Syntheses of Amino Acid Based Phosphodiester Linkage-Containing Cryptands as well as Diphosphorylated Macrocycles

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The syntheses of two amino acid based phosphodiester linkage-containing cryptands (**30** and **44**) as well as diphosphorylated macrocycles (**28**, **29**, **32** and **33**) are described. Boc-L-Ser(Bn)-OH and/or Boc-D-Ser(Bn)-OH were used for the construction of the precursors for the diphosphitylation and macrocyclization by phosphitylation. The carboxylic acid groups were connected with a diethylene glycol unit and the amino functionalities were linked using (ethylenedioxy)diacetic acid, oxydiacetic acid, or an isophthalic acid derivative. The LD-cryptands **30** and **44** were obtained after phosphitylation of the precursors **12** and **16**, respectively, containing (ethylenedioxy)acetic acid or an isophthalic acid derivative as a bottom-spacer, using 4-chlorobenzyl phosphorodichlorodite followed by oxidation and hydrogenolysis. Phosphitylation of the precursors containing (ethylenedioxy)acetic acid or oxydiacetic acid as bottom-spacers **11**–**14**, using bis(4-chlorobenzyl) *N,N*-diisopropylphosphoramidite and subsequent oxidation resulted in the corresponding diphosphorylated macrocycles **28**, **29**, **32**, and **33**.

Introduction

Macrocyclic structures, which contain a phosphate group, have not been widely studied.[1-4] The presence of a "P=O" moiety could lead to interesting receptor molecules, which might be able to bind metal ions and organic cations.[4,5]

Macrocyclic compounds containing tricoordinated trivalent or tetracoordinated pentavalent phosphorus atoms bonded to carbon, oxygen, sulfur, or less frequently nitrogen have been prepared, but only specific syntheses have been reported so far.[4,6] In addition, some Li^+ ion selective carriers which contain arylphosphonoyl groups as well as mixed carrier systems comprising combinations of a crown ether with an alkylphosphoric acid have been developed.[7]

So far, the phosphate moiety has not been used as a possible recognition unit in the construction of macrocyclic receptor molecules. In contradistinction, the carboxylic acid moiety has been extensively studied as a recognition unit in the elegant receptor molecules of Rebek *et al.*[8]

As part of a program on the synthesis and structure of phospho amino acids and phosphopeptides[1,2,9] we have described the synthesis of cyclic phosphopeptides containing a phosphodiester linkage between two hydroxy amino acids, which could serve as a model for an *intramolecular* phosphodiester cross-link in a protein.[1,2] The synthesis of these cyclic phosphopeptides[1,2] aroused our interest in the possibility to employ the phosphodiester linkage as a constraint in the construction of semi-peptide phosphate-containing macrocycles. In a recent com-

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munication,[3] we described the synthesis of an amino acid based phosphodiester linkage containing cryptand.

Amino acids are especially attractive building blocks in the construction of macrocyclic receptor molecules[10] because, (a) a whole range of natural and unnatural amino acids is available, (b) in many instances the functional groups of amino acids can be handled independently, thus facilitating the construction of multifunctional receptor molecules, (c) the availability of often both enantiomers will allow the construction of chiral receptor molecules and simultaneously will expand the possibilities for the construction of receptor molecules even more, and finally, (d) one can take advantage of the formation of amide bonds to impose a certain rigidity on the designed receptor molecules.

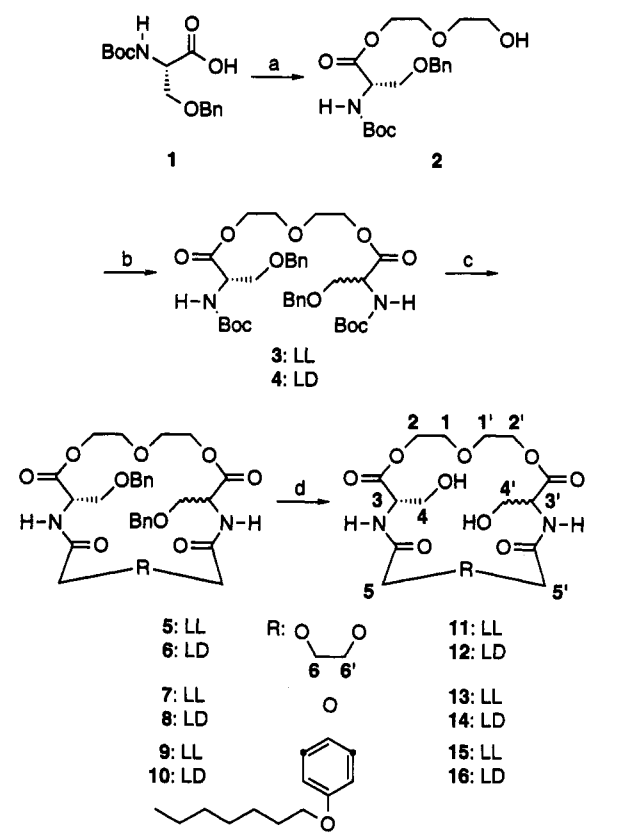
In this paper, we wish to report the design and syntheses of two amino acid based, phosphodiester linkage containing cryptands. In addition, the synthesis of diphosphorylated macrocycles is described. For construction of the cryptands and the diphosphorylated macrocyclic molecules, two serine residues were used as the amino acid building blocks of these potential receptor molecules. The carboxylic acid groups were connected with a diethylene glycol unit and the amino functionalities were linked using (ethylenedioxy)diacetic acid, oxydiacetic acid, or an isophthalic acid derivative. The phosphodiester linkage was employed to connect the hydroxyl groups of the serine residues, in order to obtain the cryptands.

Results and Discussion

The synthesis of the macrocycles used in the preparation of the cryptands and the diphosphorylated macrocycles is shown in Scheme 1. Starting from commercially available Boc-Ser(Bn)-OH (1), coupling with 0.5 equiv of diethylene glycol using DCC/DMAP[11] did not result in LL-"top-half"[12] 3. The two-step procedure was more successful. Coupling of Boc-Ser(Bn)-OH with a 10-fold excess of diethylene glycol using DCC/DMAP gave compound 2 in 80% yield. Subsequent coupling with a second Boc-Ser(Bn)-OH residue or a Boc-D-Ser(Bn)-OH residue using DCC/DMAP[11] afforded LL- and LD-top-halves 3 and 4 with yields of 79 and 87%, respectively.

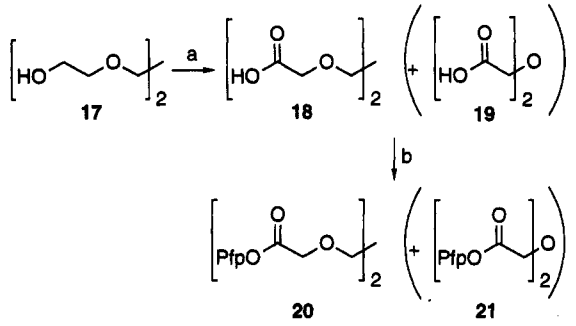
The synthesis of the "bottom-spacers"[12] 20 and 21 derived from (ethylenedioxy)diacetic acid (18) and oxydiacetic acid (19), respectively, is depicted in Scheme 2. Triethylene glycol (17) was oxidized with concentrated HNO_3 at 45 °C as described by Dietrich *et al.*[13] The obtained (ethylenedioxy)diacetic acid (18) was contaminated with oxydiacetic acid (19) at about 20% due to oxidative ether cleavage.[14] The combined yield was 95%.

Scheme 1



Key: (a) diethylene glycol (10 equiv), DMAP, CH_2Cl_2, DCC (80%); (b) 3 (79%): Boc-L-Ser(Bn)-OH, DMAP, CH_2Cl_2, DCC or 4 (87%): Boc-D-Ser(Bn)-OH, DMAP, CH_2Cl_2, DCC; (c) 5 (35% and 53%): (i) TFA/CH_2Cl_2, (ii) 20, THF, 4-methylmorpholine or (i) HCl/Et_2O, (ii) 18, CH_2Cl_2, 4-methylmorpholine, BOP; 6 (32%): (i) TFA/CH_2Cl_2, (ii) 20, THF, 4-methylmorpholine; 7 (36%) and 8 (31%): (i) TFA/CH_2Cl_2, (ii) 21, THF, 4-methylmorpholine; 9 (30%) and 10 (30%): (i) HCl/Et_2O, (ii) 40, CH_2Cl_2, 4-methylmorpholine, BOP; (d) *t*-BuOH, H_2O or MeOH, 10% Pd/C, H_2.

Scheme 2



Key: (a) HNO_3, ΔT; (b) Pfp-OH, dioxane, DCC.

Reaction of the crude 18 with pentafluorophenol (Pfp-OH) and DCC gave the corresponding di-Pfp-ester[15] 20. Purification of the product and concomitant removal of the contaminating di-Pfp-ester 21 of oxydiacetic acid was achieved by recrystallization from hexane (77% yield). Reaction of commercially available oxydiacetic acid (19) with Pfp-OH and DCC[15] gave the di-Pfp-ester 21 in 86% yield.

Acidolysis (TFA) of the Boc groups in the LL- or LD-top-half 3 or 4, followed by coupling with the Pfp-ester 20

(10) For examples of amino acid based receptor molecules see: (a) Kellogg, R. M. Bioorganic Modelling - Stereoselective Reactions with Chiral Neutral Ligand Complexes as Model Systems for Enzyme Catalysis. *Top. Curr. Chem.* **1982**, *101*, 111. (b) Kellogg, R. M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 782. (c) Kaptein, B.; Kellogg, R. M.; Van Bolhuis, F. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 388. (d) Kilburn, J. D.; McKenzie, A. R.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 1307. (e) Sanderson, P. E.; Kilburn, J. D.; Still, W.C. *Ibid.* **1989**, *111*, 8314. (f) Hong, J.-I.; Namgoong, S. K., Bernardi, A.; Still, W. C. *Ibid.* **1991**, *113*, 5111.

(11) Marston, A.; Hecker, E. *Z. Naturforsch.* **1983**, *38b*, 1015.

(12) The compounds in which two serine residues are linked, via their carboxylic acid function, to a diethylene glycol unit are referred to as "top-half" compounds. The derivatives which are coupled to the top-halves in order to obtain the "precursor" macrocycles are referred to as "bottom-spacers".

(13) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629.

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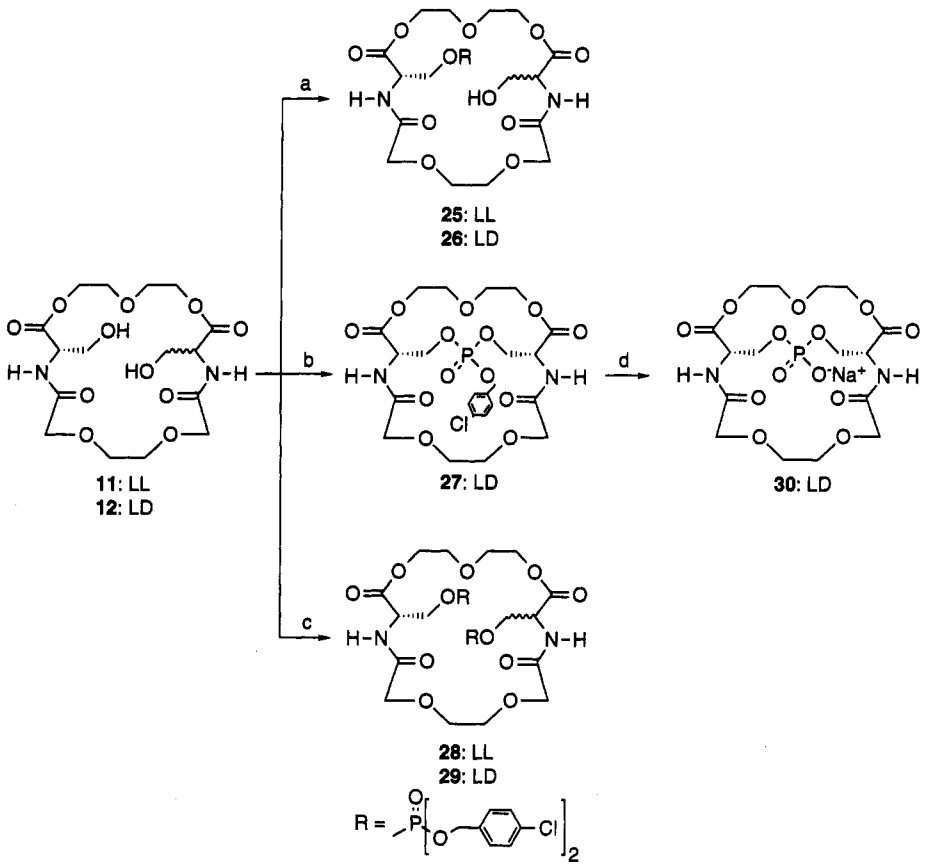
Scheme 3



Key: (a) (i) **22**, 1*H*-tetrazole, MeCN, (ii) *tert*-butyl hydroperoxide: **25** (24%), **26** (22%); (b) (i) **23**, DIPEA, CH_2Cl_2, (ii) *m*-CPBA: 31%; (c) **24**, 1*H*-tetrazole, CH_2Cl_2, (ii) *m*-CPBA: **28** (81%), **29** (68%); (d) (i) *t*-BuOH/H_2O, 10% Pd/C, H_2, NaOAc, (ii) Sephadex LH-20: 90%.

