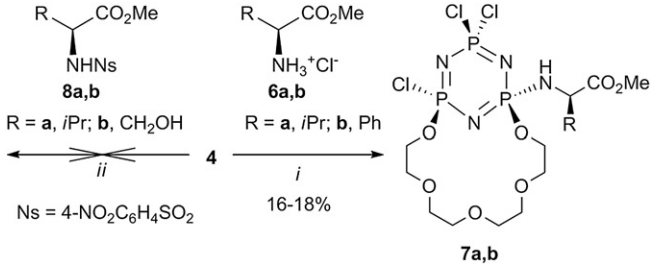
Scheme 1.

1.2. Cyclophosphazenes containing amino functions

CyP bearing one or more amino derivative side arms are found to display interesting structural properties, finding remarkable applications in different fields of inorganic, organic, and medicinal chemistry.[13–20] In spite of this, only a few papers describing compounds of this class have appeared in a relatively large span of time. Brandt reported the synthesis of PNP-crown polytopic receptors by reaction of PNP16C6 (**4**) and polymethylene-diamines: three classes of new compounds—ansa–ansa, bino-ansa, and bis-bino-ansa—have been screened as metal-cation complexing agents.[13] Labarre et al. studied CyP-lariats and their stable gadolinium cryptates, for NMR-imaging applications.[14] Çiftçi analyzed the *syn*/*anti* conformational polymorphism of spermine-bridged bis-CyP derivatives.[15] Siwy prepared and studied in vitro the cytostatic and anti-leukemic activity of some poly-aziridinyl-PNP-crowns.[16] In the sixties, Kropacheva reported CyP-glycinate esters for the first time,[17] to our knowledge, and some 20 years later, Smaardijk prepared a few compounds of this type, which may serve as anti-cancer drug precursors.[18] Sohn described CyP bearing poly(oxyethylene) and α-amino acid or oligopeptide units, as potential thermosensitive drug delivery systems.[19] Recently, the synthesis and the properties of a novel star-shaped CyP, containing glycine ester units linked to the phosphazenic ring by phenolic spacers, have been reported by Li.[20] Stimulated by the features of these new functionalized CyP, we studied the strategy for an original regioselective synthesis of new PNP-crowns bearing α-amino acid units on the phosphazene ring.

2. Preliminary results

A series of reactions on **4** were carried out to link optically pure α-amino acid derivative units to the PNP16C6 moiety through a N–P_{ansa} bond. The features of these molecules are a free carboxylic acid function and a very crowded α-amino group, as a result of the phosphazenic ring proximity. The reaction under homogeneous conditions of **4** with the *N*-free amino esters **6a**,**b** (Scheme 2, path i) gave only minor amounts of the corresponding mono-ansa substituted compounds **7a**,**b**, together with mono-spiro and poly-substituted CyP that were not isolated from the reaction crude. In an attempt to use more powerful nitrogen nucleophiles, **4** was reacted with nosylamido esters of valine and serine **8a**,**b**, under heterogeneous conditions. As previously found in the N-alkylation of these α-amino acid derivatives,[21] the reactivity of the nucleophilic center is strongly conditioned by the steric hindrance of the electrophilic counterpart: **8a**,**b** did not react with PNP16C6 **4**, neither with potassium carbonate, under solid–liquid phase transfer catalysis (SL-PTC) conditions, nor using a stronger base in a heterogeneous non-catalyzed system, but slowly decomposed (Scheme 2, path ii). In addition, to check the reactivity of sulfonamido nucleophiles, **4** was reacted with $TsNH_2$ under SL-PTC, but the starting materials were recovered unchanged after prolonged reaction time.



Scheme 2. i) DIPEA, DCM, 20 °C, 48 h. (ii) K_2CO_3, $TEBA_{cat}$, MeCN, 25 °C (SL-PTC), 14 days or NaH, THF, 60 °C, 7 days.

3. Results and discussion

Considering the above findings and the good reactivity of alkaline phenoxides toward chlorophosphazenes, due to the formation in the condensation products of energetically more favored P–O bonds (P–O ~336 kJ mol^{-1}; P–N ~230 kJ mol^{-1}),[22] we decided to change the synthetic approach. With this objective in mind, L-tyrosine and D-4-hydroxy-phenylglycine derivatives **9a**,**b** and **10a**,**b** (Fig. 2),[23] which contain a phenol function, were chosen as nucleophiles for the condensation with **4**.

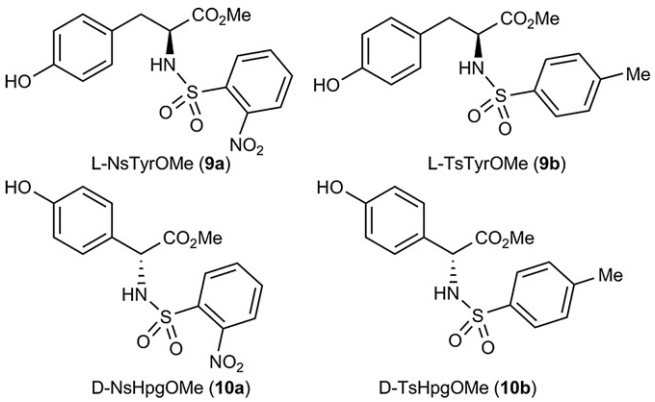
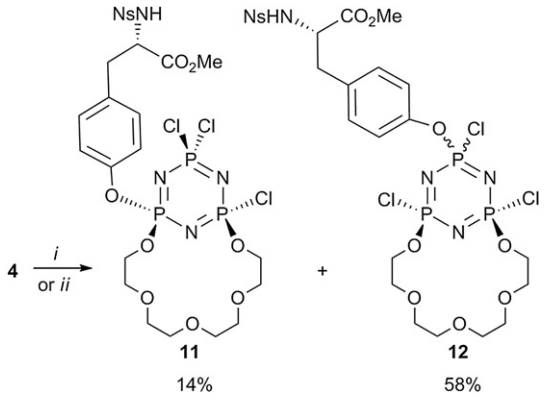


