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A Prototype Calix[4]arene-Based Receptor for Carbohydrate Recognition Containing Peptide and Phosphate Binding Groups

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A novel class of macrobicyclic receptors for carbohydrate recognition based on *upper rim*, peptide-bridged calix[4]arenes has been designed and synthesized. Receptor **12**, in which a charged phosphate group cooperates with peptide hydrogen-bonding donor and acceptor groups in the binding process, is the most efficient and selective in the complexation of simple carbohydrate derivatives. The selectivity observed is toward β-glucoside **13a**, which is better bound ($\Delta G° = 19.6$ kJ mol^{-1}) compared to the corresponding α anomer **13b** ($\Delta G° = 17.0$ kJ mol^{-1}) and to the β-galactoside **13c** ($\Delta G° = 17.7$ kJ mol^{-1}) in $CDCl_3$. A substantial drop in the stability constant is observed by esterification of the phosphate group in the host **12** or by alkylation of the OH groups in the 2 and 3 positions in the β-glucoside and β-galactoside derivatives. On the basis of a careful analysis of the ^{1}H NMR data available, a binding mode of the β-octylglucoside **13a** to receptor **12** is proposed.

Introduction

Carbohydrates are involved in numerous, very important, biological molecular recognition processes ranging from cell adhesion and migration to infection by bacteria and viruses, toxins, or vaccine action, etc. The need of understanding the biological role of carbohydrates in molecular terms has stimulated the birth of chemical glycobiology,[1] a field mainly devoted to the study of multivalent glycoclusters,[2] and the flowering of the biomimetic[3] and supramolecular[4] approaches to carbohydrate recognition. Several synthetic receptors for carbohydrate recognition and sensing have been designed and synthesized in recent years, some exploiting the formation of covalent adducts with boronic acids,[5] others employing charged phosphate and phosphonate groups[6] or a variety of hydrogen-bonding acceptor and donor groups[7] on several molecular scaffolds. Most of these artificial receptors are able to complex carbohydrates in organic media and only few in water solution,[8] where hydrophobic interactions could strengthen the sugar binding. Calixarenes are a versatile class of cavity containing macrocycles used in several areas of supramolecular chemistry.[9] In the past few years, we have been interested to extend the use of calixarenes in bio-organic chemistry[10] by synthesizing several hydrogen bonding macrocyclic receptors for anions,[11] amino acids,[12] and small peptides.[13] Few of these receptors are water soluble,[12b] and others show interesting antibacterial

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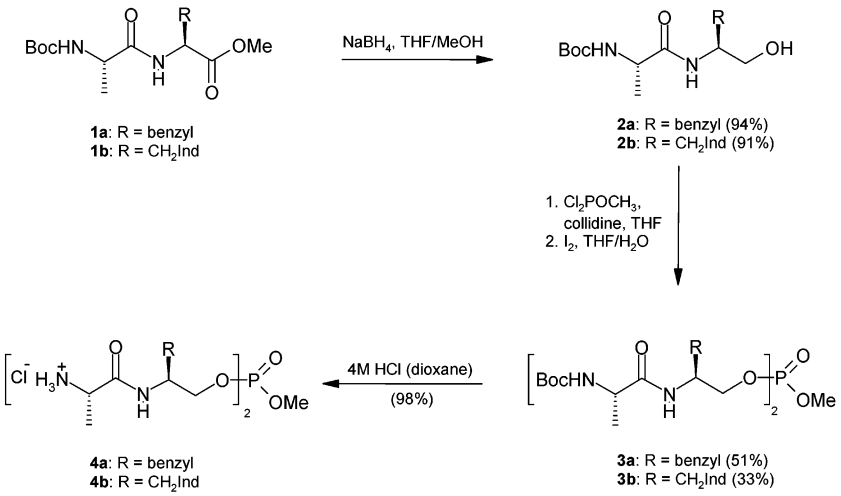
SCHEME 1. Synthesis of Pseudopeptides 4a,b



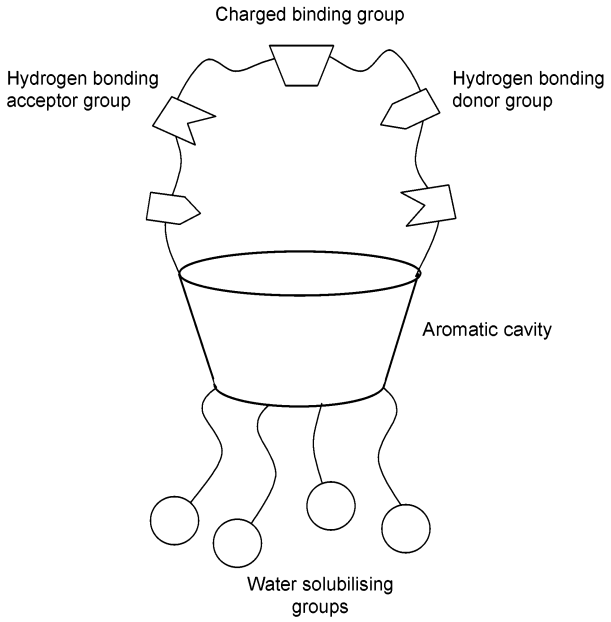


FIGURE 1. Basic design feature of a calixarene-based macrobicyclic carbohydrate receptor.

activity behaving as vancomycin mimics.[13,14] The aim of this work was to explore the potential of functionalized calix[4]arenes in carbohydrate recognition.

Results and Discussion

Design and Synthesis of the Receptors. We designed a general host architecture (Figure 1) on a calix[4]arene platform which is able to organize several binding motives, differently from the other receptors reported so far which exploit only one or two types of supramolecular interactions to bind carbohydrates.[5−8]

Moreover, the minimized prototype of the novel host family reported in this paper, which combines a phosphate negative charge and four amino acid units held in close proximity to a hydrophobic pocket by a pseudopeptide bridge, is already predisposed for water solubility due to the hydrolyzable ester substituents at the *lower rim*.