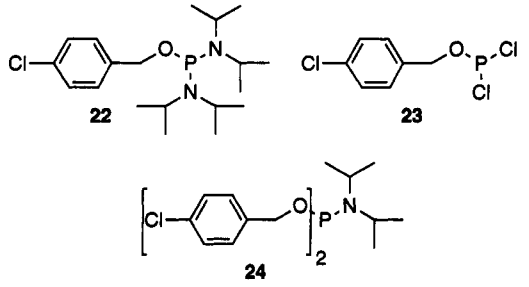


Figure 1.

of (ethylenedioxy)diacetic acid in the presence of 4-methylmorpholine, gave the LL- and LD-macrocycles **5** and **6** in 35 and 32% yield, respectively. Alternatively, LL-macrocycle **5** could be prepared by deprotection of **3** with HCl in ether followed by macrocyclization using the BOP-reagent[16] in 53% yield. Removal of the benzyl-protecting groups gave LL- and LD-"precursors"[12] **11** and **12** in quantitative yields (Scheme 1).

The phosphite triester method was employed for the introduction of the phosphodiester linkage, using 4-chlorobenzyl bis(*N,N*-diisopropyl)phosphorodiamidite (**22**)[2] (Figure 1) as a phosphitylating agent. However, addition of a solution of the phosphitylating agent to a solution containing the LL-precursor **11** and 2 equiv of 1*H*-tetrazole in acetonitrile, followed by oxidation with *tert*-butyl hydroperoxide, did not result in the formation of the corresponding protected LL-cryptand. The isolated product, obtained in 24% yield, was identified by NMR spectroscopy and FAB mass spectrometry as a monophosphorylated product, *viz.* compound **25** (Scheme 3). This monophosphorylated product **25** (Scheme 3) was probably formed by reaction of the phosphitylated intermediate and 4-chlorobenzyl alcohol, present as a contaminant in the phosphitylating agent **22**.

We assumed that the bisamidite phosphitylating agent might not have been reactive enough for the desired phosphitylation and that the more-reactive phosphitylating agent 4-chlorobenzyl phosphorodichloridite (**23**)[2] (Figure 1) would be more promising. However, despite many attempts we were still unable to introduce the phosphate linkage leading to the protected LL-cryptand. As expected, the monophosphorylated product **25** was not formed.[17] In trying to explain the unwillingness of forming the phosphodiester linkage, we reasoned that there might be some kind of geometrical constraint preventing the formation of the phosphate linkage. The most obvious cause of geometrical constraint is the stereochemistry of one of the serine residues.[3]

Indeed, addition of *N,N*-diisopropylethylamine and phosphitylating agent **23**[2] to a solution containing the corresponding LD-precursor **12** and subsequent oxidation with 3-chloroperbenzoic acid (*m*-CPBA) led to the protected LD-cryptand **27** in 31% yield (Scheme 3). Interestingly, it was not possible to obtain this compound using the less-reactive phosphitylating agent 4-chlorobenzyl bis-

(16) Castro, B.; Domoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219.

(17) Since the phosphitylating agent **23** is purified by distillation, it is not contaminated with 4-chlorobenzyl alcohol in contrast to **22**, which is prepared *in situ* and used without purification.

(*N,N*-diisopropyl)phosphorodiamidite (**22**) (Figure 1), although this reagent has been used previously with success to prepare cyclic phosphopeptides.[1,2] Phosphitylation of LD-precursor **12** using phosphitylating agent **22** gave the monophosphorylated LD-precursor **26** in 22% yield, analogous to the phosphitylation of LL-precursor **11** using phosphitylating agent **22** (*vide supra*). The diastereomeric phosphotriesters of **27**, in which the 4-chlorobenzyl group can be located either above the diethylene glycol chain of the molecule or above the bottom-spacer, could not be separated by short-column chromatography. However, separation using HPLC chromatography with a CN-column was possible. The diastereomeric ratio was 11:9, as was estimated by ^{1}H NMR spectroscopy, which is in agreement with the estimation by HPLC.

The diphosphorylated LL- and LD-macrocycles **28** and **29** (Scheme 3) were prepared using bis(4-chlorobenzyl) *N,N*-diisopropylphosphoramidite (**24**)[9c] (Figure 1) as a phosphitylating agent. To a solution containing the LL- or LD-precursor **11** or **12** and 2 equiv of phosphitylating agent **24**, was added 2 equiv of 1*H*-tetrazole. The intermediate phosphite triester was not isolated but directly oxidized using 3-chloroperbenzoic acid. Subsequent purification by short-column chromatography afforded the diphosphorylated LL- and LD-precursors **28** and **29** in 81 and 68%, respectively.

Hydrogenolysis of LD-cryptand **27** (Scheme 3) under buffered[9c] conditions, *i.e.* in the presence of sodium acetate, afforded the sodium salt of the LD-cryptand **30** in 90% yield (Scheme 3).

Instead of bottom-spacer **18**, also bottom-spacer **19** (Scheme 2), *viz.* oxydiacetic acid, was employed in order to obtain LL- and LD-precursor molecules, as is shown in Scheme 1. Removal of the Boc-groups of LL- and LD-top-halves **3** and **4**, followed by coupling with the di-Pfp-ester **21** of oxydiacetic acid in the presence of 4-methylmorpholine gave LL- and LD-macrocycles **7** and **8** in 36 and 32% yield, respectively. Removal of the benzyl-protecting groups gave LL- and LD-precursors **13** and **14** in quantitative yields.

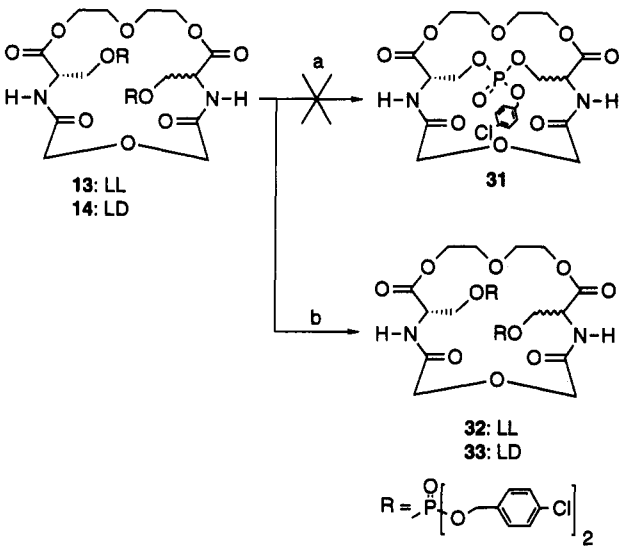
Introduction of the phosphodiester linkage by phosphitylation of LL- and LD-precursors **13** and **14**, using 4-chlorobenzyl bis(*N,N*-diisopropyl)phosphorodiamidite (**22**) or the more reactive 4-chlorobenzyl phosphorodichloridite (**23**), turned out to be impossible (Scheme 4). All attempts to obtain LL- or LD-cryptands **31** failed.

Computer-assisted molecular modeling studies showed that the LL- as well as the LD-precursor have to undergo extensive unfolding to form the protected LL- and LD-cryptands **31**, as was discussed in the case of the LL-precursor **11** containing (ethylenedioxy)diacetic acid as the bottom-spacer.[3] This indicated that not only the stereochemistry but also the length of the bottom-spacer is important in formation of the cryptand.

According to the procedure described for the diphosphitylation of LL- and LD-precursors, containing bottom-spacer **18** (*vide supra*), the diphosphorylated LL- and LD-precursors **32** and **33**, containing bottom-spacer **19**, were obtained with yields of 70 and 72%, respectively, as is shown in Scheme 4.

Unfortunately, cryptand **30** turned out to be quite soluble only in very polar solvents (*e.g.* methanol, water). As a consequence, studies of the binding properties were difficult and the results were poor. ^{1}H NMR spectroscopy (CD_3OD, D_2O) was used to investigate binding of cations

Scheme 4



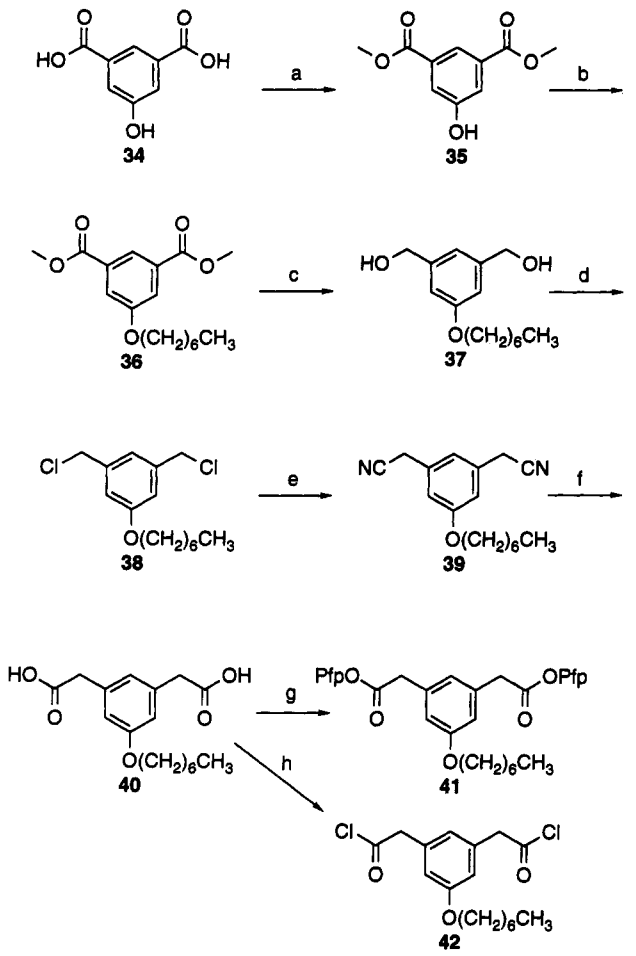
Key: (a) (i) **22**, 1*H*-tetrazole, MeCN, (ii) *tert*-butyl hydroperoxide or (i) **23**, DIPEA, CH_2Cl_2, (ii) *m*-CPBA; (b) **24**, 1*H*-tetrazole, CH_2Cl_2, (ii) *m*-CPBA: 36 (70%), **37** (72%).

by the cryptand, by looking at changes in the chemical shift values of the cryptand. In these solvents, the various proton signals, except for the (5 + 5′) signal, partly overlap, and therefore changes in the chemical shifts were difficult to detect. Upon addition of NaCl and KCl, only a small change in the chemical shift of the (5 + 5′) signal was observed. Addition of 1 equiv of NaCl led to the development of an AB pattern, and a maximum $\Delta\delta$ of 0.006 and 0.018 ppm, respectively, was observed. Addition of 0.5 equiv of KCl caused the appearance of an AB pattern, and a maximum $\Delta\delta$ of 0.007 and 0.026 ppm, respectively, was observed. Addition of up to 10 equiv of LiCl or *t*-$BuNH_3Cl$ did not influence any of the chemical shift values. The appearance of an AB pattern of the (5 + 5′) signal seems to indicate that the sodium and potassium ions interact in the vicinity of the bottom-spacer of the macrocycle.