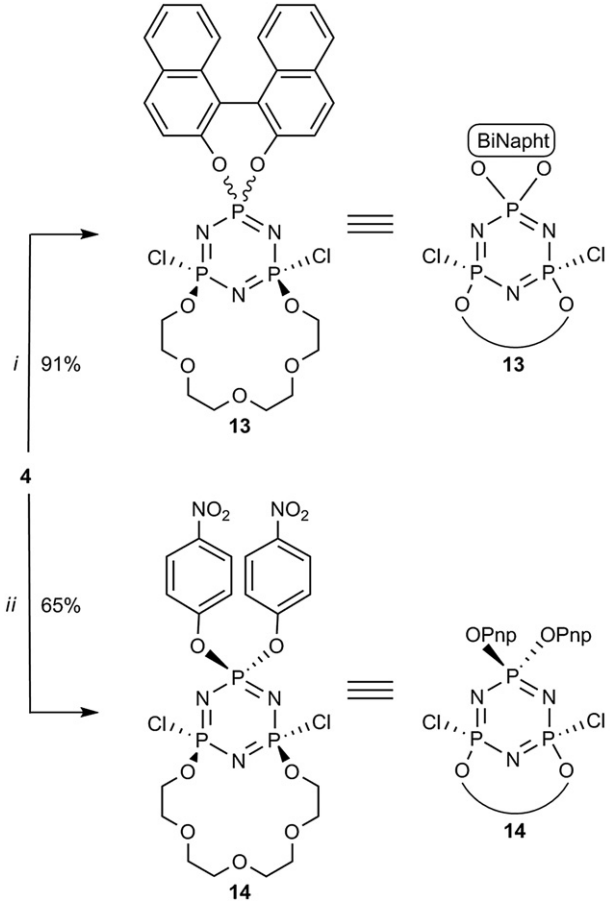
Fig. 2. L-Tyrosine and D-4-hydroxy-phenylglycine derivatives **9a,b** and **10a,b** used as nucleophiles.

As expected, in the reaction of **4** with the L-tyrosine derivative **9a** (Scheme 3), the nucleophilic attack was completely *O*-chemoselective. However, a mixture of mono-OP_{ansa} **11**[24] and mono-OP_{spiro} **12**[25] (as major, less hindered product) formed with this nucleophile, under both SL-PTC (path i) and non-catalyzed heterogeneous conditions (path ii).



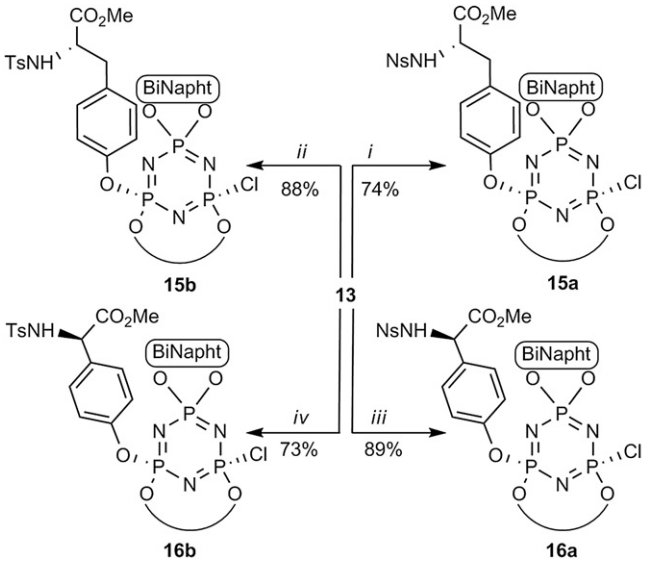
Scheme 3. i) L-NsTyrOMe (**9a**), K_2CO_3, $TEBA_{cat}$, MeCN, 25 °C, 24 h. (ii) **9a**, Na_2CO_3, THF, 25 °C, 48 h.

In order to introduce the amino acid unit exclusively on the P_{ansa} atom, the P_{spiro} position was 'blocked' by forming the (±)-1,1′-bi(2-naphthol) (**13**) or 4-nitrophenol (**14**) bis-spiro derivatives (Scheme 4).



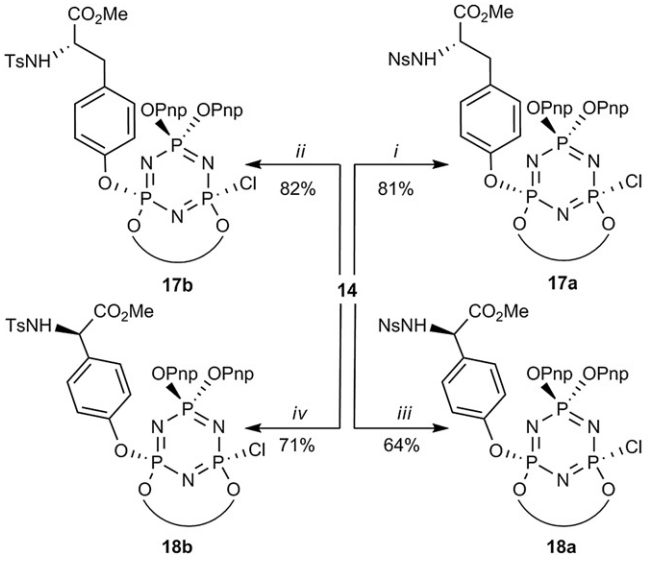
Scheme 4. i) (*R*)-1,1′-bi-(2-naphthol) (**13**), K_2CO_3, MeCN, 60 °C, 21 h. (ii) 4-NO_2-C_6H_4OK, MeCN, 25 °C, 2 h.