To obtain the final receptor, the convergent approach consisted of the preparation of the phosphate-containing pseudopeptides, the parallel synthesis of the calix[4]arene platform, and the condensation of the two subunits. Two different pseudopeptide chains were prepared (Scheme 1), one having two L-alanine and two L-phenylalanine units and the other made up of two L-alanine and two L-tryptophan moieties. The methyl ester group of the dipeptides **1a**,**b**, synthesized according to literature procedures,[15] was reduced to the corresponding alcohol using $NaBH_4$, which gave **2a**,**b**. These were first treated with methyl dichlorophosphite in the presence of 2,4,6-collidine and then with iodine to afford the phosphates **3a**,**b**, which were finally deprotected from Boc group by using 4 M HCl in dioxane, yielding the bisammonium salts **4a**,**b**.

To form a macrocyclic loop with the pseudopeptides **4**, we chose the calix[4]arene derivative **9**, blocked in the *cone* conformation through the *lower rim* functionalization with four ethyl acetate groups, which could be eventually hydrolyzed to ensure water solubility to the receptors. To this end, calix[4]arene was first dialkylated in the diametral position to give the 25,27-bis(ethoxycarbonylmethoxy)-26,28-dihydroxycalix[4]arene[16] (**5**) which was reacted with Cl_2CHOCH_3 and $TiCl_4$ to afford the bisaldehyde derivative **6** (Scheme 2).

We completed the functionalization at the *lower rim* by refluxing an acetonitrile solution of **6** in the presence of ethyl bromoacetate and sodium carbonate in order to obtain the tetraester **7** in the *cone* conformation. Oxidation of the aldehyde to carboxylic acid groups, with $NaClO_2$, afforded compound **8**. This was subsequently transformed into the corresponding diacyl chloride **9,** which can be isolated and characterized or, alternatively, reacted in situ with the pseudopeptides **4a**,**b** (Scheme 2),

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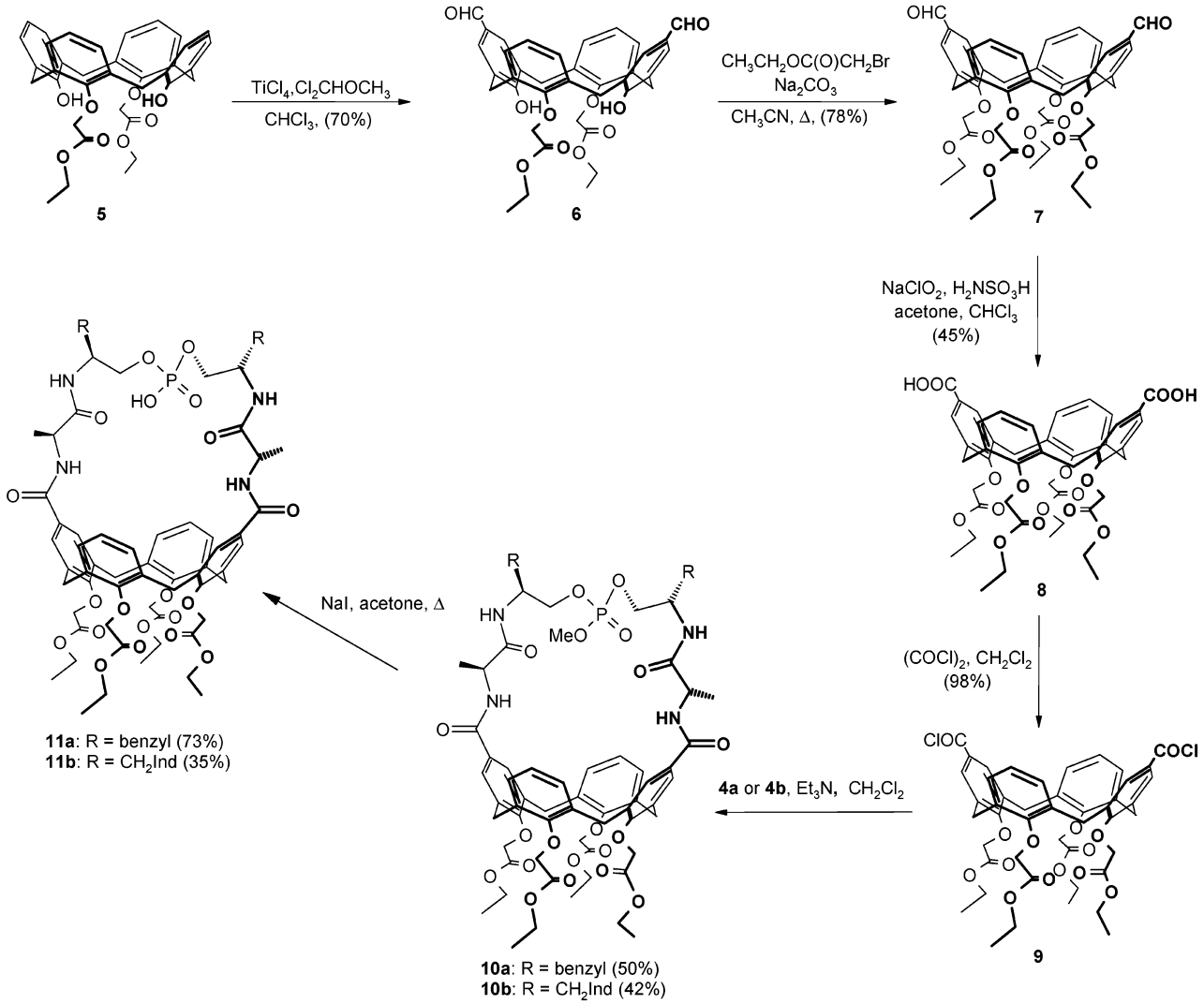
SCHEME 2. Synthesis of the Calixarene Scaffold 9 and of the Macrobicyclic Receptors 10 and 11



after removal of the excess of oxalyl chloride. The cyclization reactions were performed under high dilution conditions, by the slow addition of the two reagent solutions, to minimize the formation of oligomers. The macrobicyclic compounds **10a**,**b** were isolated in 42−50% yield and subsequently transformed into the phosphoric acid derivatives **11a**,**b** by treatment with NaI in acetone, which allowed the selective hydrolysis of the phosphoric methyl ester in the presence of the *lower rim* carboxylic ethyl ester groups. The compound **11a** was titrated with Bu_4-NOH in MeOH to give the anionic receptor **12** (Chart 1).