In order to be able to study ultimately the host–guest complexation behavior of this type of receptor molecules, more lipophilic cryptand derivatives were designed. For ion-extraction and ion-transport studies, a more lipophilic cryptand, which is soluble in relatively nonpolar solvents such as chloroform, seems preferable. We designed cryptands in which the bottom-spacer was significantly more lipophilic. The length of this lipophilic spacer connecting the amino functions, and forming the bottom part of the molecule *i.e.* the bottom-spacer,[12] had to correspond roughly with the size of (ethylenedioxy)diacetic acid, since we found that a molecule containing a smaller bottom-spacer, *viz.* oxydiacetic acid, did not result in formation of the corresponding cryptand (*vide supra*). We decided to prepare the more lipophilic bottom-spacer based on commercially available 5-hydroxyisophthalic acid **34**, as is shown in Scheme 5. The corresponding dimethyl ester **35** was obtained after reaction with MeOH in presence of H_2SO_4 (cat.)[18] under reflux in 89% yield. Alkylation of **35** with heptyl iodide in the presence of K_2CO_3 afforded compound **36** in 94% yield. When octyl *bromide* was used

(18) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B.S., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R., Eds.; Longman Scientific & Technical: Harlow, Essex, 1989: p 1077.

Scheme 5

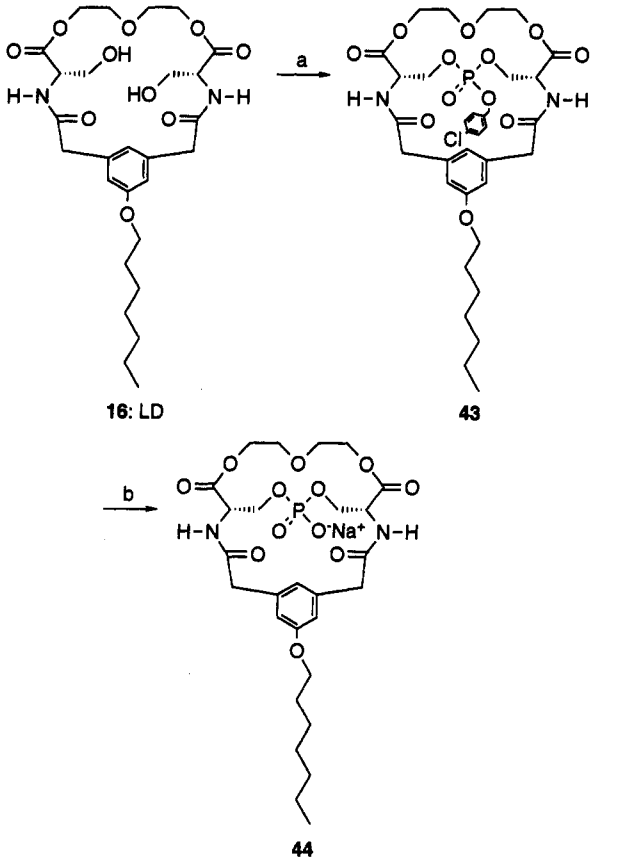


Key: (a) concd H_2SO_4 (cat.), MeOH, reflux (89%); (b) K_2CO_3, MeCN, 1-iodoheptane (94%); (c) $LiBH_4$, DME (100%); (d) MsCl, Et_3N, CH_2Cl_2 (100%); (e) 18-crown-6, Et_3N, KCN, MeCN (91%); (f) concd HCl, ΔT (92%); (g) Pfp-OH, dioxane; (h) oxalyl chloride, CH_2Cl_2.

instead of heptyl *iodide*, the monomethyl monooctyl ester monooctyl ether was obtained. Reduction of alkyl diester **36**, using $LiBH_4$ in dimethoxyethane,[19] gave diol **37** in a quantitative yield. Reaction of **37** with mesyl chloride in the presence of triethylamine did not lead to the expected mesylated product, but to the dichloride **38**, which was obtained in a quantitative yield. Substitution of the chloride atoms was achieved by reaction of **38** with KCN in the presence of 18-crown-6, as was described by Cook *et al.*[20] and afforded the dinitrile **39** in 91% yield. Hydrolysis of the dinitrile **39** by refluxing in concd HCl, gave diacid **40** in 92%. Reaction of **40** with pentafluorophenol and DCC gave the corresponding di-Pfp-ester[15] **41**, which was used without purification. The corresponding acid chloride **42** was obtained after reaction of diacid **41** with oxalyl chloride in CH_2Cl_2 (Scheme 5).

Macrocycles **9** and **10** were obtained by deprotection of the top-halves **3** and **4** with HCl in ether followed by coupling of the lipophilic diacid **40** using BOP[16] (Scheme 1). Other methods, previously used for the synthesis of macrocyles **5-8** were either unsuccesful (*e.g.* using di-Pfp-ester **41**), gave rise to a product which could not be purified

Scheme 6



Key: (a) (i) **23**, DIPEA, CH_2Cl_2, (ii) *m*-CPBA: 27%; (b) (i) *t*-BuOH/H_2O, 10% Pd/C, H_2, NaOAc, (ii) Sephadex LH-20: 95%.

(using the DCC/HOBt method[21]), or were low yielding (using acid chloride **42**: 7%).

Removal of the benzyl-protecting groups of LL- and LD-macrocycles **9** and **10** with 10% Pd/C under H_2 (4 atm, Parr apparatus), gave LL- and LD-precursors **15** and **16** both in a quantitative yield (Scheme 1).

Analogous to the preparation of cryptand **27** (Scheme 3) addition of *N,N*-diisopropylethylamine and phosphitylating agent **23** to a solution containing LD-precursor **16** and subsequent oxidation with 3-chloroperbenzoic acid (*m*-CPBA) led to the protected LD-cryptand **43** in 27% yield (Scheme 6). The diastereomeric phosphotriesters, in which the 4-chlorobenzyl group can be located either above the bottom-spacer or above the diethylene glycol chain of the molecule, could not be separated by short-column chromatography. The diastereomeric ratio was 9:7, as was estimated by ^1H NMR spectroscopy.

Removal of the 4-chlorobenzyl-protecting group of protected LD-cryptand **43** under buffered[9c] conditions, *i.e.* the presence of sodium acetate, afforded the sodium salt of LD-cryptand **44** in 95% yield.

Conclusions

In conclusion, the described method for the introduction of a phosphodiester linkage leading to a phosphocryptand provides a synthetic route to amino acid based phosphodiester linkage containing cryptands. As was shown

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by computer-assisted molecular modeling, the distance between both oxygens of the hydroxyl groups, and therefore the structure of the precursor molecules, is crucial to the formation of the phosphodiester linkage. An acid functionality, the phosphodiester, can be introduced in this type of molecules in a convergent manner. Due to the solubility of LD-cryptand **30** in only polar solvents, studies toward the host–guest complexation behavior were difficult and the results were poor.

In the preparation of the more lipophilic LD-cryptand **44**, a different macrocyclization reaction between the top-half and the bottom-spacer in order to prepare **10** had to be used. In this case, instead of using the Pfp-ester of the bottom-spacer, the macrocyclization was achieved using BOP[16] as a coupling agent. When the same conditions were used for the macrocyclization reaction between the Boc-deprotected LL-top-half **3** and the ethylene dioxyacetic acid bottom-spacer **18**, the yield of **5** increased from 35 to 53%.

The solubility of LD-cryptand **44** in more apolar solvents (*e.g.* CH_2Cl_2 and $CHCl_3$) is improved considerably as compared to LD-cryptand **30**. Therefore, we have high expectations that studies toward the binding properties of **44** will lead to better results. Indeed, preliminary studies of the binding of cations by cryptand **44** showed the binding of Zn^{2+}. Addition of 1 equiv of $ZnCl_2$ led to changes in the chemical shifts of the aromatic hydrogens (C^2H (0.024 ppm), C^4H and C^6H (0.023 ppm)), heptyl-OCH_2 (0.012 ppm), and the (5 + 5′) signals (0.026 and 0.022 ppm). For the protons (1 + 1′), (2 + 2′), Ser-C^2H, and Ser-C^3H, of which the signals overlap, $\Delta\delta$'s in the same order of magnitude were observed.

Experimental Section

General. Unless otherwise stated, chemicals were obtained from commercial sources and used without further purification. *N,N*-Diisopropylethylamine (DIPEA), oxalyl chloride, and mesyl chloride (MsCl) were distilled before use. "Dry" solvents were distilled immediately prior to use from an appropriate drying agent. Tetrahydrofuran (THF), ether, and dioxane were distilled from $LiAlH_4$. 4-Methylmorpholine, triethylamine, dimethoxyethane (DME), CH_2Cl_2, and CH_3CN were distilled from CaH_2. Reactions were monitored and R_f values were determined by thin-layer chromatography (TLC) on Merck precoated silica gel 60 F254 (0.25 mm) or on Merck precoated silica gel 60 F254, silanized (RP-2, 0.25 mm), with the indicated eluents. Eluents that were used: A, ether/petroleum ether, 9/1, v/v; B, EtOAc/MeOH, 9/1, v/v; C, CH_2Cl_2/MeOH, 9/1, v/v; D, MeOH/H_2O, 1/1, v/v; E, CH_2Cl_2/MeOH, 95/5, v/v; and F, CH_2Cl_2/MeOH, 96/4, v/v. Compounds were visualized by UV light and by dipping in one of the detection solutions, followed by heating the plate for a few minutes. Detection solutions that were used: A, ninhydrin solution, containing 3 mL of acetic acid and 0.30 g of ninhydrin in 1-butanol (100 mL); B, 10% aqueous H_2SO_4 solution (1 L), containing ammonium molybdate (25 g) and ammonium cerium(IV) sulfate (10 g); C, 4-methoxybenzaldehyde solution, containing 4-methoxybenzaldehyde (10 mL), acetic acid (5 mL), and concd H_2SO_4 (5 mL) in EtOH (180 mL); and D, potassium permanganate solution, an aqueous solution containing 2% potassium permanganate and 1% K_2CO_3. Short-column chromatography was performed on silica gel 60 (Merck, 230–400 mesh ASTM), with the indicated eluents. Flash chromatography[22] was performed on silica gel 60H (Merck) using the indicated eluents. Sephadex LH-20 (Pharmacia) was used for gel filtration. Organic layers, obtained after washing procedures, were dried on $MgSO_4$, filtered, and concentrated *in vacuo*.

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured on a 200-MHz spectrometer and when indicated on a 300-MHz or a 400-MHz spectrometer, operating in the Fourier transform mode. ^{31}P NMR spectra were measured on a 200-MHz apparatus. $CDCl_3$ was used as the solvent unless stated otherwise. TMS was used as internal and 85% H_3PO_4 as external standard. ^{13}C NMR spectra were measured using the Attached Proton Test (APT)[23] technique. The numbering of the carbon atoms in the amino acids is according to IUPAC recommendations.[24] The numbering of the atoms in the LL- and LD-macrocycles and their derivatives is according to the numbering as indicated in Scheme 1. The compounds were homogeneous according to NMR and TLC.