The reaction of **13** with L-NsTyrOMe (**9a**), under heterogeneous conditions by using anhydrous sodium carbonate as a solid base (Scheme 5), gave the mono-OP_{ansa} derivative **15a** (path i), after



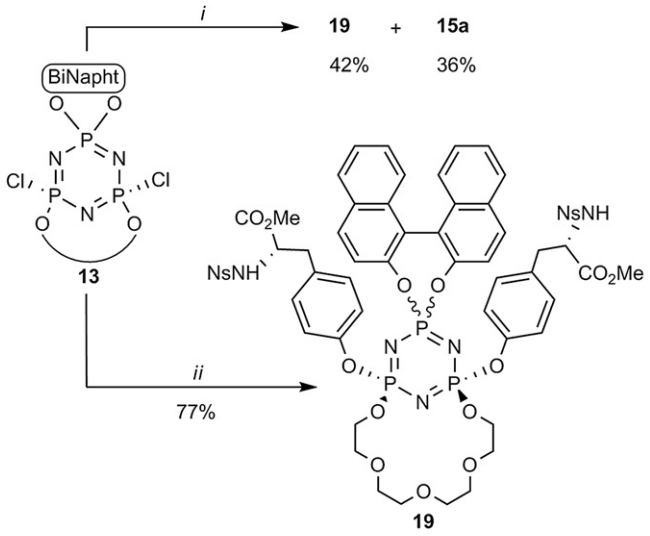
Scheme 5. i) L-NsTyrOMe (**9a**), Na_2CO_3, MeCN, 40 °C, 6 days. (ii) L-TsTyrOMe (**9b**), Na_2CO_3, MeCN, 40 °C, 4 days. (iii) D-NsHpgOMe (**10a**), Na_2CO_3, MeCN, 30 °C, 24 h. (iv) D-TsHpgOMe (**10b**), Na_2CO_3, MeCN, 25 °C, 5 days.

prolonged heating at 40 °C. The *N*-tosyl derivative L-TsTyrOMe (**9b**) showed a similar behavior and reactivity (path ii). Much more reactive (Scheme 5) were the D-4-hydroxy-phenylglycine derivatives D-NsHpgOMe (**10a**) (path iii) and D-TsHpgOMe (**10b**) (path iv), which reacted with **13** at 25–30 °C. Analogous reactions were performed on the bis-spiro-4-nitrophenol derivative **14** (Scheme 6), which showed a reactivity toward the α-amino acid derivatives **9a**,**b** and **10a**,**b** similar to that of **13**.



Scheme 6. i) L-NsTyrOMe (**9a**), Na_2CO_3, MeCN, 40 °C, 5 days. (ii) L-TsTyrOMe (**9b**), Na_2CO_3, MeCN, 40 °C, 4 days. (iii) D-NsHpgOMe (**10a**), Na_2CO_3, MeCN, 60 °C, 48 h. (iv) D-TsHpgOMe (**10b**), Na_2CO_3, MeCN, 40 °C, 3 days.

In order to substitute both the chlorine atoms on the ansa-position, **13** was reacted with excess L-NsTyrOMe (**9a**) and Na_2CO_3 (Scheme 7).



Scheme 7. i) L-NsTyrOMe (**9a**) (2 mol equiv), Na_2CO_3 (6 mol equiv), MeCN, 60 °C, 6 days. (ii) L-NsTyrOMe (**9a**) (3 mol equiv), NaH (5 mol equiv), MeCN, 40 °C, 24 h.

Under the usual heterogeneous conditions (path i), the bis-substitution is only partial and the target compound **19** was isolated together with a relevant quantity of mono-ansa compound **15a**. The use of sodium hydride (path ii), resulted in milder reaction conditions and very good yields of bis-ansa CyP **19**.

The bis-substitution in the presence of the stronger base NaH is likely favored by the formation of the complex **A** (Fig. 3), i.e., the *N*-sodium salt of the mono-ansa substituted intermediate **15a**. The sodium cation, coordinated by the oxygen atoms of the crown ether, is brought in close proximity to the residual ansa-chlorine atom that, consequently, is activated toward a second nucleophilic *O*-attack by the **B** dianion.

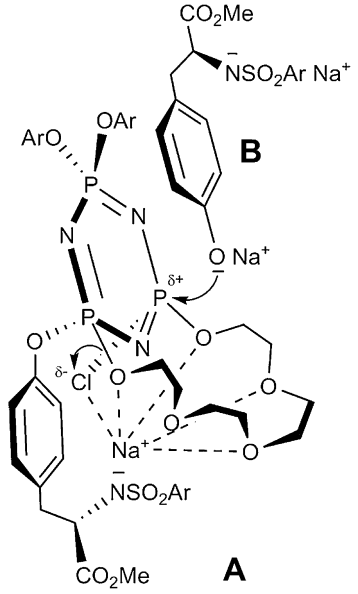


Fig. 3. Proposed mechanism for the bis-substitution on substrate **13**.

4. Stereochemical considerations

As reported above, the racemic mixture (±)-1,1′-bi(2-naphthol) has been used in the synthesis of the bis-spiro derivative **13** that, in turn, is racemic. The reaction of **13** with a stoichiometric amount of an achiral nucleophile produces two racemic mono-ansa diastereoisomers, whereas the products **15**, **16** of mono-substitution of **13** with the optical pure nucleophiles **9**, **10** are equimolar amounts of four diastereoisomers. These latter result from the attack of the nucleophile on one of the two P_{ansa} atoms of the CyP ring, bearing one of the two enantiomeric bi(2-naphthol) substituents (*R* or *S*), e.g., **16a** exists as a mixture of D-*R*-P_1, D-*R*-P_2, D-*S*-P_1, and D-*S*-P_2 isomers (Fig. 4).[26]

The bis-spiro 4-nitrophenoxy mono-ansa derivatives **17**, **18** derive from the achiral CyP **14** and therefore exist as couple of diastereoisomers, e.g., D-P_1 and D-P_2 of **18a** (Fig. 5).[27]

Finally the bis-ansa derivative **19** is an equimolar mixture of the two diastereoisomers L-*R*-L and L-*S*-L (Fig. 6).[28]