Conformational Properties of the Receptors. The ^{1}H NMR spectra of the methyl ester derivatives **10a**,**b** and the negatively charged macrocycle **12** are sharp and well resolved in $CDCl_3$, whereas those of acids **11a**,**b** are quite broad. However, when the temperature is increased (373 K) or a more polar solvent like DMSO-d_6 is used the spectra of **11a**,**b** become sharp. Dilution experiments (range 10^{-2}−10^{-4} M) performed with compound **11a** in $CDCl_3$ cause no change in the ^{1}H NMR spectrum, thus ruling out the presence of extensive intermolecular aggregation. All together, these data suggest that the observed broadening of the NMR signals of **11a**,**b** in nonpolar solvents can be ascribed to the presence of an intramolecular hydrogen bond between the acidic P−OH group and the neighbor amide carboxy groups, which determines a slow exchange (on the NMR time scale) among different conformers at the level of the pseudopeptide bridge in equilibrium. Aside from this peculiarity, the basic features of the ^{1}H NMR spectra of all macrobicyclic compounds **10**−**12** are quite similar, indicating that the calix[4]arene scaffold imposes a severe conformational constrain to the entire macrocyclic pseudopeptide loop. The calix[4]arene backbone is not regular but adopts a *flattened cone* conformation[17] with the two unsubstituted aromatic rings pointing outside and the substituted ones being almost parallel each to the other. This structure is clearly indicated by the high-field resonance (6.50−6.60 ppm) of the protons belonging to these latter rings which experience the shielding effect of the π systems of the other two unsubstituted aromatic nuclei, whose protons resonate at lower field (7.11−7.29 ppm).

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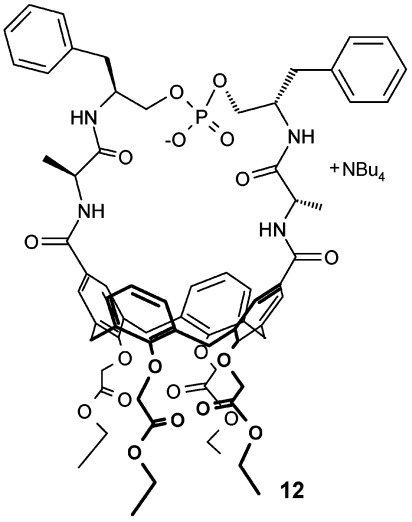
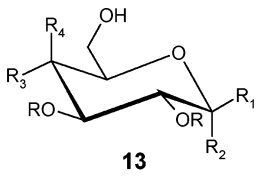
CHART 1





a: R = R_2 = R_4 = H, R_1 = OC_8H_{17}, R_3 = OH
b: R = R_1 = R_4 = H, R_2 = OC_8H_{17}, R_3 = OH
c: R = R_2 = R_3 = H, R_1 = OC_8H_{17}, R_4 = OH
d: R_2 = R_4 = H, R = C_7H_{15}, R_1 = OC_8H_{17}, R_3 = OH
e: R_2 = R_3 = H, R = C_7H_{15}, R_1 = OC_8H_{17}, R_4 = OH

The presence of the chiral centers in the pseudopeptide loop is felt by several protons of all the macrobicyclic derivatives. For instance, the four pseudoequatorial protons of the calix[4]arene methylene bridge in **10a** give two doublets (δ = 3.26 and 3.24 ppm) and the same happens with the *lower rim* methylene groups CH_2COOR (δ = 5.01 and 4.93 ppm) and the aromatic protons in ortho to the *upper rim* substituents (δ = 6.50 and 6.40 ppm). In addition, because of the phosphoric methyl ester group determining for this compound the loss of all symmetry elements, the amide NH protons give rise to four distinct doublets (δ = 7.46, 7.34, 6.63, and 6.60 ppm). COSY NMR experiments (see the Supporting Information) with compounds **10a**, **10b**, and **12** allowed, in particular, the distinction between the NH and CH protons of the different amino acid units. In all cases, the amide protons of the alanine units, directly linked to the calixarene scaffold, resonate at significantly higher fields (δ = 6.84 and 6.78 ppm in **10b**, δ = 6.63 and 6.60 ppm in **10a**, and δ = 6.52 ppm in **12a**) with respect to those of tryptophan (δ = 7.26 ppm in **10b**) or phenylalanine (7.46 and 7.34 ppm in **10a** and 7.91 ppm in **12**). It is to be noted that, in the case of anionic receptor **12**, the phenylalanine NH protons are ca. 0.5 ppm downfield shifted with respect to the corresponding signals in the methyl ester derivative **10a**, suggesting the presence of a weak intramolecular H-bonding interaction with the neighboring negatively charged phosphate group.

Carbohydrate Recognition. To evaluate the binding properties of this novel class of macrobicyclic receptors, we used only the phenylalanine-containing derivatives, since those functionalized with tryptophan show poor solubility in most of the organic solvents examined. The ^{1}H NMR titration experiments were performed by adding increasing amounts of the glycosides **13a**−**e** (Chart 1) to a $CDCl_3$ solution of the host. The titration of **10a** and **12** causes several changes in the ^{1}H NMR spectra both of hosts and guests, which were analyzed by nonlinear regression methods showing a 1:1 stoichiometry for the complexes in all cases. On the other hand, the ^{1}H NMR spectrum of the phosphoric acid derivative **11a** shows very little changes upon guests addition, indicating low binding. In the case of host **12**, the 1:1 stoichiometry of its complexes with both β and α anomers of octylglucoside (**13a** and **13b**) was also established by ESI-MS experiments.