Boc-Ser(Bn)-O$(CH_2)_2$O$(CH_2)_2$OH 2. In dry CH_2Cl_2 (50 mL) were dissolved Boc-Ser(Bn)-OH (1, 5.91 g, 20.0 mmol), diethylene glycol (19.1 mL, 0.20 mol), and 4-(dimethylamino)pyridine (DMAP) (615 mg, 5.03 mmol). At 0 °C, *N,N*-dicyclohexylcarbodiimide (DCC) (4.74 g, 23.0 mmol) was added. After 1 h the ice bath was removed and the mixture was stirred for 1 h at ambient temperature. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (EtOAc) (50 mL) and washed with aqueous 1 N $KHSO_4$ (2 × 50 mL), aqueous saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL). After purification on a silica column (100 g silica, eluent: ether/petroleum ether, 85/15, v/v) afforded compound **2** (6.16 g, 16.1 mmol) in 80% yield as a colorless oil. Also some of the disubstituted diethylene glycol compound **3** was isolated (8%, 524 mg, 0.79 mmol): R_f(**2**) = 0.17; R_f(**3**) = 0.48 (eluent A, detection A). **2**: ^1H NMR δ 1.44 (s, 9 H), 2.90 (br s, 1 H), 3.52 (m, 2 H), 3.67 (m, 5 H), 3.89 (4 lines, B of ABX, 1 H, J_{BX} = 3.4 Hz, J_{AB} = 9.5 Hz), 4.30 (m, 2 H), 4.51 (m, 1 H), 4.47, 4.54 (2 d, 2 H, J = 12.1 Hz), 5.57 (d, 1 H, J = 8.7 Hz), 7.31 (m, 5 H); ^{13}C NMR δ 28.1, 53.8, 61.2, 64.1, 68.5, 69.6, 72.2, 73.0, 79.7, 127.4, 127.6, 128.1, 137.2, 155.3, 170.4.

LL-Top-Half 3. To a solution of compound **2** (3.07 g, 8.00 mmol) in dry CH_2Cl_2 (25 mL) were added DMAP (248 mg, 2.03 mmol) and Boc-Ser(Bn)-OH (1, 2.38 g, 8.05 mmol). At 0 °C, DCC (1.74 g, 8.42 mmol) was added. After 1 h the ice bath was removed and the mixture was stirred overnight at ambient temperature. The mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and washed with aqueous 1 N $KHSO_4$ (2 × 50 mL), aqueous saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL). After column chromatography on silica gel (100 g silica, eluent: ether/petroleum ether, 3/2, v/v) compound **3** (4.23 g, 6.40 mmol) was obtained as a white solid in 79% yield: R_f = 0.48 (eluent A, detection A); mp = 50 °C; ^1H NMR δ 1.44 (s, 18 H), 3.58 (m, 4 H), 3.68, 3.88 (8 lines, AB of ABX, 4 H, J_{AX} = J_{BX} = 3.3 Hz, J_{AB} = 9.5 Hz), 4.24 (m, 4 H), 4.45, 4.54 (2 d, 4 H, J = 12.2 Hz), 4.50 (m, 2 H), 5.45 (d, 2 H, J = 8.5 Hz), 7.30 (m, 10 H); ^{13}C NMR δ 28.2, 53.9, 64.2, 68.7, 69.9, 73.1, 79.8, 127.5, 127.7, 128.3, 137.4, 155.3, 170.5.

LD-Top-Half 4. To a solution of compound **2** (1.32 g, 3.44 mmol) in dry CH_2Cl_2 (10 mL) were added DMAP (107 mg, 0.88 mmol), Boc-D-Ser(Bn)-OH (1.02 g, 3.44 mmol), and DCC (752 mg, 3.64 mmol), according to the procedure described for the preparation of LL-top-half **3**. Purification on a silica gel column (50 g silica, eluent: ether/petroleum ether, 3/2, v/v) gave **4** (1.98 g, 2.99 mmol) as a colorless oil in 87% yield: R_f = 0.45 (eluent A, detection A); ^1H NMR δ 1.44 (s, 18 H), 3.59 (m, 4 H), 3.68, 3.85 (8 lines, AB of ABX, 4 H, J_{AX} = J_{BX} = 3.3 Hz, J_{AB} = 9.5 Hz), 4.24 (m, 4 H), 4.46, 4.53 (2 d, 4 H, J = 10.9 Hz), 4.48 (m, 2 H), 5.40 (d, 2 H, J = 8.0 Hz), 7.28 (m, 10 H); ^{13}C NMR δ 28.2, 53.9, 64.2, 68.7, 69.9, 73.1, 79.8, 127.5, 127.7, 128.3, 137.4, 155.3, 170.5.

Protected LL-Precursor 5. Method A. To a cooled (0 °C) solution of LL-top-half **3** (4.31 g, 6.53 mmol) in dry CH_2Cl_2 (15 mL) was added trifluoroacetic acid (TFA) (15 mL) and the mixture was stirred for 1 h at 0 °C. The reaction mixture was concentrated *in vacuo* and coevaporated with dry ether (5 × 10 mL). The residue was dissolved in dry THF (65 mL, c = 50 mM) and the pH was adjusted to pH 7–8 using 4-Me-morpholine. After addition of di-Pfp-ester **20** (3.49 g, 6.84 mmol), the mixture was stirred for 4 h at ambient temperature. The reaction mixture

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was then concentrated *in vacuo* and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with 1 N aqueous HCl (2 × 50 mL), water (50 mL), 5% aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL). Purification on a silica gel column (150 g silica, eluent: EtOAc/MeOH, 92.5/7.5, v/v) gave compound 5 (1.38 g, 2.28 mmol) in 35% yield as a colorless oil: R_f = 0.40 (eluent B, detection B).

Method B. The Boc groups of LL-top-half 3 (196 mg, 0.30 mmol) were removed by addition of a cold saturated solution of HCl in dry ether (5 mL). After 2 h at rt, the reaction mixture was concentrated *in vacuo*. The obtained solid was dissolved in dry CH_2Cl_2 (6 mL, c = 50 mM) and the pH was adjusted to pH 7–8 using 4-Me-morpholine. (Ethylenedioxy)acetic acid (18) (54 mg, 0.30 mmol) and BOP (280 mg, 0.63 mmol) were added at 0 °C. After 10 min, the ice bath was removed and the mixture was stirred overnight at rt. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in EtOAc (25 mL) and subsequently washed with 1 N aqueous $KHSO_4$ (2 × 15 mL), 5% aqueous $NaHCO_3$ (2 × 15 mL), and brine (15 mL). Purification by short-column chromatography (5 g silica, eluent CH_2Cl_2/MeOH, 99/1, v/v) afforded 5 (94 mg, 0.16 mmol) in 53% yield: 300-MHz ^{1}H NMR δ 3.62 (t, 4 H, J_{vic} = 4.5 Hz), 3.64 (m, 4 H), 3.77, 3.95 (8 lines, AB of ABX, 4 H, J_{AX} = 3.8 Hz, J_{AB} = 9.8 Hz, J_{BX} = 4.6 Hz), 3.93, 4.00 (2 d, 4 H, J = 15.9 Hz), 4.23, 4.30 (2 dt, 4 H, J_{gem} = 12.1 Hz), 4.52 (s, 4 H), 4.87 (m, 2 H), 7.29 (s, 10 H), 7.70 (d, 2 H, J = 8.7 Hz); 75-MHz ^{13}C NMR δ 52.0, 64.2, 68.7, 69.6, 70.3, 70.4, 73.0, 127.4, 127.6, 128.2, 137.4, 169.7, 169.9.

Protected LD-Precursor 6. Deprotection of 4 (2.28 g, 3.45 mmol) followed by macrocyclization was identical to that described for the preparation of LL-precursor 5 (method A). After purification on a silica gel column (80 g silica, eluent: EtOAc/MeOH, 92.5/7.5, v/v), 6 was obtained as a colorless oil (666 mg, 1.10 mmol, 32% yield): R_f = 0.40 (eluent B, detection B); ^{1}H NMR δ 3.61 (m, 4 H) 3.73 (s, 4 H), 3.75, 3.93 (8 lines, AB of ABX, 4 H, J_{AX} = 3.9 Hz, J_{AB} = 9.8 Hz, J_{BX} = 4.8 Hz), 4.05 (s, 4 H), 4.27 (m, 4 H), 4.46, 4.52 (2 d, 4 H, J = 8.3 Hz), 4.83 (m, 2 H), 7.29 (s, 10 H), 7.59 (d, 2 H, J = 8.3 Hz); ^{13}C NMR δ 51.9, 64.0, 68.4, 69.0, 70.0, 70.3, 72.6, 127.3, 127.4, 127.9, 137.1, 169.1, 169.7.

Protected LL-Precursor 7. The Boc groups of LL-top-half 3 (2.14 g, 3.24 mmol) were removed in CH_2Cl_2/TFA (1/1, v/v), according to the procedure described for the deprotection of compound 3 in the synthesis of the protected LL-precursor 5 (method A). The residue was dissolved in dry THF (c = 50 mM), and di-Pfp-ester 21 (1.59 g, 3.42 mmol) was added according to the procedure for the preparation of compound 5 (method A). Compound 7 (652 mg, 1.17 mmol) was obtained after purification on a silica gel column (40 g silica, eluent: EtOAc/MeOH, 92.5/7.5, v/v) as a colorless oil in 36% yield: R_f = 0.40 (eluent B, detection B); ^{1}H NMR δ 3.54 (m, 4 H), 3.72, 4.01 (8 lines, AB of ABX, 4 H, J_{AX} = 3.3 Hz, J_{AB} = 9.3 Hz, J_{BX} = 3.1 Hz), 3.93 (m, 2 H, 3.99), 4.24, J = 15.1 Hz), 4.44 (m, 2H), 4.50 (s, 4 H), 4.87 (dt, 2 H, J_{XA} = J_{XB} = 3.2 Hz, J_{XNH} = 9.3 Hz), 7.28 (m, 10 H), 7.39 (d, 2 H); ^{13}C NMR δ 52.4, 64.8, 68.7, 70.3, 70.4, 73.3, 127.6, 127.8, 128.2, 137.2, 167.7, 169.0.

Protected LD-Precursor 8. The Boc groups of LD-top-half 4 (3.00 g, 4.55 mmol) were removed in CH_2Cl_2/TFA (1/1, v/v), according to the procedure described for the deprotection of LL-top-half 3 in the synthesis of LL-precursor 5 (method A). The residue was dissolved in dry THF (c = 50 mM), and di-Pfp-ester 21 (2.23 g, 4.78 mmol) was added according to the procedure for the preparation of compound 5 (method A). Purification on a silica gel column (50 g silica, eluent: EtOAc/MeOH, 92.5/7.5, v/v) gave 8 (789 mg, 1.41 mmol) as a colorless oil in 31% yield: R_f = 0.40 (eluent B, detection B); ^{1}H NMR δ 3.64 (m, 4 H), 3.71, 3.98 (8 lines, AB of ABX, 4 H, J_{AX} = 3.5 Hz, J_{AB} = 9.6 Hz, J_{BX} = 3.7 Hz), 4.19, 4.34 (16 lines, AB of ABXY, 4 H, J_{AX} = 5.1 Hz, J_{AY} = 2.3 Hz, J_{AB} = 12.1 Hz, J_{BX} = 2.6 Hz, J_{BY} = 6.8 Hz), 4.08, 4.16 (2 d, 4 H, J = 14.9 Hz), 4.47 (s, 4 H), 4.98 (dt, 2 H, J_{AX} = J_{BX} = 3.6 Hz, J_{XNH} = 9.3 Hz), 7.28 (m, 10 H), 7.59 (d, 2 H); ^{13}C NMR δ 51.9, 64.5, 68.4, 69.7, 70.0, 72.9, 127.4, 127.6, 128.1, 137.0, 167.8, 168.9.