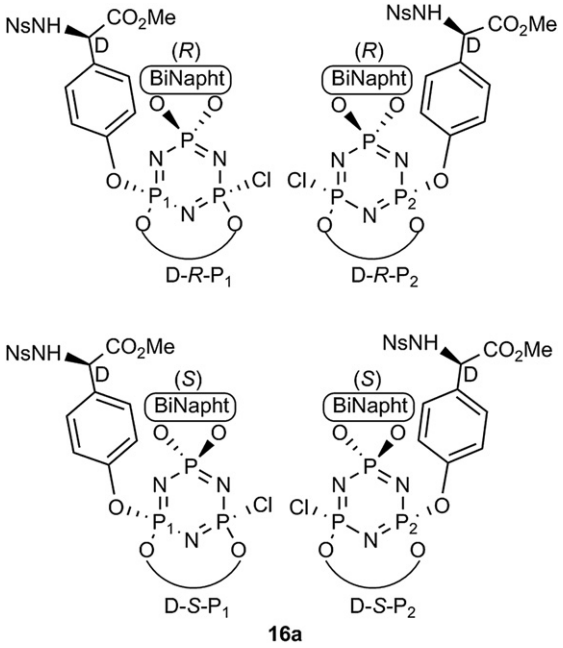


Fig. 4. Mono-ansa Cyp **16a** isomers formed.

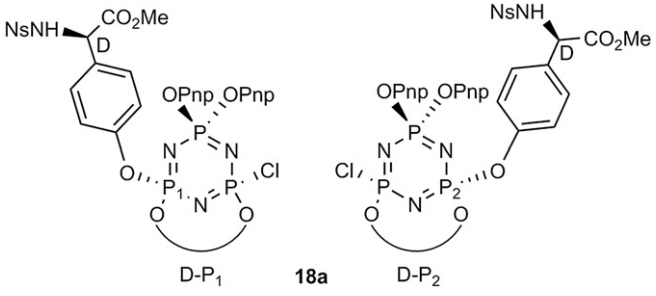


Fig. 5. Mono-ansa Cyp **18a** regioisomers formed.

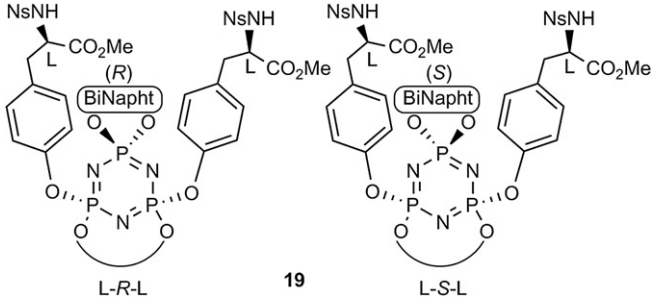


Fig. 6. Bis-substituted Cyp **19** diastereoisomers formed.

5. Conclusions

In conclusion, products **15**–**19** can be considered lariat ethers[29] in which amido esters residues are linked to the macrocyclic ring via the phosphorus in the 'ansa' position. Due to their topology, these compounds could give stable inclusion complexes, especially with alkali metal and alkaline-earth metal cations, in organic solvents and hence could behave as good potential carriers for cations in analogy with crown ethers and the related open-chain analogs. The unprotected derivatives of these compounds should be exactly defined 'proton-ionizable lariat ethers' due to the presence in the molecule of a pendent amino acid group.[29,30] Such a property is known to be very useful because the complexation and the release of the cation are controlled by the pH of the medium ('proton switch') and the metal ion extraction does not involve transfer of the aqueous phase anion into the organic phase.[30] More in general, these lariat ethers could be potentially useful as 'pH-controlled active ion carriers' in liquid membranes. In addition, it is also possible to introduce hydrophobic chains in both the 'spiro' and the left 'ansa' positions so obtaining functionalized crown ethers capable to form aggregates in aqueous media and hence to behave as active 'liquid ion carriers'.[31] Alternatively, the potential stacking of two or more phosphazenic rings, by linking difunctionalized lipophilic chains of appropriate length, could provide the driving force to form channel-like structures.[32] Very recently, bis-PNP-lariat ethers were found to behave as efficient ion carriers for heavy metal (Zn^{2+}, Cd^{2+}, Pb^{2+}) transport across polymer inclusion membranes, in particular for lead(II), due to the formation of 'sandwich' complexes with the macrocycle.[33] Finally, since PNP-crown amido esters **15**–**19** contain optically active α-amino acid residues the possibility of stereoselective interactions with chiral guests could also be envisaged.

6. Experimental section

6.1. General

All reactions were carried out in oven-dried glassware with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Arylsulfonamido esters **9a**,**b** and **10a**,**b** were prepared as previously described.[23] Reagent-grade commercially available reagents and solvents were used; anhydrous solvents were used as purchased. DCM indicated dichloromethane, and PE is petroleum ether having bp 40–60 °C. Tetraethyleneglycol was distilled from anhydrous K_2CO_3 and stored over 4 Å molecular sieves. The reactions were monitored by TLC on silica gel 60 F_{254} (Merck, 0.15–0.20 mm), and visualized by UV-254 light and CAM staining. Reaction mixtures were purified by flash column (FCC) and medium pressure liquid chromatography (MPLC) using silica gel 60 (Merck, 0.040–0.063 mm). Melting points were determined with a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Jasco FT-IR-4100 spectrophotometer, using KBr cells, and are reported in frequency of absorption (cm^{-1}). Optical rotations were determined on a Perkin–Elmer 241 polarimeter operating at 589 nm, using a (10 cm×5 mL) cell; *c* is in g/100 mL. NMR spectra were recorded on Bruker AC-300 and AMX-300 spectrometers, operating at 300 MHz, 75 MHz, and 121 MHz for ^1H, ^{13}C, and ^{31}P, respectively. TMS was used as external reference. Chemical shifts are given on the δ scale (ppm). Coupling constants (*J*) are given in hertz. Electrospray ionization (ESI) HRMS were obtained with a Bruker Daltonics ICR-FTMS APEX II at the Unimi-CIGA Interdepartmental Analytical Centre.