The ^{1}H NMR spectra of the charged receptor **12** and its complexes were analyzed in more details. Surprisingly, the phenylalanine NH protons (NH_{phe}) experience a significant upfield shift upon guest addition ($\Delta\delta$ = 0.3 ppm in the case of β-glucoside **13a** with the concentrations of host and guest being 2.5×10^{-3} and 2.2×10^{-2} M, respectively). This can be explained assuming that complexation breaks a possible intramolecular hydrogen bond between the NH_{phe} and the phosphate anion, now engaged in guest binding, or that the NH_{phe} move under the shielding zone of the phenylalanine aromatic nuclei, as observed in other systems.[7a] The involvement of the phosphate group of host **12** in the complexation was also proved by the downfield shift ($\Delta\delta_\infty$ = 0.8 ppm) shown by the phosphorus nucleus in the ^{31}P NMR spectrum of the complex with **13a** compared with the free ligand. On the other hand, the conformational changes induced in host **12** by the glycoside binding are quite modest as indicated by the very small shifts experienced by the host protons not directly involved in the binding. Moreover, the NOESY maps (see the Supporting Information) of the free host **12** and its complex with **13a** show a very similar pattern of NOE peaks. Unfortunately, no intermolecular NOE correlation peak was detectable in this complex as well as in others. Interestingly, the signals of the diastereotopic phenylalanine benzylic protons, which are partially overlapped in the free ligand **12**, split into two signals upon complexation with **13a**, probably as a consequence of the freezing of the pseudopeptide bridge. All the OH groups of the β-glucoside derivative **13a** undergo substantial downfield shifts ($\geq$1 ppm) by interacting with **12**, which proves their involvement in complexation.

Table 1 reports the stability constants obtained for the complexes of hosts **10a** and **12** with a selection of lipophilic carbohydrates, including two derivatives **13d** and **13e** whose OH groups in 2 and 3 position are selectively alkylated. As expected, the best efficiency was obtained with the negatively charged receptor **12** which shows, in all cases, a better binding toward carbohydrates

TABLE 1. Association Constants (298 K, Errors ≤ 10%) and, in Parentheses, $\Delta G°$ (kJ mol^{-1}) Values for the Interaction between the Carbohydrate Derivatives 13a−d and Receptors 12, 10a, and 11a in $CDCl_3$

	guest				
host	**13a** β-Glu	**13b** α-Glu	**13c** β-Gal	**13d** β-Glu(4,6-OH)	**13e** β-Gal(4,6-OH)
12	2700 (19.6)	950 (17.0)	1260 (17.7)	320 (14.3)	<5 (<4.0)
10a	460 (15.2)	510 (15.5)	<5 (<4.0)		
11a	<5 (<4.0)	<5 (<4.0)			

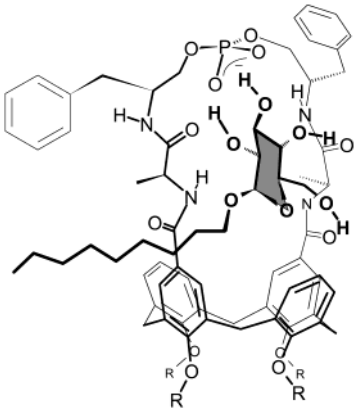


FIGURE 2. Proposed mode of binding of β-octylglucoside **13a** to receptor **12**.

compared to the ester **10a**. Interestingly, a good selectivity is observed for the β anomer **13a** of octylglucoside with respect both to its α anomer **13b** and to the β-galactoside derivative **13c**.

The dramatic drop in the association constant of the β-galactoside **13c**, going from the charged receptor **12** to the neutral derivative **10a**, indicates that this carbohydrate derivative is mainly interacting with the anionic center of receptor **12**. On the other hand, the β-glucoside **13a** takes advantage of both the negative charge and additional H-bonding interactions with the pseudopeptide backbone of receptor **12**. In fact, this monosaccharide is also complexed, although to a minor extent, by the neutral receptor **10a**. Compared to **13a** and **13c**, a reduction in the stability constants is observed with **12** and sugars **13d** and **13e** where the 2 and 3 OH are alkylated. This, together with the observation that a similar drop is obtained with substrates **13a** and **13c** going from **12** to the neutral receptor **10a**, suggests that the the OH-2 and OH-3 groups of **13a** and **13c** are involved in hydrogen bonding with the phosphate anion of the host. All the experimental data obtained are in agreement with the proposed structure shown in Figure 2 for the complex between the anionic receptor **12** and the β-octylglucoside **13a**, which explains the observed selectivity. In this structure, all OH groups of the guest converge toward the H-bonding acceptor groups of the host (either (O)PO$^-$ or amide carbonyl groups) and can form hydrogen bonds with them as also suggested by the ^{1}H NMR titration experiments (vide supra). Assuming an equivalent mode of binding for the β-galactoside derivative **13c**, with OH-2 and OH-3 positioned toward the phosphate anion, the axial OH-4 group is pointing toward the outside and is not H-bonded to the pseudopeptide loop, thus explaining the glucose/galactose selectivity. On the other hand, the α-glucoside complex is destabilized by a noncorrect orientation of the anomeric OR group which, ideally, should be oriented toward the exterior of the binding region as in fact occurs in the β anomers. The change in configuration of the anomeric position not only changes the accessibility of the sugar to the binding pocket, but also reduces the donor nature of OH-2 in the α derivative due to the presence of an intramolecular hydrogen bond OH-2···O-1 which is less efficient in the β anomer.[7g,18]

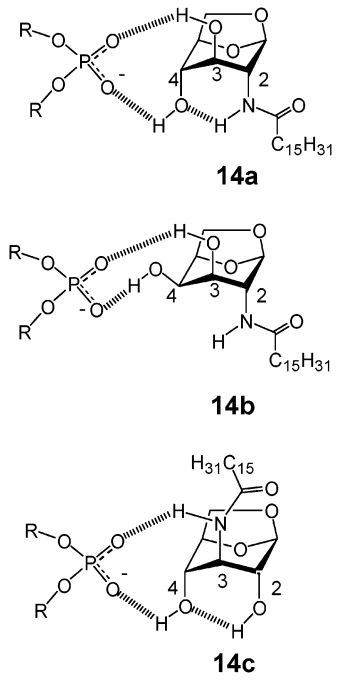


FIGURE 3. Mode of binding of carbohydrates **14a−c** toward phosphate anion.