Protected LL-Precursor Benzene Derivative 9. The synthesis of this precursor was analogous to that described for LL-precursor 5 via method B. The Boc groups of LL-top-half 3 (1.13 g, 1.70 mmol) were removed using a saturated solution of HCl in dry ether. The residue was dissolved in dry CH_2Cl_2 (c = 50 mM); subsequently diacid 40 (525 mg, 1.70 mmol) and BOP (1.58 g, 3.57 mmol) were added. Purification by short-column chromatography (30 g silica, eluent: CH_2Cl_2/MeOH, 99/1, v/v) afforded compound 9 (374 mg, 0.51 mmol) as a colorless oil in 30% yield: R_f = 0.45 (eluent F, detection A and B); 400-MHz ^{1}H NMR δ 0.89 (t, 3 H, J = 6.8 Hz), 1.31 (m, 6 H), 1.42 (m, 2 H), 1.75 (5 lines, 2 H), 3.52, 3.58 (2 d, 4 H, J = 15.8 Hz), 3.55 (m, 4 H), 3.66, 3.87 (8 lines, AB of ABX, 4 H, J_{AX} = 3.6 Hz, J_{AB} = 9.6 Hz, J_{BX} = 3.9 Hz), 3.89, 3.93 (2 dt, 2 H, J_{AX} = J_{BX} = 6.5 Hz, J_{AB} = 9.0 Hz), 4.18, 4.22 (14 lines, AB of ABXY, 4 H, J_{AX} = 3.7 Hz, J_{AY} = 5.7 Hz, J_{AB} = 11.9 Hz, J_{BX} = 3.6 Hz, J_{BY} = 5.4 Hz), 4.46 (s, 4 H), 4.70 (dt, 2 H, J_{HNH} = 8.0 Hz), 6.43 (d, 2 H), 6.75 (d, 2 H, J = 1.1 Hz), 6.93 (t, 1 H), 7.26 (m, 10 H); 100-MHz ^{13}C NMR δ 14.0, 22.6, 26.0, 29.0, 29.2, 31.7, 43.6, 52.9, 64.5, 68.0, 69.0, 69.3, 73.2, 114.6, 122.2, 127.6, 127.8, 128.4, 136.6, 137.5, 159.9, 169.8, 170.5.

Protected LD-Precursor Benzene Derivative 10. Deprotection of 4 (1.13 g, 1.70 mmol) followed by macrocyclization was identical to that described for the preparation of LL-precursor 9. Compound 10 (369 mg, 0.50 mmol) was obtained after column chromatography (30 g silica, eluent: CH_2Cl_2/MeOH, 99/1, v/v) as a colorless oil in 30% yield: R_f = 0.45 (eluent F, detection A and B); 400-MHz ^{1}H NMR δ 0.89 (t, 3 H, J = 6.8 Hz), 1.32 (m, 6 H), 1.41 (m, 2 H), 1.75 (5 lines, 2 H, J = 6.6 Hz), 3.50, 3.60 (2 d, 4 H, J = 15.8 Hz), 3.53, 3.61 (16 lines, AB of ABXY, J_{AX} = 5.5 Hz, J_{AY} = 2.7 Hz, J_{AB} =11.5 Hz, J_{BX} =2.6 Hz, J_{BY} = 6.9 Hz), 3.64, 3.81 (8 lines, AB of ABX, 4 H, J_{AX} = 3.6 Hz, J_{AB} = 9.7 Hz, J_{BX} = 4.4 Hz), 3.90 (t, 2 H, J = 6.5 Hz), 4.14, 4.28 (16 lines, XY of ABXY, 4 H, J_{XY} = 12.1 Hz), 4.39, 4.41 (2 d, 4 H, J = 12.0 Hz), 4.85 (dt, 2 H, J_{vic} = 3.9 Hz, J_{HNH} = 8.3 Hz), 6.66 (d, 2 H,), 6.74 (d, 2 H, C^{4}H, C^{6}H, J = 1.1 Hz), 6.86 (t, 1 H), 7.24 (m, 10 H); 100-MHz ^{13}C NMR δ 14.0, 22.5, 26.0, 29.0, 29.2, 31.7, 43.6, 52.6, 64.5, 68.1, 68.9, 69.7, 73.0, 114.6, 122.6, 127.6, 127.8, 128.4, 136.5, 159.8, 169.7, 170.5.

LL-Precursor 11. To a solution of protected LL-precursor 5 (1.45 g, 2.40 mmol) in MeOH (20 mL) was added a catalytic amount of 10% Pd/C. The mixture was slowly stirred overnight under a H_2 atmosphere (balloon). The reaction mixture was centrifuged, and the supernatant was filtered over a millipore filter (0.2 μm) and concentrated *in vacuo* to yield 11 (1.02 g, 2.40 mmol) quantitatively as a colorless oil: R_f = 0.35 (eluent C, detection C); 300-MHz ^{1}H NMR δ 3.58, 3.67 (16 lines, AB of ABXY, 4 H, J_{AX} = 4.6 Hz, J_{AY} = 2.7 Hz, J_{AB} = 11.4 Hz, J_{BX} = 2.5 Hz, J_{BY} = 7.8 Hz), 3.70, 3.74 (2 d, 4 H, J = 9.7 Hz), 3.80, 3.98 (8 lines, AB of ABX, 4 H, J_{AX} = 3.9 Hz, J_{AB} = 11.6 Hz, J_{BX} = 4.4 Hz), 3.91 (s, 2 H), 3.98, 4.07 (2 d, 4 H, J = 15.9 Hz), 4.12, 4.49 (16 lines, XY of ABXY, 4 H, J_{XY} = 12.1 Hz), 4.59 (dt, 2 H, J_{XA} = J_{XB} = 4.1 Hz, J_{XNH} = 8.3 Hz), 7.82 (d, 2 H); ^{13}C NMR δ 54.0, 61.7, 63.5, 68.6, 69.8, 70.5, 170.1, 170.7.

LD-Precursor 12. The hydrogenolysis of 6 (1.25 g, 2.07 mmol) was carried out as was described for the preparation of LL-precursor 11. A colorless oil (874 mg, 2.07 mmol) was obtained in a quantitative yield: R_f = 0.38 (eluent C, detection C); 300-MHz ^{1}H NMR δ (CD_3OD) 3.71 (t, 4 H, J_{vic} = 4.2 Hz), 3.77 (m, 4 H), 3.84, 3.97 (8 lines, AB of ABX, 4 H, J_{AX} = 4.0 Hz, J_{AB} = 11.4 Hz, J_{BX} = 4.9 Hz), 4.10 (s, 4 H), 4.29, 4.35 (2 dt, 4 H, J_{gem} = 11.7 Hz), 4.61 (dd, 2 H); ^{13}C NMR δ (CD_3OD) 55.8, 62.8, 65.5, 69.9, 71.0, 71.8, 171.2, 172.6.

LL-Precursor 13. The hydrogenolysis of 7 (652 mg, 1.17 mmol) was carried out as was described for the preparation of LL-precursor 11. A colorless oil (442 mg, 1.17 mmol) was obtained in a quantitative yield: R_f = 0.22 (eluent C, detection C); 300-MHz ^{1}H NMR δ 3.73 (m, 4 H), 3.88, 3.99 (8 lines, AB of ABX, 4 H, J_{AX} = 4.2 Hz, J_{AB} = 11.3 Hz, J_{BX} = 4.8 Hz), 4.15, 4.23 (2 d, 4 H, J = 15.1 Hz), 4.23, 4.43 (2 × 7 lines, 4 H), 4.53 (br s, 2 H), 4.68 (m, 2 H), 8.33 (d, 2 H, 2 Ser-NH, J = 8.4 Hz); 75 MHz ^{13}C NMR δ ($CDCl_3$) 55.2, 62.4, 65.1, 69.4, 71.1, 170.4, 170.7; ^{13}C NMR δ (CD_3OD) 56.0, 62.8, 65.8, 70.1, 71.7, 171.1, 171.7.

LD-Precursor 14. The hydrogenolysis of 8 (789 mg, 1.41 mmol) was carried out as was described for the preparation of LL-precursor 11. Compound 14 (534 mg, 1.41 mmol) was obtained in a quantitative yield as a colorless oil: R_f = 0.29 (eluent C, detection C); 300-MHz ^{1}H NMR δ (CD_3OD) 3.70, 3.77 (16 lines, AB of ABXY, 4 H, J_{AX} = 4.6 Hz, J_{AY} = 2.6 Hz, J_{AB} = 11.3 Hz, J_{BX} = 2.3 Hz, J_{BY} = 7.7 Hz), 3.86, 3.95 (8 lines, AB of ABX, 4 H, J_{AX} = 4.3 Hz, J_{AB} = 11.3 Hz, J_{BX} = 5.2 Hz), 4.12, 4.21 (2 d,

4 H, J = 15.0 Hz), 4.21, 4.39 (16 lines, XY of ABXY, 4 H, J_{XY} = 12.4 Hz), 4.78 (t, 2 H, $J_{XA} = J_{XB}$ = 4.7 Hz); ^{13}C NMR δ (CD_3OD) 55.6, 62.8, 65.9, 70.0, 71.3, 171.4.

LL-Precursor Benzene Derivative 15. To a solution of protected LL-precursor **9** (374 mg, 0.51 mmol) in MeOH (25 mL) was added a catalytic amount of 10% Pd/C. The mixture was shaken under H_2 atmosphere (4 atm, Parr apparatus) overnight at ambient temperature. The mixture was filtered over Celite and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered over a millipore filter (0.2 μm), and concentrated *in vacuo* to afford **15** (282 mg, 0.51 mmol) in a quantitative yield as a colorless solid: R_f = 0.39 (eluent C, detection B); 300-MHz ^{1}H NMR (CD_3OD) δ 0.90 (t, 3 H, J = 6.9 Hz), 1.33 (m, 6 H), 1.45 (m, 2 H), 1.76 (6 lines, 2 H), 3.44, 3.62 (2 d, 4 H, J = 14.4 Hz), 3.48 (m, 4 H), 3.76, 3.82 (8 lines, AB of ABX, 4 H, J_{AX} = 4.7 Hz, J_{AB} = 11.2 Hz, J_{BX} = 5.5 Hz), 3.97 (t, 2 H, J = 6.3 Hz), 4.12, 4.15 (12 lines, AB of ABX_2, 4 H, J_{AX} = 4.8 Hz, J_{AB} = 11.9 Hz, J_{BX} = 4.9 Hz), 4.42 (t, 2 H), 6.84 (d, 2 H, J = 1.4 Hz), 6.87 (t, 1 H); ^{13}C NMR (CD_3OD) δ 14.7, 23.9, 27.2, 30.1, 30.4, 32.9, 43.5, 56.7, 62.5, 65.6, 68.9, 70.1, 115.2, 123.3, 138.3, 160.5, 171.6, 173.1.

LD-Precursor Benzene Derivative 16. Protected LD-precursor **10** (984 mg, 1.34 mmol) in MeOH was treated under the same conditions as were employed for the hydrogenolysis of protected LL-precursor **9**. A colorless solid (702 mg, 1.34 mmol) was obtained in a quantitative yield: R_f = 0.36 (eluent F, detection A and B); 300-MHz ^{1}H NMR (CD_3OD) δ 0.90 (t, 3 H, J = 6.8 Hz), 1.34 (m, 6 H), 1.46 (m, 2 H), 1.78 (5 lines, 2 H), 3.57, 3.62 (2 d, 4 H, J = 15.1 Hz), 3.59 (m, 4 H), 3.79, 3.94 (8 lines, AB of ABX, J_{AX} = 3.9 Hz, J_{BX} = 4.4 Hz, J_{AB} = 11.5 Hz), 3.97 (t, 2 H, J = 6.4 Hz), 4.20, 4.32 (16 lines, AB of ABX_2, J_{AX} = 3.6 Hz, J_{AY} = 5.0 Hz, J_{AB} = 12.0 Hz, J_{BX} = 3.8 Hz, J_{BY} = 5.9 Hz), 4.55 (m, 2 H), 6.81 (d, 2 H, J = 1.4 Hz), 6.93 (t, 1 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 14.2, 22.0, 25.5, 28.5, 28.7, 31.2, 42.5, 54.6, 61.3, 63.9, 67.5, 68.4, 113.9, 121.7, 136.0, 159.3, 169.7, 171.5.