6.2. Synthesis of PNP16C6 (4)

PNP16C6 (**4**) was prepared following a modification of the synthesis described by Brandt.[8] To a solution of hexachlorocyclophosphazene (10.43 g, 30 mmol) in anhydrous THF (150 mL) was added NaH 60% (2.64 g, 66 mmol). This suspension was stirred under nitrogen at room temperature while tetraethyleneglycol (5.85 g, 30 mmol) was added in 3 h by syringe pump, then the suspension was stirred 1 h more. TLC control (Et_2O; staining with I_2 then CAM) indicated that no further starting materials were present and evidenced product **4** as an orange spot. The reaction mixture was quenched with water (0.2 mL) and filtered over Celite. After removal of THF under vacuum, a whitish oil was obtained (13.74 g). Product **4** (4.22 g, 30%) was isolated by FCC (Et_2O) as white solid; mp 91.4–92.0 °C (lit.[8] 85.9 °C); δ_H (300 MHz, $CDCl_3$) 4.48–4.20 (4H, m), 3.86–3.73 (4H, m), 3.73–3.63 (8H, m); δ_P (121 MHz, $CDCl_3$) 25.7 ($1P_{spiro}$ (Cl_2), dd, *J* 65.0, 70.0 Hz), 19.4 ($1P_{ansa}$ (Cl, OCH_2), d, *J* 65.0 Hz), 19.4 ($1P_{ansa}$ (Cl, OCH_2), d, *J* 70.0 Hz).

6.3. Reaction of PNP16C6 4 with L-NsTyrOMe 9a: synthesis of mono-ansa 11 and mono-spiro 12 derivatives

In a screw cap vial, anhydrous, finely ground K_2CO_3 (31 mg, 0.225 mmol) was added to a solution of **4** (70 mg, 0.15 mmol), L-NsTyrOMe **9a** (57, 0.15 mmol), and TEBA (3.4 mg, 0.015 mmol) in anhydrous acetonitrile (0.75 mL). This heterogeneous mixture was stirred at room temperature for 24 h (TLC, DCM/PE/MeOH—19:10:1) and then filtered on Celite. After removal of the solvent under vacuum, the crude (yellow oil, 115 mg) was purified by FCC (Et_2O/AcOEt—6:1).

Mono-ansa derivative **11** (17 mg, 14%); colorless oil; δ_H (300 MHz, $CDCl_3$) 7.97 (1H, dd, *J* 9.0, 2.4 Hz), 7.89 (1H, dd, *J* 7.1, 1.9 Hz), 7.78–7.68 (2H, m), 7.10–7.02 (4H, m), 6.01 (1H, br s), 4.42–4.39 (1H, m), 4.33–3.90 (4H, m), 3.82–3.59 (12H, m), 3.51 (3H, s), 3.13 (1H, dd, *J* 5.2, 5.0 Hz), 3.00 (1H, dd, *J* 14.2, 7.0 Hz); δ_P (121 MHz, $CDCl_3$) 26.9 ($1P_{spiro}$ (Cl_2), dd, *J* 77.2, 75.0 Hz), 22.3 ($1P_{ansa}$ (Cl, OCH_2), dd, *J* 77.2, 70.2 Hz), 9.3 ($1P_{ansa}$ (OAr', Cl), dd, *J* 75.0, 70.2 Hz). IR (Nujol, cm^{-1}) 3286, 2925, 2855, 1786, 1554, 1343, 1326, 1200, 1165, 1109, 905, 604. HRMS, calcd for $C_{24}H_{32}Cl_3N_5O_{12}P_3S$ ($M+H^+$): 812.0047; found 812.0045.

Mono-spiro derivative **12** (71 mg, 58%); colorless oil; δ_H (300 MHz, $CDCl_3$) 7.94 (1H, dd, *J* 9.4, 2.4 Hz), 7.86 (1H, dd, *J* 7.3, 1.8 Hz), 7.74–7.64 (2H, m), 7.17–7.09 (4H, m), 6.10 (1H, br s), 4.46–4.17 (5H, m), 3.85–3.60 (12H, m), 3.54 and 3.52 (3H, s+s), 3.16 (1H, dd, *J* 14.2, 5.3 Hz), 3.03 (1H, dd, *J* 14.0, 7.1 Hz); δ_P (121 MHz, $CDCl_3$) 21.7 ($2P_{ansa}$ (Cl, OCH_2), d, *J* 77.2 Hz), 17.8 ($1P_{spiro}$ (OAr', Cl), t, *J* 77.2 Hz). IR (Nujol, cm^{-1}) 3291, 2918, 2863, 1780, 1544, 1358, 1326, 1196, 1159, 1108, 910, 599. HRMS, calcd for $C_{24}H_{32}Cl_3N_5O_{12}P_3S$ ($M+H^+$): 812.0047; found 812.0047.

6.4. Synthesis of 1,3-[oxy(tetraethyleneoxy)]-5,5-(1,1′-binaphthalene-2,2′-dioxy)cyclotriphosphazene (13)

Anhydrous, finely ground K_2CO_3 (655 mg, 4.74 mmol) was added to a solution of **4** (708 mg, 1.51 mmol) and (±)-1,1′-binaphthol (452 mg, 1.58 mmol) in anhydrous acetonitrile (9 mL), placed in a screw cap vial. The heterogeneous mixture was stirred at 60 °C for 20 h (TLC, Et_2O/AcOEt—6:1), then cooled to room temperature and filtered on Celite. After removal of MeCN under vacuum, a yellow solid (1.05 g) was obtained. The bis-spiro derivative **13** (942 mg, 91%) was isolated by FCC (Et_2O) as white solid; mp 130 °C (lit.[34] 135 °C); δ_H (300 MHz, $CDCl_3$) 8.02 (1H, d, *J* 8.8 Hz), 8.00 (1H, d, *J* 8.8 Hz), 7.94 (1H, d, *J* 8.2 Hz), 7.92 (1H, d, *J* 8.2 Hz), 7.56 (1H, d, *J* 8.8 Hz), 7.55 (1H, d, *J* 8.8 Hz), 7.49–7.38 (4H, m), 7.31–7.25 (2H, m), 4.40–4.21 (4H, m), 3.89–3.62 (12H, m); δ_P (121 MHz, $CDCl_3$) 24.6 ($2P_{ansa}$ (Cl, OCH_2), d, *J* 78.7 Hz), 22.2 ($1P_{spiro}$ (OAr_2), t, *J* 78.7 Hz). IR (Nujol, cm^{-1}) 3325, 2880, 1207, 1159, 1111, 600.