In addition to the classical and more studied carbohydrates **13a−e**, we have also investigated the binding properties of hosts **10a** and **12** toward diols and amido alcohols **14a−c**[19] (see in Figure 3) which are activated as hydrogen bonding donors by intramolecular interactions and have previously been shown to interact with a phosphate salt (tetrabutylammonium bis(3,5-di-*tert*-butyl) phenyl phosphate, **Phos**) through the binding mode depicted in Figure 3.[20] The 1,2-trans-diaxial diol **14a** and the 1,2-trans-diaxial amido alcohol **14c** present a *cooperative* D/D H-bonding motif that is very efficient for phosphate binding (Figure 3).

The results with hosts **12** and **10a** are reported in Table 2 and were obtained following the changes of the

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TABLE 2. Association Constants (298 K, Errors ≤ 10%) and, in Parentheses, $\Delta G°$ (kJ mol^{-1}) Values for the Interaction between the Carbohydrate Derivatives 14a−c and Receptors 12, 10a, and the Phosphate Salt (Tetrabutylammonium Bis(3,5-di-*tert*-butyl)phenyl Phosphate, Phos) in $CDCl_3$

	guest		
host	**14a**	**14b**	**14c**
12	1530 (18.2)	520 (15.5)	840 (16.7)
10a			540 (15.6)
Phos[20]	1796 (18.6)	554 (15.7)	4160 (20.7)

guest signals upon addition of increasing amounts of the host solutions, in the same conditions previously employed with **Phos**.[20]

Compared to **Phos**, receptor **12** shows a lower efficiency and an inverse selectivity since it binds the diol **14a** better than the amide alcohol **14c**, whereas the reverse is true for **Phos**. The very similar association constants found for **12** and **Phos** in the case of diols **14a** and **14b** indicate that these guests mainly interact with the phosphate anionic center of receptor **12**. On the other hand, the substantial decrease in the association constant of the 1,2-trans-diaxial amido alcohol **14c** with receptor **12** in comparison to **Phos**, suggests a different host−guest binding mode. Probably the presence of a bulky *n*-$C_{15}H_{31}CO$ substituent on the nitrogen atom hinders the formation of an efficient hydrogen bond with the phosphate anion of receptor **12** and the observed weak binding is due to the guest interaction with other donor centers of the pseudopeptide bridge. In line with this interpretation is the quite similar value of the association constant observed for **14c** and the neutral macrobicyclic receptor **10a**.

Conclusion

In summary, we have synthesized the first members of a new family of macrobicyclic carbohydrate receptors by bridging the *upper rim* of a calix[4]arene tetraester, blocked in the *cone* conformation, with a pseudopeptide chain bearing a phosphate anionic group in the center. Detailed binding studies in $CDCl_3$, using lipophilic derivatives of simple carbohydrates as guests, revealed a good selectivity for β-glucosides which are able to take advantage, in the binding, of both hydrogen bonding and anion-sugar interactions, thanks to a better host−guest complementarity compared to other sugars.

The modular and convergent synthetic approach adopted should lead to a broad range of carbohydrate receptors having peptide bonds and anionic centers as binding units. An attractive feature of these receptors is the presence of four ester groups at the *lower rim* of the calix[4]arene scaffold, which can eventually be hydrolyzed to give water soluble carbohydrate receptors.

Experimental Section

***N-tert*-Butyloxycarbonyl-L-alanyl-L-phenylalaninol (2a).** A solution of **1a**[15] (0.39 g, 1.14 mmol) in dry THF (7 mL) was stirred under N_2. Then $NaBH_4$ (0.086 g, 2.27 mmol) was added, and the suspension was heated at 60 °C. Dry MeOH (1.5 mL) was added dropwise, and the mixture was heated at that temperature for 50 min. The solution was cooled to room temperature, and water (2 mL) was carefully added. The solvent was removed at reduced pressure, the residue was dissolved in CH_2Cl_2 (15 mL), washed with brine, and dried over Na_2SO_4, and the solvent was removed at reduced pressure. The residue was purified by precipitation with cold Et_2O, yielding **2a** as a white solid: yield 94%; TLC eluent hexane/ethyl acetate 1:1; mp 114−115 °C; $[\alpha]^{20}_D = -49.5$ ($c = 1.0$ in EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (d, $^3J = 8.4$ Hz, 1H), 7.28−7.16 (m, 5H), 6.76 (d, $^3J = 7.0$ Hz, 1H), 4.74 (t, $^3J = 5.2$ Hz,1H), 3.89−3.85 (m, 2H), 3.37−3.25 (m, 2H), 2.82 (dd, $^3J = 5.8$ Hz, $^2J = 13.6$ Hz, 1 H), 2.65 (dd, $^3J = 7.8$ Hz, $^2J = 13.6$ Hz, 1 H), 1.37 (s, 9 H), 1.09 (d, $^3J = 7.1$ Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 154.8, 138.9, 129.1, 128.0, 125.8, 78.0, 62.1, 52.1, 49.8, 36.3, 28.1, 18.3; CI-MS *m*/*z* 323 (4, $[M + H]^+$), 292 (4, $[M + H - CH_2OH]^+$), 267 (53, $[M + H - ((CH_3)_2C{=}CH_2)]^+$), 223 (100, $[(M + H - Boc)]^+$). Anal. Calcd for $C_{17}H_{26}O_4N_2$ (322.2): C, 63.33; H, 8.13; N, 8.69. Found: C, 63.23; H, 8.10; N, 8.63.