(Ethylenedioxy)diacetic Acid 18. This dicarboxylic acid was prepared according to the procedure as described by Dietrich *et al.*[13] After recrystallization from acetone/benzene, **18** was obtained contaminated with ca. 20% (by NMR) oxydiacetic acid (**19**) (21.99 g, 0.13 mol, combined yield of 95%). NMR data of **18**: ^{1}H NMR δ (D_2O) 3.78 (s, 4 H), 4.23 (s, 4 H), 4.94 (s, 2 H); ^{13}C NMR δ (D_2O) 68.0, 70.5, 174.6. NMR data of **19**: ^{1}H NMR δ (D_2O) 4.29 (s, 4 H), 4.94 (s, 2 H); ^{13}C NMR δ (D_2O) 68.0, 174.6.

(Ethylenedioxy)diacetic Acid Pfp-Ester 20. A solution of the contaminated (ethylenedioxy)diacetic acid (assuming pure **18**, 4.84 g, 27.2 mmol) and pentafluorophenol (Pfp-OH) (10.0 g, 54.3 mmol) in dry dioxane (50 mL) was cooled to 0 °C, and DCC (11.2 g, 54.5 mmol) was added. After 30 min, the ice bath was removed and the mixture was stirred for 3.5 h at rt. After filtration and concentration *in vacuo*, compound **20** was obtained as white solid. Crystallization from hexane afforded pure **20** (10.7 g, 20.9 mmol) in 77% yield; compound **21** remained in the mother liquor. **20**: mp = 75 °C; ^{1}H NMR δ 3.91 (s, 4 H), 4.57 (s, 4 H); ^{13}C NMR δ 67.8, 71.3, 166.5.

Oxydiacetic Acid Pfp-Ester 21. The Pfp-ester of oxydiacetic acid was prepared according to the procedure described for the preparation of the di-Pfp-ester **20** of (ethylenedioxy)diacetic acid, starting from oxydiacetic acid (**19**, 1.59 g, 11.8 mmol). Crystallization from hexane yielded **21** (4.64 g, 9.96 mmol) in 84% yield: mp = 100 °C; ^{1}H NMR δ 4.70 (s); ^{13}C NMR δ 67.3.

Monophosphorylated LL-Precursor 25. LL-Precursor **11** (283 mg, 0.67 mmol) and 1*H*-tetrazole (94 mg, 1.35 mmol) were coevaporated with dry dioxane (5 × 5 mL) and subsequently dissolved in dry CH_3CN (13.4 mL). Under argon a 0.15 M solution of freshly prepared 4-chlorobenzyl bis(*N*,*N*-diisopropyl)phosphorodiamidite[2] (**22**) in dry CH_3CN (8.95 mL) was added dropwise (0.4 mL/h). After stirring overnight, another 2 equiv of 1*H*-tetrazole and **22** were added and the mixture was stirred for 24 h. The intermediate phosphite triester (R_f = 0.45, eluent C, detection C) was oxidized with 80% *tert*-butyl hydroperoxide (0.50 mL, 4.01 mmol) in 2 h at rt. A solution of 10% aqueous $NaHSO_3$ (25 mL) was then added, and the reaction mixture was concentrated *in vacuo* after 10 min. EtOAc (50 mL) was added to the residue and the organic layer was washed with 10% aqueous $NaHSO_3$ (2 × 25 mL) and brine (25 mL). After purification by flash chromatography (eluent E), compound **25** (121 mg, 0.16 mmol) was obtained as a white solid in 24% yield: R_f = 0.41 (eluent C, detection C); 300-MHz ^{1}H NMR δ ($CDCl_3/CD_3OD$) 3.66 (m, 4 H), 3.73 (s, 4 H), 3.86, 3.98 (8 lines, AB of ABX, 2 H, J_{AX} = 4.0 Hz, J_{AB} = 11.4 Hz, J_{BX} = 5.1 Hz), 4.00, 4.14 (2 d, 2 H, J = 16.1 Hz), 4.06 (s, 2 H, 4.21 (8 lines, A of ABXY, 1 H, J_{AX} = 2.5 Hz, J_{AY} = 5.2 Hz, J_{AB} = 12.1 Hz), 4.34 (m, 2 H), 4.43 (m, 3 H), 4.64 (t, 1 H, $J_{XA} = J_{XB}$ = 4.4 Hz), 4.88 (dt, 1 H, J_{vic} = 5.1 Hz, J_{HP} = 1.0 Hz), 2 × 5.03 (2 d, 4 H, J_{HP} = 8.7 Hz), 7.32 (m, 8 H); ^{13}C NMR δ ($CDCl_3/CD_3OD$) 52.9 (J = 7.3 Hz), 55.0, 62.5, 64.5, 64.9, 67.2 (J = 5.9 Hz), 69.4, 2 × 69.5, 69.6, 70.6 (J = 8.8 Hz), 2 × 71.4, 129.4, 130.1, 169.1, 171.0, 171.8, 171.9; ^{31}P NMR δ ($CDCl_3/CD_3OD$) −0.44. MS (FAB) *m/e* 773 $(M + Na)^+$, 751 $(M + H)^+$, 405 $(M + H - C_{14}H_{12}O_4PCl_2)^+$.

Monophosphorylated LD-Precursor 26. To a solution of LD-precursor **12** (196 mg, 0.46 mmol) and 1*H*-tetrazole (72 mg, 1.02 mmol) in dry CH_3CN was added dropwise a solution of 4-chlorobenzyl bis(*N*,*N*-diisopropyl)phosphorodiamidite (**22**) in dry CH_3CN, as was described for the preparation of monophosphorylated LL-precursor **25**. Purification by flash chromatography (E) yielded compound **26** (77 mg, 0.10 mmol) as a white solid in 22% yield: R_f = 0.39 (eluent C, detection C); 300-MHz ^{1}H NMR δ ($CDCl_3/CD_3OD$) 3.67 (m, 4 H), 3.75 (s, 4 H), 3.83, 3.96 (8 lines, AB of ABX, 2 H, J_{AX} = 4.0 Hz, J_{AB} = 11.2 Hz, J_{BX} = 5.1 Hz), 3.98, 4.10 (2 d, 2 H, J = 16.0 Hz), 4.08 (s, 2 H, 4.25 (8 lines, A of ABXY, 1 H, J_{AX} = 2.2 Hz, J_{AY} = 5.0 Hz, J_{AB} = 12.1 Hz), 4.36 (m, 2 H), 4.40 (m, 3 H), 4.63 (t, 1 H, $J_{XA} = J_{XB}$ = 4.4 Hz), 4.85 (dt, 1 H, J_{vic} = 5.3 Hz, J_{HP} = 1.2 Hz), 4.99, 5.01 (2 d, 4 H, J_{HP} = 8.8 Hz), 7.29 (m, 8 H); ^{13}C NMR δ ($CDCl_3/CD_3OD$) 52.9 (J = 7.2 Hz), 54.9, 62.6, 64.5, 64.9, 67.4 (J = 5.9 Hz), 69.3, 2 × 69.4, 69.5, 70.4 (J = 8.8 Hz), 2 × 71.3, 129.2, 129.9, 169.1, 170.9, 171.7, 171.9; ^{31}P NMR δ ($CDCl_3/CD_3OD$) −0.51.

LD-Cryptand with a Protected Phosphodiester 27. LD-Precursor **12** (166 mg, 0.39 mmol) was coevaporated with dry dioxane (5 × 5 mL) and subsequently dissolved in dry CH_2Cl_2 (2.00 mL) resulting in a 0.25 M solution of the starting material. Under argon, successively DIPEA (175 μL, 1.03 mmol) and 4-chlorobenzyl phosphorodichloridite[2] (**23**, 50 μL, 0.48 mmol) were added. The reaction mixture was stirred overnight at ambient temperature. Oxidation of the obtained phosphite triester to the corresponding phosphate triester was carried out by addition of 3-chloroperbenzoic acid (*m*-CPBA) (55%, 314 mg, 1.00 mmol) at 0 °C, followed by stirring for 2 h at rt. A solution of 10% aqueous $NaHSO_3$ (25 mL) was then added and the reaction mixture was concentrated *in vacuo* after 10 min. The residue was dissolved in EtOAc (50 mL) and the organic layer was washed with 10% aqueous $NaHSO_3$ (2 × 25 mL) and brine (25 mL). After purification by column chromatography (10 g silica, eluent: EtOAc/MeOH, 9/1, v/v) compound **27** (75 mg, 0.12 mmol) was isolated as a white solid in 31% yield. The diastereoisomers could not be separated using short-column chromatography. However, separation using HPLC chromatography with a CN-column (eluent: gradient from 0.1% TFA in water to 0.1% TFA in acetonitrile/water (2/1, v/v)) was possible and the diastereomers were obtained in a ratio of 11:9, which was in agreement with the estimation by ^{1}H NMR: R_f = 0.51 (eluent C, detection C).

NMR data of diastereoisomer **27a** formed in excess: 400-MHz ^{1}H NMR δ 3.61 (m, 6 H), 3.82 (m, 2 H), 4.02, 4.08 (2 d, 4 H, J = 15.6 Hz), 4.14, 4.56 (14 lines, AB of ABX, 4 H, J_{AX} = 3.6 Hz, J_{AB} = 10.4 Hz, J_{AP} = 6.6 Hz, J_{BX} = 3.0 Hz, J_{BP} = 7.8 Hz), 4.22, 4.64 (16 lines, AB of ABXY, 4 H, J_{AX} = 2.4 Hz, J_{AY} = 4.5 Hz, J_{AB} = 12.1 Hz, J_{BX} = 8.0 Hz, J_{BY} = 2.5 Hz), 4.91 (7 lines, 2 H, $J_{XA} = J_{XB} = J_{XP}$ = 3.0 Hz, J_{XNH} = 8.9 Hz), 5.06 (d, 2 H, J_{HP} = 9.9 Hz), 7.33 (m, 4 H), 7.45 (d, 2 H); 100-MHz ^{13}C NMR δ 51.7 (J = 6.4 Hz), 64.6, 67.5 (J = 4.9 Hz), 69.0, 69.6, 70.3, 70.5, 129.0, 129.6, 133.7, 135.0, 168.3, 169.5; ^{31}P NMR δ (CD_3OD) −1.09.

NMR data of diastereoisomer **27b**: 400-MHz ^{1}H NMR δ 3.61 (m, 4 H), 3.82 (m, 4 H, 4.07, 4.15 (2 d, 4 H, J = 15.8 Hz), 4.38 (m, 8 H), 4.83 (7 lines, 2 H, $J_{vic} = J_{HP}$ = 2.7 Hz, J_{HNH} = 8.0 Hz), 5.01 (d, 2 H, J_{HP} = 9.5 Hz), 7.33 (m, 4 H), 8.07 (d, 2 H); 100-MHz ^{13}C NMR δ 52.9 (J = 4.0 Hz), 64.4, 67.8 (J = 4.3 Hz), 68.8, 69.3 (J = 5.8 Hz), 70.4, 70.6, 129.0, 129.3, 133.5, 134.9, 168.4, 170.2; ^{31}P NMR δ (CD_3OD) 2.51; MS (FAB) *m/e* 631 $(M + Na,^{35}Cl)^+$, 611 $(M + H,^{37}Cl)^+$, 609 $(M + H,^{35}Cl)^+$, 387 $(M + H - C_7H_6O_4PCl)^+$.