6.5. Synthesis of 1,3-[oxy(tetraethyleneoxy)]-5,5-bis(4-nitrophenoxy)cyclotriphosphazene (14)

In a screw cap vial, **4** (469 mg, 1.0 mmol) in anhydrous acetonitrile (1.6 mL), was reacted with potassium 4-nitrophenate

(354 mg, 2.0 mmol) for 2 h at room temperature, under stirring (TLC, DCM/AcOEt—3:1). After filtration on Celite and removal of MeCN under vacuum, the resultant yellow oil (670 mg) was purified by FCC (AcOEt/PE—1:1). The bis-spiro derivative **14** (440 mg, 65%) was isolated as yellow solid; mp 108–110 °C (we previously[10] reported **14** as a wax); δ_H (300 MHz, $CDCl_3$) 8.29 (2H, d, *J* 9.1 Hz), 8.28 (2H, d, *J* 9.0 Hz), 7.43 (2H, d, *J* 9.1 Hz), 7.42 (2H, d, *J* 9.0 Hz), 4.35–4.20 (2H, m), 4.20–4.05 (2H, m), 3.75–3.65 (4H, m), 3.64–3.50 (8H, m); δ_P (121 MHz, $CDCl_3$) 23.5 ($2P_{ansa}$ (Cl, OCH_2), d, *J* 84.4 Hz), 4.8 ($1P_{spiro}$ (OAr_2), t, *J* 84.4 Hz). IR (Nujol, cm^{-1}) 3310, 2895, 2850, 1528, 1324, 1201, 1160, 1113, 850, 600.

6.6. General procedure for the synthesis of mono-ansa derivatives 15–18

In a screw cap vial, a heterogeneous mixture of the bis-spiro derivative **13**, **14** and the sulfonamido ester **9**, **10** solution in anhydrous acetonitrile, and lyophilized Na_2CO_3 (0.3 mol equiv) was stirred until no further starting materials were detected by TLC analysis (DCM/PE/MeOH—19:10:1). After filtration on Celite and evaporation under vacuum of the solvent, the crude was purified by FCC. Starting materials and solvent, reaction time and temperature, amount of the crude, FCC eluant, product yield, physical, spectroscopic and analytical data are as follows.

*6.6.1. Synthesis of mono-ansa(L-NsTyrOMe) bis-spiro(binaphthoxy) derivative **15a**.* Bis-spiro derivative **13** (137 mg, 0.2 mmol), sulfonamido ester **9a** (76 mg, 0.2 mmol), MeCN (0.6 mL), Na_2CO_3 (64 mg, 0.6 mmol); 6 days at 40 °C; the crude is a yellow oil (197 mg); FCC eluant (Et_2O/AcOEt—7:1); **15a** (152 mg, 74%) white wax; δ_H (300 MHz, $CDCl_3$) 8.02–6.98 (20H, m), 6.10–5.97 (1H, NH, m), 4.60–4.08 (5H, m), 3.95–3.53 (12H, m), 3.521, 3.517, 3.498, and 3.478 (3H, s+s+s+s), 3.25–2.95 (2H, m); δ_P (121 MHz, $CDCl_3$) 28.5–25.0 ($1P_{ansa}$ (Cl, OCH_2)+$1P_{spiro}$ (OAr_2), m), 12.5–10.7 ($1P_{ansa}$ (OAr′), m). IR (Nujol, cm^{-1}) 3330, 2912, 2853, 1783, 1551, 1340, 1203, 1156, 1113, 899, 602. HRMS, calcd for $C_{44}H_{44}ClN_5O_{14}P_3S$ ($M+H^+$): 1026.1507; found 1026.1508.

*6.6.2. Synthesis of mono-ansa(L-TsTyrOMe) bis-spiro(binaphthoxy) derivative **15b**.* Bis-spiro derivative **13** (96 mg, 0.14 mmol), sulfonamido ester **9b** (49 mg, 0.14 mmol), MeCN (0.6 mL), Na_2CO_3 (45 mg, 0.42 mmol); 4 days at 40 °C; the crude is an uncolored oil (148 mg); FCC eluant (Et_2O); **15b** (123 mg, 88%) wax; δ_H (300 MHz, $CDCl_3$) 8.10–7.00 (20H, m), 5.12, 5.11, 5.09, and 5.08 (1H, NH, br s+br s+br s+br s), 4.60–4.05 (5H, m), 3.92–3.57 (12H, m), 3.451, 3.433, 3.425, and 3.398 (3H, s+s+s+s), 3.06–3.02 (2H, m), 2.36 (3H, s); δ_P (121 MHz, $CDCl_3$) 28.0–25.2 ($1P_{ansa}$ (Cl, OCH_2)+$1P_{spiro}$ (OAr_2), m), 12.5–10.9 ($1P_{ansa}$ (OAr′), m). IR (Nujol, cm^{-1}) 3318, 2910, 1778, 1353, 1205, 1165, 1110, 901, 611. HRMS, calcd for $C_{45}H_{47}ClN_4O_{12}P_3S$ ($M+H^+$): 995.1813; found 995.1811.