***N-tert*-Butyloxycarbonyl-L-alanyl-L-tryptophanol (2b).** Compound **2b** was prepared from **1b**[15] with the same procedure used for **2a**. The product was purified by flash column chromatography (hexane/ethyl acetate 1:1 → ethyl acetate): yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.64 (d, $^3J = 7.7$ Hz, 1H), 7.35 (d, $^3J = 7.9$ Hz, 1H), 7.19 (dt, $^3J = 1.2$ Hz, $^3J = 7.0$ Hz, 1H), 7.12 (dt, $^3J = 0.7$ Hz, 7.1 Hz, 1H), 7.06 (s, 1H), 6.43 (d, $^3J = 7.4$ Hz, 1H), 4.88 (bs, 1H), 4.27−4.22 (m, 1H), 4.08−4.04 (m, 1H), 3.70 (dd, $^3J = 3.8$ Hz, $^2J = 11.1$ Hz, 1H), 3.60 (dd, $^3J = 5.2$ Hz, $^2J = 11.2$ Hz, 1H), 3.01 (d, $^3J = 6.9$ Hz, 2H), 1.41 (s, 9H), 1.27 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 154.4, 136.3, 127.6, 122.6, 122.3, 119.7, 118.7, 111.6, 111.2, 80.4, 64.3, 52.2, 28.3, 26.5, 18.2; CI-MS *m*/*z* 361 (11, $[M]^+$), 306 (18, $[M + H - ((CH_3)_2C{=}CH_2)]^+$), 262 (49, $[M + H - Boc]^+$). Anal. Calcd for $C_{19}H_{27}O_4N_3$ (361.2): C, 63.14; H, 7.53; N, 11.63. Found: C, 63.03; H, 7.46; N, 11.55.

Methyl bis(*N-tert*-butyloxycarbonyl-L-alanyl-L-phenylalaninolyl)phosphate (3a). To a solution of dry 2,4,6-collidine (0.18 mL, 1.36 mmol) in dry THF (1 mL) was added methyl dichlorophosphite (0.031 mL, 0.33 mmol) under N_2. The suspension was vigorously stirred at room temperature for 15 min, and then a solution of **2a** (0.20 g, 0.62 mmol) in dry THF (2 mL) was added dropwise. The resulting white suspension was stirred at room temperature for 4 h (TLC monitoring: hexane/ethyl acetate 3:7). A solution of iodine (0.085 g, 1.08 mmol) in a mixture of THF (1 mL) and water (0.25 mL) was added and the mixture stirred at room temperature for 45 min. After concentration to dryness, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with $Na_2S_2O_3$ (10%) until decoloration. The organic layer was dried over Na_2SO_4 and the solvent removed at reduced pressure to give a residue that was purified by flash column chromatography (dichloromethane/methanol 20:1), yielding **3a** as a white solid: yield 51%; TLC eluent hexane/ethyl acetate 3:7; mp 107−108 °C; $[\alpha]^{20}_D = -22.3$ ($c = 1.11$ in EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, $^3J = 8.2$ Hz, 1H), 7.79 (d, $^3J = 8.2$ Hz, 1H), 7.27−7.15 (m, 10H), 6.71 (d, $^3J = 6.9$ Hz, 2H), 4.13−4.09 (m, 2H), 3.84−3.80 (m, 2H), 3.87 (t, $^3J = 5.8$ Hz, 4H), 3.64 (d, ^3J(H,P) = 11.2 Hz, 3H), 2.73 (dd, $^3J = 5.8$ Hz, $^2J = 8.0$ Hz, 2H), 2.81 (dd, ^3J(H,P) = 5.7 Hz, $^2J = 8.1$ Hz, 2H), 1.42 (s, 18H), 1.08 (d, $^3J = 7.0$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 155.5, 136.9, 129.2, 128.6, 126.8, 80.0, 67.7, 54.6, 50.7, 50.5, 36.9, 36.8, 28.3, 18.3; ESI-MS *m*/*z* 743.2 (55, $[M + Na]^+$), 360.9 (90, $[M + 2H]^{2+}$). Anal. Calcd for $C_{35}H_{53}O_{10}N_4P$ (720.4): C, 58.33; H, 7.41; N, 7.77. Found: C, 58.26; H, 7.39; N, 7.69.

Methyl bis(*N-tert*-butyloxycarbonyl-L-alanyl-L-tryptophanolyl)phosphate (3b). Compound **3b** was prepared from **2b** with the same procedure used for **3a**. The product was purified by flash column chromatography (hexane/ethyl acetate 1:1 → ethyl acetate): yield 33%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (bs, 2H), 7.84 (d, $^3J = 6.9$ Hz, 1H), 7.82 (d, $^3J = 6.9$ Hz, 1H), 7.55 (d, $^3J = 7.6$ Hz, 2H), 7.32 (d, $^3J = 8.1$ Hz, 2H), 7.14 (bs, 2H), 7.05 (t, $^3J = 7.6$ Hz, 2H), 6.95 (t, $^3J = 7.4$ Hz, 2H), 6.76 (d, $^3J = 8.6$ Hz, 2H), 4.21−4.17 (m, 2H), 4.04−3.99 (m, 2H), 3.91−3.88 (m, 4H), 3.61 (d, ^3J(H,P) = 11.0 Hz,

3H), 2.87−2.85 (m, 4H), 1.36 (s, 18H), 1.14 (d, ^3J = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 154.2, 136.3, 127.5, 123.4, 123.1, 122.2, 119.7, 118.8, 111.3, 110.5, 82.8, 67.3, 54.7, 54.6, 49.6, 28.3, 26.2, 18.6, 18.4; ESI-MS *m/z* 821.4 (60, $[M + Na]^+$), 399.2 (90, $[M + 2H]^{2+}$). Anal. Calcd for $C_{39}H_{55}O_{10}N_6P$ (798.9): C, 58.64; H, 6.94; N, 10.52. Found: C, 58.58; H, 6.90; N, 6.89.