Diphosphorylated LL-Precursor 28. LL-Precursor **11** (190 mg, 0.45 mmol) and bis(4-chlorobenzyl) *N*,*N*-diisopropylphosphorodiamidite (**24**)[9c,h] (391 mg, 0.95 mmol) were coevaporated

with dry dioxane (5 × 5 mL) and subsequently dissolved in dry CH_2Cl_2 (2.00 mL). Under argon, 1*H*-tetrazole (82 mg, 1.17 mmol) was added. After stirring for 6 h the intermediate phosphite triester (R_f = 0.82, eluent C, detection C) was oxidized with *m*-CPBA (55%, 567 mg, 1.81 mmol) in 2 h at rt. A solution of 10% aqueous $NaHSO_3$ (25 mL) was then added and the reaction mixture was concentrated *in vacuo* after 10 min. EtOAc (50 mL) was added to the residue and the organic layer was washed with 10% aqueous $NaHSO_3$ (2 × 25 mL) and brine (25 mL). After purification by column chromatography (15 g silica, eluent: CH_2Cl_2/MeOH, 97.5/2.5, v/v), compound **28** (396 mg, 0.37 mmol) was obtained as a white solid in 81% yield: R_f = 0.59 (eluent C, detection C); 300-MHz ^{1}H NMR δ ($CDCl_3/CD_3OD$) 3.59 (m, 4 H), 3.66 (s, 4 H), 3.98, 4.05 (2 d, 4 H, J = 16.0 Hz), 4.21, 4.38 (16 lines, AB of ABXY, 4 H, J_{AX} = 2.8 Hz, J_{AY} = 5.0 Hz, J_{AB} = 12.1 Hz, J_{BX} = 6.7 Hz, J_{BY} = 3.4 Hz), 4.40 (dd, 4 H), J_{vic} = 5.3 Hz, J_{HP} = 7.3 Hz), 4.84 (dt, 2 H, J_{HP} = 1.1 Hz), 5.01, 5.02 (2 d, 8 H, J_{HP} = 8.8 Hz), 7.31 (m, 16 H), 8.17 (d, 2 H, J = 8.3 Hz); ^{13}C NMR δ 52.1 (J = 7.3 Hz), 63.8, 66.6 (J = 5.9 Hz), 68.5 (J = 4.4 Hz), 68.7, 70.1, 70.6, 128.7, 129.2, 133.8, 134.4, 168.3, 171.1; ^{31}P NMR δ ($CDCl_3/CD_3OD$) −0.41. MS (FAB) *m/e* 1104 (M + Na)$^+$, 977 (M + H − $C_7H_6Cl)^+$, 733 (M + H − $C_{14}H_{12}O_4PCl_2)^+$, 609 (M + H − $C_{21}H_{18}O_4PCl_3)^+$.

Diphosphorylated LD-Precursor 29. To a solution of LD-precursor **12** (202 mg, 0.48 mmol) and bis(4-chlorobenzyl) *N,N*-diisopropylphosphorodiamidite (**24**) (391 mg, 0.95 mmol) in dry CH_2Cl_2 was added 1*H*-tetrazole (139 mg, 1.98 mmol), according to the procedure described for the preparation of the protected diphosphate **28**. Compound **29** (353 mg, 0.33 mmol) was obtained after purification on a silica gel column (15 g silica, eluent: CH_2Cl_2/MeOH, 97.5/2.5, v/v) as a white solid in 68% yield: R_f = 0.61 (eluent C, detection C); 300-MHz ^{1}H NMR δ (CD_3OD) 3.59 (m, 8 H), 3.91, 4.07 (2 d, 4 H, J = 16.0 Hz), 4.19, 4.28 (12 lines, AB of ABX_2, 4 H, J_{AX} = 4.4 Hz, J_{AB} = 12.1 Hz, J_{BX} = 4.1 Hz), 4.46 (m, 4 H) 4.85 (t, 2 H, J_{vic} = 5.0 Hz), 4.96, 4.98 (2 d, 8 H, J_{HP} = 8.5 Hz, J_{HP} = 8.7 Hz), 7.23 (m, 16 H); ^{13}C NMR δ ($CDCl_3/CD_3OD$) 51.7 (J = 7.3 Hz), 63.9, 66.1 (J = 4.4 Hz), 68.0, 68.3, 68.4 (J = 4.4 Hz), 69.3, 70.1, 128.1, 129.0, 133.2, 133.3, 133.9, 167.7, 170.8; ^{31}P NMR δ ($CDCl_3/CD_3OD$) −0.60.

LD-Cryptand 30. A suspension of LD-cryptand phosphotriester **27** (75 mg, 0.12 mmol), sodium acetate (18 mg, 0.13 mmol), and 10% Pd/C in *t*-BuOH/H_2O (4/1, v/v, 5 mL) was slowly stirred under a H_2 atmosphere (balloon) for 2 h at rt. The reaction mixture was centrifuged, and the supernatant was filtered over a millipore filter (0.2 μm) and concentrated *in vacuo*. The reaction afforded, after purification on Sephadex LH-20 (100% MeOH) and lyophilization, a white solid (55 mg, 0.11 mmol) in 90% yield. Compound **30** was pure on TLC (RP-2, R_f = 0.76, eluent D, detection C) and according to NMR: 400-MHz ^{1}H NMR δ (CD_3OD) 3.60 (m, 4 H), 3.82 (m, 4 H), 3.99, 4.17 (2 d, 4 H, J = 15.8 Hz), 4.31 (m, 4 H), 4.28, 4.34 (12 lines, AB of ABX, 4 H, J_{AX} = 3.3 Hz, J_{AB} = J_{AP} = J_{BP} = 12.1 Hz, J_{BX} = 5.6 Hz), 4.58 (dd, 2 H); 100-MHz ^{13}C NMR δ (CD_3OD) 56.0, 65.6, 65.6 (J = 4.8 Hz), 69.9, 71.6, 71.9, 171.0, 173.1; ^{31}P NMR δ (CD_3OD) 4.56. MS (FAB) *m/e* 529 (M + Na)$^+$, 413 (M + H − $PO_4)^+$.

Diphosphorylated LL-Precursor 32. To a solution of LL-precursor **13** (189 mg, 0.50 mmol) and bis(4-chlorobenzyl) *N,N*-diisopropylphosphorodiamidite (**24**) (456 mg, 1.10 mmol) in dry CH_2Cl_2 was added 1*H*-tetrazole (77 mg, 1.10 mmol), according to the procedure described for the preparation of diphosphate **28**. Purification by column chromatography (10 g silica, eluent: CH_2Cl_2/MeOH, 39/1, v/v) gave compound **32** (363 mg, 0.35 mmol) as a white solid in 70% yield: R_f = 0.50 (eluent C, detection C); ^{13}C NMR δ (CD_3OD) 53.5 (J = 5.9 Hz), 65.7, 67.4 (J = 5.9 Hz), 67.6 (J = 4.4 Hz), 69.8, 71.4, 129.5, 130.3, 135.3, 169.3, 171.1; ^{31}P NMR δ (CD_3OD) −0.27.

Diphosphorylated LD-Precursor 33. To a solution of LD-precursor **14** (202 mg, 0.53 mmol) and bis(4-chlorobenzyl) *N,N*-diisopropylphosphorodiamidite (**24**) (489 mg, 1.18 mmol) in dry CH_2Cl_2 was added 1*H*-tetrazole (83 mg, 1.18 mmol), according to the procedure described for the preparation of diphosphate **28**. Compound **33** (398 mg, 0.38 mmol) was obtained after purification on a silica gel column (10 g silica, eluent: CH_2Cl_2/MeOH, 97.5/2.5, v/v) as a white solid in 72% yield: R_f = 0.53 (eluent C, detection C); ^{13}C NMR δ (CD_3OD) 53.1 (J = 5.9 Hz), 53.6 (J = 4.4 Hz), 66.0, 67.5 (J = 4.4 Hz), 68.1 (J = 5.9 Hz), 69.6, 70.8, 129.5, 129.0, 136.7, 169.4, 170.6; ^{31}P NMR δ (CD_3OD) −0.21.

Dimethyl 5-Hydroxyisophthalate 35. 5-Hydroxyisophthalic acid (**34**, 9.11 g, 50.0 mmol) was dissolved in MeOH (50 mL), and concd H_2SO_4 (5.90 mL, 11.0 mmol) was added. The reaction mixture was refluxed for 4 h. The reaction mixture was concentrated *in vacuo* to a small volume and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (2 × 75 mL) and brine (75 mL). The combined aqueous layers were extracted with EtOAc (2 × 100 mL). The combined organic layers were dried. Crystallization from EtOH gave compound **35** (9.36 g, 44.5 mmol) in 89% yield as white crystals: R_f = 0.66 (eluent C, detection D); mp = 159 °C; ^{1}H NMR (CD_3OD) δ 3.93 (s, 6 H), 4.28 (br s, 1 H), 7.65 (s, 2 H), 8.12 (s, 1 H); ^{13}C NMR (CD_3OD) δ 52.5, 120.9, 122.0, 131.7, 157.6, 166.9.

Dimethyl 5-(Heptyloxy)isophthalate 36. In dry CH_3CN (75 mL) were suspended dimethyl 5-hydroxyisophthalate (**35**, 9.46 g, 45.0 mmol) and K_2CO_3 (7.49 g, 54.0 mmol). In the dark, heptyl iodide (7.40 mL, 45.0 mmol) was added and the mixture was refluxed overnight. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ether/water (1/1, v/v, 250 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL). The aqueous layers were extracted with ether (3 × 150 mL). The collected organic layers were dried. After purification by column chromatography (250 g silica, eluent: ether/petroleum ether, 15/85, v/v), compound **36** (13.1 g, 42.5 mmol) was obtained in 94% yield as white solid: R_f = 0.33 (ether/petroleum ether, 15/85, v/v, detection D); mp = 32 °C; ^{1}H NMR δ 0.90 (t, 3 H, J = 6.9 Hz), 1.30 (m, 8 H), 1.76 (5 lines, 2 H), 3.92 (s, 6 H), 3.99 (t, 2 H, J = 6.6 Hz), 7.67 (d, 2 H, J = 1.5 Hz), 8.18 (t, 1 H); ^{13}C NMR δ 13.8, 22.3, 25.7, 28.8, 31.5, 51.9, 68.2, 119.3, 122.3, 131.3, 158.8, 165.7.

1,3-Bis(hydroxymethyl)-5-(heptyloxy)benzene 37. To a solution of LiI·$2H_2O$ (10.0 g, 59.0 mmol) in dry DME (35 mL) was added $NaBH_4$ (2.84 g, 75.0 mmol). The mixture was cooled to −30 °C and dimethyl ester **36** (4.62 g, 15.0 mmol) in dry DME (10 mL) was added dropwise. After stirring for 1 h at ambient temperature, the reaction mixture was refluxed overnight. Quenching of the reaction with 1 N HCl was followed by evaporation of the solvent *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 mL). The organic layer was washed with 1 N HCl (2 × 75 mL) and brine (75 mL). Compound **37** (3.78 g, 15.0 mmol) was obtained in quantitative yield as a white solid and used without purification. If necessary, **37** can be crystallized from ether with *n*-pentane: R_f = 0.29 (eluent A, detection B); mp = 63 °C; ^{1}H NMR δ 0.88 (t, 3 H, J = 6.4 Hz), 1.29 (m, 8 H), 1.71 (5 lines, 2 H), 3.83 (t, 2 H, J = 6.6 Hz), 4.40 (s, 6 H), 6.65 (s, 2 H), 6.74 (s, 1 H); ^{13}C NMR δ 13.9, 22.5, 25.8, 29.0, 29.1, 31.7, 64.3, 67.9, 111.7, 117.2, 142.4, 159.0.

1,3-Bis(chloromethyl)-5-(heptyloxy)benzene 38. A solution of 1,3-bis(hydroxymethyl)-5-(heptyloxy)benzene (**37**, 1.26 g, 5.01 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C, and triethylamine (1.53 mL, 11.0 mmol) and MsCl (0.85 mL, 11.0 mmol) were added. The mixture was stirred overnight at 50 °C. The reaction mixture was then concentrated *in vacuo*, and the residue was dissolved in EtOAc (75 mL) and subsequently washed with 5% aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The aqueous layers were extracted with EtOAc (2 × 75 mL). Compound **38** (1.45 g, 5.01 mmol) was obtained in quantitative yield as pale yellow oil: R_f = 0.83 (eluent A, detection B); ^{1}H NMR δ 0.90 (t, 3 H, J = 6.4 Hz), 1.34 (m, 8 H), 1.77 (m, 2 H), 3.96 (t, 2 H, J = 6.4 Hz), 4.53 (s, 4 H), 6.88 (s, 2 H), 6.96 (s, 1 H); ^{13}C NMR δ 14.0, 22.6, 26.0, 29.0, 29.2, 31.7, 45.8, 68.2, 114.6, 120.6, 139.2, 159.6.