*6.6.3. Synthesis of mono-ansa(L-NsHpgOMe) bis-spiro(binaphthoxy) derivative **16a**.* Bis-spiro derivative **13** (55 mg, 0.08 mmol), sulfonamido ester **10a** (29 mg, 0.08 mmol), MeCN (0.3 mL), Na_2CO_3 (25 mg, 0.24 mmol); 24 h at 30 °C; the crude is a yellowish oil (71 mg); FCC eluant (Et_2O/AcOEt—7:1); **16a** (72 mg, 89%) uncolored oil; δ_H (300 MHz, $CDCl_3$) 7.99–6.99 (20H, m), 6.69, 6.66, 6.60, and 6.55 (1H, NH, br s+br s+br s+br s), 5.33–5.19 (1H, m), 4.60–4.18 (4H, m), 4.12–3.56 (12H, m), 3.605, 3.594, 3.586, and 3.583 (3H, s+s+s+s); δ_P (121 MHz, $CDCl_3$) 27.1–24.8 ($1P_{ansa}$ (Cl, OCH_2)+$1P_{spiro}$ (OAr_2), m), 12.6–10.7 ($1P_{ansa}$ (OAr′), m). IR (Nujol, cm^{-1}) 3316, 2898, 2860, 1736, 1537, 1355, 1200, 1148, 1109, 910, 610. HRMS, calcd for $C_{43}H_{42}ClN_5O_{14}P_3S$ ($M+H^+$): 1012.1350; found 1012.1354.

*6.6.4. Synthesis of mono-ansa(L-TsHpgOMe) bis-spiro(binaphthoxy) derivative **16b**.* Bis-spiro derivative **13** (68 mg, 0.10 mmol), sulfonamido ester **10b** (34 mg, 0.10 mmol), MeCN (0.45 mL), Na_2CO_3 (32 mg, 0.30 mmol); 5 days at 25 °C; the crude is an uncolored wax (89 mg); FCC eluant (Et_2O); **16b** (72 mg, 73%) wax; δ_H (300 MHz, $CDCl_3$) 8.06–6.91 (20H, m), 5.76, 5.74, 5.70, and 5.65 (1H, NH, br s+br s+br s+br s), 5.10–4.98 (1H, m), 4.60–3.40 (16H, m), 3.540, 3.538, 3.518, and 3.516 (3H, s+s+s+s), 2.36 and 2.34 (3H, s+s); δ_P (121 MHz, $CDCl_3$) 28.0–24.8 ($1P_{ansa}$ (Cl, OCH_2) +$1P_{spiro}$ (OAr_2), m), 14.0–10.0 ($1P_{ansa}$ (OAr′), m). IR (Nujol, cm^{-1}) 3326, 2912, 1724, 1349, 1199, 1154, 1116, 910, 606. HRMS, calcd for $C_{44}H_{45}ClN_4O_{12}P_3S$ ($M+H^+$): 981.1656; found 981.1653.

*6.6.5. Synthesis of mono-ansa(L-NsTyrOMe) bis-spiro(4-nitrophenoxy) derivative **17a**.* Bis-spiro derivative **14** (56 mg, 0.083 mmol), sulfonamido ester **9a** (32 mg, 0.083 mmol), MeCN (0.35 mL), Na_2CO_3 (26 mg, 0.25 mmol); 5 days at 40 °C; the crude is a yellowish oil (93 mg); FCC eluant (Et_2O/AcOEt—6:1); **17a** (67 mg, 81%) yellow oil; δ_H (300 MHz, $CDCl_3$) 8.26 (2H, d, *J* 9.6 Hz), 8.15 (2H, d, *J* 9.1 Hz), 7.99–7.68 (4H, m), 7.44 (2H, d, *J* 9.0 Hz), 7.27 (2H, d, *J* 8.8 Hz), 7.18–7.02 (4H, m), 6.01 (1H, d, *J* 8.8 Hz), 4.41–4.38 (1H, m), 4.35–3.92 (4H, m), 3.80–3.53 (12H, m), 3.50 and 3.49 (3H, s+s), 3.13 (1H, dd, *J* 5.3, 5.1 Hz), 3.00 (1H, dd, *J* 14.1, 7.0 Hz); δ_P (121 MHz, $CDCl_3$) 25.7 ($1P_{ansa}$ (Cl, OCH_2), dd, *J* 94.1, 74.4 Hz), 10.5 ($1P_{ansa}$ (OAr′), dd, *J* 94.8, 74.4 Hz), 7.7 ($1P_{spiro}$ (OAr_2), dd, *J* 94.8, 94.1 Hz). IR (Nujol, cm^{-1}) 3322, 2906, 2853, 1781, 1549, 1340, 1319, 1203, 1162, 1109, 899, 853, 602. HRMS, calcd for $C_{36}H_{40}ClN_7O_{18}P_3S$ ($M+H^+$): 1018.1052; found 1018.1050.

*6.6.6. Synthesis of mono-ansa(L-TsTyrOMe) bis-spiro(4-nitrophenoxy) derivative **17b**.* Bis-spiro derivative **14** (58 mg, 0.086 mmol), sulfonamido ester **9b** (30 mg, 0.086 mmol), MeCN (0.35 mL), Na_2CO_3 (27 mg, 0.26 mmol); 4 days at 40 °C; the crude is a yellow oil (86 mg); FCC eluant (Et_2O); **17b** (69 mg, 82%) wax; δ_H (300 MHz, $CDCl_3$) 8.24 (2H, d, *J* 9.1 Hz), 8.15 (2H, d, *J* 9.1 Hz), 7.63 (2H, d, *J* 8.3 Hz), 7.43 (2H, d, *J* 9.1 Hz), 7.28–7.24 (4H, m), 7.04–6.95 (4H, m), 5.20 and 5.14 (1H, d+d, *J* 9.2+8.3 Hz), 4.35–3.90 (5H, m), 3.90–3.50 (12H, m), 3.46 and 3.45 (3H, s+s), 3.02 (1H, dd, *J* 15.0, 6.0 Hz), 2.92 (1H, dd, *J* 15.0, 6.0 Hz), 2.39 (3H, s); δ_P (121 MHz, $CDCl_3$) 25.7 ($1P_{ansa}$ (Cl, OCH_2), dd, *J* 94.4, 74.5 Hz), 10.5 ($1P_{ansa}$ (OAr′), dd, *J* 95.5, 74.5 Hz), 7.7 ($1P_{spiro}$ (OAr_2), dd, *J* 95.5, 94.4 Hz). IR (Nujol, cm^{-1}) 3308, 2898, 2844, 1780, 1533, 1361, 1324, 1199, 1159, 1113, 900, 850, 612. HRMS, calcd for $C_{37}H_{43}ClN_6O_{16}P_3S$ ($M+H^+$): 987.1358; found 987.1359.