Methyl bis(L-alanyl-L-phenylalaninolyl)phosphate, dihydrochloride (4a). Compound **3a** (0.10 g, 0.13 mmol) was dissolved in a solution of HCl in dioxane (4 M, 2 mL), and the mixture was stirred at room temperature for 30−40 min. The solvent was removed at reduced pressure, and the residue was dried under vacuum to give product **4a** as a white foam in quantitative yield: mp 63−64 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.77−8.75 (m, 2H), 8.16 (bs, 6H), 7.32−7.19 (m, 10H), 4.19−4.16 (m, 2H), 3.97−3.90 (m, 4H), 3.81−3.79 (m, 2H), 3.68 (d, ^3J(H,P) = 11.1 Hz, 3H), 2.85−2.81 (m, 4H), 1.36 (d, ^3J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.9, 138.6, 130.2, 129.7, 127.9, 69.5, 55.6, 52.7, 52.6, 37.3, 17.9; ESI-MS *m/z* 543 (100, $[M - 2HCl + Na]^+$). Anal. Calcd for $C_{25}H_{39}O_6N_4PCl_2$ (593.5): C, 50.59; H, 6.62; N, 9.44. Found: C, 50.51; H, 6.68; N, 9.38.

Methyl bis(L-alanyl-L-triptophanolyl)phosphate, dihydrochloride (4b). Compound **4b** was prepared from **3b** in quantitative yield, with the same procedure used for **4a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 (bs, 2H), 8.68 (d, ^3J = 7.6 Hz, 2H), 8.14 (bs, 6H), 7.58 (d, ^3J = 7.9 Hz, 2H), 7.35 (d, ^3J = 8.2 Hz, 2H), 7.20 (s, 2H), 7.07 (t, ^3J = 7.4 Hz, 2H), 6.97 (t, ^3J = 7.3 Hz, 2H), 4.26−4.22 (m, 2H), 3.99−3.96 (m, 4H), 3.85−3.81 (m, 2H), 3.64 (d, ^3J(H,P) = 11.2 Hz, 3H), 2.94−2.90 (m, 4H), 1.36 (d, ^3J = 6.9 Hz, 6H); ESI-MS *m/z* 623.2 (100, $[M - 2Cl + Na]^+$). Anal. Calcd for $C_{29}H_{41}O_6N_6PCl_2$ (671.5): C, 51.87; H, 6.15; N, 12.51. Found: C, 51.79; H, 6.11; N, 12.46.

5,17-Diformyl-25,27-bis(ethoxycarbonylmethoxy)-26,28-dihydroxycalix[4]arene (6). A solution of **5**[16] (0.10 g, 1.23 mmol) in dry chloroform (30 mL) was stirred at room temperature under N_2 atmosphere. Then, Cl_2CHOCH_3 (2.3 mL, 25.42 mmol) was added, followed by $TiCl_4$ (5.4 mL, 49.24 mmol), and the reaction was stirred at room temperature for 19 h. The solution was carefully poured into cold HCl (5%, 20 mL), and the black residue was extracted with chloroform (2 × 30 mL). The combined organic layers were washed with water and dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate 6:4) to give a yellow solid which was re-crystallized from ethyl acetate yielding the product **6** as a white solid: yield 70%; mp 180−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 2H), 8.68 (s, 2H), 7.62 (s, 4H), 6.96 (d, ^3J = 12.0 Hz, 4H), 6.80 (t, ^3J = 8.1 Hz, 2H), 4.72 (s, 4H), 4.40 (d, ^2J = 13.3 Hz, 4H), 4.35 (q, ^3J = 7.2 Hz, 4H), 3.50 (d, ^2J = 13.3 Hz, 4H), 1.33 (t, ^3J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 166.9, 153.0, 152.4, 133.2, 129.2, 128.6, 128.4, 128.2, 125.6, 118.1, 72.5, 61.4, 31.5, 14.7; CI-MS *m/z* 653 (100, $[M + H]^+$). Anal. Calcd for $C_{38}H_{38}O_{10}$ (654.7): C, 69.71; H, 5.85. Found: C, 64.63; H, 5.80.

5,17-Diformyl-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (7). Compound **6** (1.07 g, 1.64 mmol) was refluxed with ethyl bromoacetate (2.75 mL, 24.57 mmol) and anhydrous sodium carbonate (4.86 g, 45.85 mmol) in dry acetonitrile (80 mL) for 19 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with HCl (5%) and water, dried over $MgSO_4$, and concentrated to dryness. A small amount of cold Et_2O was added to precipitate out the product **7** as a white solid: yield 78%; TLC eluent hexane/ethyl acetate 1:1; mp125−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 2H), 7.11 (s, 4H), 6.68 (s, 6H), 6.64−6.63 (m, 4H), 4.80 (d, ^2J = 13.7 Hz, 4H), 4.80 (s, 4H), 4.68 (s, 4H), 4.20 (q, ^3J = 7.2 Hz, 8H), 3.32 (d, ^2J = 13.7 Hz, 4H), 1.27 (t, ^3J = 7.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 169.8, 169.5, 161.2, 155.8, 136.0, 135.8, 135.3, 134.0, 133.8, 130.8, 130.2, 129.0, 128.5, 123.5, 123.3, 71.3, 60.7, 31.4, 14.2; CI-MS *m/z* 825 (100, $[M + H]^+$). Anal. Calcd for $C_{46}H_{48}O_{14}$ (824.9): C, 66.98; H, 5.87. Found: C, 66.89; H, 5.82.