1,3-Bis(cyanomethyl)-5-(heptyloxy)benzene 39. The apparent pH of a solution of dichloride **38** (1.44 g, 5.01 mmol) in dry CH_3CN (4 mL) was adjusted to pH 7.5–8 using triethylamine. Subsequently, 18-crown-6 (793 mg, 3.00 mmol) and KCN (1.31 g, 20.1 mmol) were added and the mixture was stirred overnight at rt. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc/water (50 mL). The aqueous layer was extracted with EtOAc (5 × 25 mL). Purification on a silica gel column (30 g silica, eluent: EtOAc/petroleum ether, 4/1, v/v) gave compound **39** (1.24 g, 4.57 mmol) as a pale yellow solid in 91% yield: R_f = 0.27 (eluent A, detection C); mp = 46

°C; ^{1}H NMR δ 0.90 (t, 3 H, J = 6.6 Hz), 1.32 (m, 8 H), 1.78 (5 lines, 2 H), 3.72 (s, 4 H), 3.95 (t, 2 H, J = 6.6 Hz), 6.82 (s, 2H), 6.84 (s, 1 H); ^{13}C NMR δ 13.8, 22.3, 23.1, 25.6, 28.7, 28.8, 31.4, 68.0, 113.5, 117.4, 119.2, 132.0, 159.9.

1,3-Bis(carboxymethyl)-5-(heptyloxy)benzene 40. A suspension of dicyanide **39** (748 mg, 2.77 mmol) in concd HCl (10 mL) was refluxed for 8 h. Water (25 mL) was added and the aqueous layer was extracted with ether (5 × 10 mL). Compound **40** (784 mg, 2.54 mmol) was obtained as colorless solid in 92% yield: R_f = 0.04 (eluent A, detection B); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 0.90 (t, 3 H, J = 6.6 Hz), 1.30 (m, 8 H), 1.74 (5 lines, 2 H), 3.53 (s, 4 H), 3.92 (t, 2 H, J = 6.3 Hz), 5.47 (s, 2 H), 6.74 (s, 2 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 14.4, 23.2, 26.7, 29.7, 29.9, 32.5, 41.7, 68.6, 114.8, 123.3, 136.6, 160, 175.0.

1,3-Bis[(pentafluorophenoxycarbonyl)methyl]-5-(heptyloxy)benzene 41. The di-Pfp-ester of diacid **40** was prepared according to the procedure described for the preparation of the di-Pfp-ester **20** of (ethylenedioxy)acetic acid, starting from diacid (**40**, 159 mg, 0.52 mmol). Compound **41** (323 mg, 0.52 mmol) was obtained as a pale yellow oil and was used without purification: R_f = 0.94 (ether/petroleum ether, 1/1, v/v, detection B); ^{1}H NMR δ 0.88 (m, 3 H), 1.29 (m, 8 H), 1.72 (m, 2 H), 3.55 (s, 4 H), 3.92 (t, 2 H, J = 6.4 Hz), 6.75 (s, 2 H), 6.79 (s, 1 H); ^{13}C NMR δ 13.4, 22.2, 25.6, 28.7, 28.9, 31.4, 40.4, 67.5, 113.7, 121.9, 135.0, 159.1, 171.5.

1,3-Bis[(chlorocarbonyl)methyl]-5-(heptyloxy)benzene 42. To a cooled solution containing (0 °C) diacid **40** (253 mg, 0.82 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (0.30 mL, 3.44 mmol). The ice bath was removed and the reaction mixture was stirred overnight at rt. The mixture was concentrated *in vacuo*. Compound **42** (mg, mmol) was obtained as a pale yellow oil and was used without purification: R_f = 0.50 (eluent C, detection B); ^{1}H NMR δ 0.89 (t, 3 H, J = 6.6 Hz), 1.30 (m, 8 H), 1.76 (5 lines, 2 H, J = 6.6 Hz), 3.57 (s, 4 H), 3.69 (s, 6 H), 3.93 (t, 2 H, J = 6.4 Hz), 6.74 (s, 2 H), 6.75 (s, 1 H).

LD-**Cryptand with a Protected Phosphodiester 43.** LD-precursor **16** (668 mg, 1.21 mmol) was coevaporated with dry dioxane (5 × 20 mL) and subsequently dissolved in dry CH_2Cl_2 (24 mL), yielding a 50 mM solution of the starting material. Under argon, successively DIPEA (465 μL, 2.66 mmol) and 4-chlorobenzyl phosphorodichloridite (**23**, 140 μL, 1.35 mmol) were added. The reaction mixture was stirred overnight at ambient temperature. Oxidation of the obtained phosphite triester to the corresponding phosphate triester was carried out by addition of *m*-CPBA (55%, 817 mg, 2.60 mmol) at 0 °C, followed by stirring for 2 h at rt. A solution of 10% aqueous $NaHSO_3$ (25 mL) was then added and the reaction mixture was concentrated *in vacuo* after 10 min. EtOAc (50 mL) was added to the residue and the organic layer was washed with 10% aqueous $NaHSO_3$ (2 × 25 mL) and brine (25 mL). After purification by column chromatography (20 g silica, eluent: CH_2Cl_2/MeOH, 95/5, v/v) and on Sephadex LH-20 (100% MeOH), compound **43** (242 mg, 0.33 mmol) was obtained as a white solid in 27% yield. The diastereoisomers could not be separated and were obtained in a ratio of 9:7 as was estimated by ^{1}H NMR: R_f = 0.48 (eluent C, detection B); NMR data of diastereoisomer **43a** formed in excess: 400-MHz ^{1}H NMR δ 0.90 (t, 3 H, J = 6.8 Hz), 1.37 (m, 8 H), 1.79 (5 lines, 2 H, J = 6.7 Hz), 3.56 (m, 8 H), 3.64 (m, 4 H), 3.97 (t, 2 H, J = 6.5 Hz), 4.15, 4.26 (13 lines, AB of ABX, 4 H), J_{AX} = 2.2 Hz, J_{AP} = 8.4 Hz, J_{AB} = 10.9 Hz, J_{BX} = 2.5 Hz, J_{BP} = 10.9 Hz), 4.29, 4.37 (16 lines, AB of ABXY, 4 H, J_{AX} = 2.4 Hz, J_{AY} = 7.5 Hz, J_{AB} = 12.2 Hz, J_{BX} = 2.3 Hz, J_{BY} = 5.8 Hz), 4.75 (8 lines, 4 H), 4.91 (d, 2 H, J_{HP} = 10.5 Hz), 6.79, 6.80 (2 s, 2 H), 6.81 (d, 2 H, J_{NHH} = 8.9 Hz), 6.89 (s, 1 H), 7.35 (m, 4 H); 100-MHz ^{13}C NMR δ 13.9, 22.4, 26.0, 28.9, 29.2, 31.6, 43.5, 53.2 (J_{CP} = 4.3 Hz), 64.7, 67.4 (J_{CP} = 3.1 Hz), 68.1, 68.2, 69.3 (J_{CP} = 6.7 Hz) 115.0, 124.0, 129.0, 129.3, 133.4, 133.7, 136.4, 160.0, 167.8, 170.5, 121.5; ^{31}P NMR δ 2.7.

NMR data of the second diastereoisomer **43b**: 400-MHz ^{1}H NMR δ 0.90 (t, 3 H, J = 6.8 Hz), 1.37 (m, 8 H), 1.76 (5 lines, 2 H, J = 6.5 Hz), 3.49, 3.62 (2 d, 4 H, J = 16.4 Hz), 3.56 (m, 4 H), 3.92 (t, 2 H, J = 6.6 Hz), 3.98, 4.52 (16 lines, AB of ABXY, 4 H, J_{AX} = 2.3 Hz, J_{AY} = 4.6 Hz, J_{AB} = 12.1 Hz, J_{BX} = 2.6 Hz, J_{BY} = 7.2 Hz), 4.07, 4.42 (15 lines, AB of ABX, 4 H, J_{AX} = 3.1 Hz, J_{AP} = 7.5 Hz, J_{AB} = 10.4 Hz, J_{BX} = 2.2 Hz, J_{BP} = 6.0 Hz), 4.75 (8 lines, 2 H), 4.96 (d, 2 H, J_{HP} = 9.0 Hz), 6.18 (d, 2 H, J_{NHH} = 8.2 Hz), 6.52 (s, 1 H), 6.79, 6.80 (2 s, 2 H), 7.35 (m, 4 H); 100-MHz ^{13}C NMR δ 13.9, 22.4, 25.9, 28.9, 29.1, 31.6, 43.5, 52.6 (J_{CP} = 7.0 Hz), 64.7, 66.8 (J_{CP} = 4.2 Hz), 68.2, 68.6, 70.0 (J_{CP} = 5.3 Hz), 115.0, 122.9, 129.1, 129.8, 133.4, 133.7, 136.2, 160.2, 168.2, 170.0; 121.5 ^{31}P NMR δ −2.1. MS (FAB) *m/e* 751 $(M + Na)^+$, 739 $(M + H)^+$.

LD-**Cryptand 44.** To a solution of protected cryptand **43** (172 mg, 0.23 mmol) in *t*-BuOH/H_2O (4/1, v/v, 5 mL) were added sodium acetate (32 mg, 0.24 mmol) and a catalytic amount of 10% Pd/C. The reaction mixture was slowly stirred under H_2 atmosphere (balloon) for 2 h at rt. The reaction mixture was centrifuged, and the supernatant was filtered over a millipore filter (0.2 μm) and concentrated *in vacuo*. Purification on Sephadex LH-20 (100% MeOH) and subsequent lyophilization yielded compound **44** (141 mg, 0.22 mmol) as a white solid in 95%. Compound **44** was pure on TLC (RP-2, R_f = 0.70 (eluent D, detection A) and according to NMR: 400-MHz ^{1}H NMR δ 0.90 (t, 3 H, J = 6.9 Hz), 1.35, 1.47 (2 m, 8 H), 1.78 (5 lines, 2 H), 3.47, 3.54 (15 lines, AB of ABXY, 4 H, J_{AX} = 2.4 Hz, J_{AY} = 8.3 Hz, J_{AB} = 10.8 Hz, J_{BX} = 4.4 Hz, J_{BY} = 2.5 Hz), 3.59, 3.64 (2 d, 4 H, J = 15.5 Hz), 3.96 (t, 2 H, J = 6.5 Hz), 4.00, 4.40 (16 lines, AB of ABXY, 4 H, J_{XY} = 12.0 Hz), 4.12, 4.22 (13 lines, AB of ABX, 4 H, J_{AX} = 2.4 Hz, J_{AP} = 9.6 Hz, J_{AB} = 11.7 Hz, J_{BX} = 3.9 Hz, J_{BP} = 11.5 Hz), 4.75 (t, 2 H, J_{vic} = 3.3 Hz), 6.77 (s, 2 H), 7.00 (s, 1 H); 100 MHz ^{13}C NMR ($CDCl_3/CD_3OD$) δ 13.6, 22.2, 25.8, 28.7, 29.0, 31.4, 43.3, 54.6 (J_{CP} = 2.9 Hz), 64.0, 64.3, 67.8, 68.0, 114.2, 123.7, 136.1, 159.5, 169.8, 172.0, 121.5; ^{31}P NMR ($CDCl_3/CD_3OD$) δ 4.4; MS (FAB) *m/e* 659 $(M + Na)^+$, 637 $(M + H)^+$.

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Supplementary Material Available: ^{1}H NMR data for compounds **2–16**, **18**, **20**, **21**, **25–30**, **35–41**, **43**, and **44**. ^{13}C and ^{31}P NMR spectra for compounds **2–16**, **18**, **20**, **21**, **25–30**, **32**, **33**, **35–41**, **43**, and **44** (49 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.