*6.6.7. Synthesis of mono-ansa(L-NsHpgOMe) bis-spiro(4-nitrophenoxy) derivative **18a**.* Bis-spiro derivative **14** (101 mg, 0.15 mmol), sulfonamido ester **10a** (55 mg, 0.15 mmol), MeCN (0.45 mL), Na_2CO_3 (48 mg, 0.45 mmol); 48 h at 60 °C; the crude is a yellow oil (157 mg); FCC eluant (Et_2O/AcOEt—7:1); **18a** (96 mg, 64%) wax; δ_H (300 MHz, $CDCl_3$) 8.24 (2H, d, *J* 9.1 Hz), 8.11 (2H, d, *J* 8.6 Hz), 7.90 (1H, d, *J* 7.5 Hz), 7.87 (1H, d, *J* 7.5 HZ), 7.63–7.60 (2H, m), 7.42 (2H, d, *J* 8.9 Hz), 7.27 (2H, d, *J* 9.4 Hz), 7.22 (1H, d, *J* 8.6 Hz), 7.21 (1H, d, *J* 8.6 Hz), 7.06 (2H, d, *J* 8.4 Hz), 6.65 and 6.60 (1H, d+d, *J* 7.9+7.7 Hz), 5.18 and 5.16 (1H, d+d, *J* 7.9+7.7 Hz), 4.25–3.45 (19H, m); δ_P (121 MHz, $CDCl_3$) 25.6 ($1P_{ansa}$ (Cl, OCH_2), dd, *J* 93.6, 77.2 Hz), 10.7 ($1P_{ansa}$ (OAr′), dd, *J* 94.3, 77.2 Hz), 7.7 ($1P_{spiro}$ (OAr_2), dd, *J* 94.3, 93.6 Hz). IR (Nujol, cm^{-1}) 3299, 2888, 2860, 1735, 1534, 1528, 1350, 1326, 1200, 1145, 1113, 909, 844, 614. HRMS, calcd for $C_{35}H_{38}ClN_7O_{18}P_3S$ ($M+H^+$): 1004.0895; found 1004.0893.

*6.6.8. Synthesis of mono-ansa(L-TsHpgOMe) bis-spiro(4-nitrophenoxy) derivative **18b**.* Bis-spiro derivative **14** (67 mg, 0.10 mmol), sulfonamido ester **10b** (34 mg, 0.10 mmol), MeCN (0.45 mL), Na_2CO_3 (32 mg, 0.30 mmol); 3 days at 40 °C; the crude is a yellow oil (96 mg); FCC eluant (Et_2O); **18b** (69 mg, 71%) pale yellow oil; δ_H (300 MHz, $CDCl_3$) 8.25 (2H, d, *J* 9.1 Hz), 8.17 (2H, d, *J* 8.4 Hz), 7.68 (2H, d, *J* 8.4 Hz), 7.42 (2H, dd, *J* 9.1, 1.5 Hz), 7.30–7.22 (4H, m), 7.18 (2H, dd, *J* 8.6, 1.5 Hz), 7.08 (2H, d, *J* 8.6 Hz), 5.67 and 5.66 (1H,

d+d, *J* 7.9+7.8 Hz), 4.94 and 4.93 (1H, d+d, *J* 7.9+7.8 Hz), 4.22–3.92 (4H, m), 3.90–3.44 (12H, m), 3.52 (3H, br s), 2.41 (3H, s); δ_P (121 MHz, $CDCl_3$) 25.7 ($1P_{ansa}$ (Cl, OCH_2), dd, *J* 94.3, 75.6 Hz), 10.7 ($1P_{ansa}$ (OAr′), dd, *J* 94.4, 75.6 Hz), 7.7 ($1P_{ansa}$ (OAr_2), dd, *J* 94.4, 94.3 Hz). IR (Nujol, cm^{-1}) 3330, 2889, 2861, 1730, 1529, 1517, 1328, 1199, 1151, 1109, 910, 842, 614. HRMS, calcd for $C_{36}H_{41}ClN_6O_{16}P_3S$ ($M+H^+$): 973.1201; found 973.1198.

6.7. Synthesis of bis-ansa(L-NsTyrOMe) bis-spiro (binaphthoxy) derivative 19

In a screw cap vial flushed with argon, 60% NaH (30 mg, 0.45 mmol) was rinsed with anhydrous pentane (3×1 mL), then a solution of **13** (102 mg, 0.15 mmol) and **9a** (171 mg, 0.45 mmol) in anhydrous THF (1 mL) was added at room temperature. This heterogeneous mixture was stirred for 24 h at 40 °C. After cooling, the reaction was quenched with water (50 μL), the solvent was evaporated under vacuum, and the crude was purified by FCC (AcOEt/PE—3:1). Bis-ansa derivative **19** (158 mg, 77%) was isolated as wax; δ_H (300 MHz, $CDCl_3$) 8.01–6.56 (28H, m), 6.13–5.95 (2H, NH, m), 4.45–4.19 (6H, m), 3.89–3.66 (12H, m), 3.53, 3.51, 3.46, and 3.44 (6H, s+s+s+s), 3.23–2.95 (4H, m); δ_P (121 MHz, $CDCl_3$) 27.6 ($1P_{spiro}$ (OAr_2), t, *J* 94.7 Hz), 13.77 ($2P_{ansa}$ (OAr′), d, *J* 94.7 Hz). IR (Nujol, cm^{-1}) 3325, 2912, 1774, 1547, 1340, 1218, 1148, 1119, 900. HRMS, calcd for $C_{60}H_{59}N_7O_{21}P_3S_2$ ($M+H^+$): 1370.2418; found 1370.2418.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.053.

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25. Mono-spiro derivative **12a** is a mixture of isomers *syn*/*anti*, relative to the crown ether ring.
26. These diastereoisomers show four methyl ester signals in the region 3.6–3.4 ppm of the compounds **15**, **16** ^1H NMR spectra.
27. In the case of the **17**, **18** diastereoisomers several ^1H NMR signals are doubled (see Experimental).
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