5,17-Dicarboxyl-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (8). Compound **7** (0.85 g, 1.03 mmol) dissolved in a mixture of acetone/$CHCl_3$ (1:1, 20 mL) was cooled at 0 °C, and a solution of H_2NSO_3H (0.40 g, 4.12 mmol) in 4 mL of water was added followed by $NaClO_2$ (0.33 g, 3.6 mmol). The mixture was stirred at room temperature overnight. The solvent was removed, the residue was partitioned between ethyl acetate (35 mL) and HCl (10%, 35 mL), and the organic layer was separated, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue was precipitated with cold MeOH to give product **8** as a white solid: yield 45%; mp > 200 °C; TLC eluent hexane/ethyl acetate 1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, ^3J = 7.2 Hz, 4H), 7.05 (t, ^3J = 7.2 Hz, 2H), 6.80 (s, 4H), 4.88 (d, ^2J = 14.1 Hz, 4H), 4.81 (s, 4H), 4.51 (s, 4H), 4.23 (q, ^3J = 7.2 Hz, 4H), 4.16 (q, ^3J = 7.2 Hz, 4H), 3.25 (d, ^2J = 14.1 Hz, 4H), 1.29 (t, ^3J = 7.2 Hz, 6H), 1.26 (t, ^3J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 170.5, 169.0, 159.2, 156.9, 135.9, 133.3, 130.1, 129.8, 124.1, 123.7, 71.5, 71.0, 60.9, 60.3, 31.4, 14.1; CI-MS *m/z* 857 (100, $[M + H]^+$). Anal. Calcd for $C_{46}H_{48}O_{16}$ (856.9): C, 64.48; H, 5.65. Found: C, 64.40; H, 5.59.

5,17-Di(chlorocarbonyl)-25,26,27,28-tetrakis(ethoxycarbonylmethoxy)calix[4]arene (9). Compound **8** (0.25 g, 0.29 mmol) was dissolved in dry CH_2Cl_2 (10 mL), oxalyl chloride (0.5 mL, 5.84 mmol) was added, and the mixture was stirred at room temperature for 6 h. The solvent was removed at reduced pressure, and the residue was dried under vacuum to give the product **9** as a white solid in quantitative yield: mp 78−79 °C; IR (liquid film) ν_{max} 1754 cm^{-1} (CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 4H), 6.60−6.45 (m, 6H), 4.90 (d, ^2J = 14.3 Hz, 4H), 4.60 (s, 8H), 4.23 (q, ^3J = 7.1 Hz, 4H), 4.22 (q, ^3J = 7.1 Hz, 4H), 3.35 (d, ^2J = 14.3 Hz, 4H), 1.30 (t, ^3J = 7.1 Hz, 6H), 1.29 (t, ^3J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 167.3, 162.5, 155.1, 136.3, 132.3, 132.3, 128.7, 127.6, 123.6, 71.2, 60.8, 60.7, 31.2, 14.0, 14.1; CI-MS *m/z* 895 (50, $[M + H]^+$).

Compound 10a. A solution of **9** (0.161 g, 0.18 mmol) in dry CH_2Cl_2, (1.5 mL) and a dry CH_2Cl_2 solution (1.5 mL) containing **4a** (0.11 g, 0.18 mmol) and Et_3N (0.10 mL, 0.72 mmol) were simultaneously perfused into a solution of Et_3N (0.051 mL, 0.365 mmol) in dry CH_2Cl_2 (170 mL) over 2.5 h. The mixture was stirred at room temperature overnight. The organic solution was washed with HCl (5%, 10 mL) and water (140 mL) and dried over $MgSO_4$ and the solvent removed at reduced pressure to give a residue that was purified by flash column chromatography (dichloromethane/methanol 10:1), yielding **10a** as a white solid: yield 50%; TLC eluent dichloromethane/methanol 11:1; mp 170−171 °C; $[\alpha]^{20}_D$ = −22.7 (*c* = 1.11, in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, ^3J = 6.8 Hz, 1H), 7.34 (d, ^3J = 7.4 Hz, 1H), 7.28−7.25 (m, 10H), 7.13−7.11 (m, 4H), 6.93−6.86 (m, 2H), 6.63 (d, ^3J = 6.9 Hz, 1H), 6.60 (d, ^3J = 6.9 Hz, 1H), 6.50 (d, ^3J = 1.7 Hz, 2H), 6.40 (d, ^3J = 1.7 Hz, 2H), 5.01 (d, ^2J = 16.6 Hz, 2H), 4.93 (d, ^2J = 16.6 Hz, 2H), 4.90 (d, ^2J = 13.4 Hz, 4H), 4.48 (bs, 6H), 4.24 (q, ^3J = 7.1 Hz, 4H), 4.20−4.18 (m, 2H), 4.14 (q, ^3J = 7.1 Hz, 4H), 3.96−3.85 (m, 4H), 3.73 (d, ^3J(H,P) = 11.2 Hz, 3H), 3.26 (d, ^2J = 13.4 Hz, 2H), 3.24 (d, ^2J = 14.3 Hz, 2H), 3.01−2.99 (m, 2H), 2.84 (dd, ^3J = 7.9 Hz, ^2J = 13.6 Hz, 2H), 1.33 (d, ^3J = 6.5 Hz, 6H), 1.30 (t, ^3J = 7.2 Hz, 6H), 1.25 (t, ^3J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.8, 170.6, 169.6, 167.0, 157.1, 156.8, 136.7, 135.9, 135.6, 133.7, 132.9, 130.9, 129.6, 128.7, 127.6, 126.8, 125.9, 123.3, 71.7, 70.9, 66.5, 60.9, 60.3, 55.2, 50.6, 49.8, 36.6, 36.1, 31.2, 17.6, 17.3, 14.1; ESI-MS *m/z* 1363.8 (100, $[M + Na]^+$), 1341.8 (20, $[M + H]^+$). Anal. Calcd for $C_{71}H_{81}O_{20}N_4P$ (1341.4): C, 63.57; H, 6.09; N, 4.18. Found: C, 63.51; H, 5.98; N, 4.10.

Compound 10b. Compound **10b** was prepared with the same procedure reported for compound **10a**. The product was purified by flash column chromatography (dichloromethane/methanol 7:1): yield 42%; TLC eluent dichloromethane/

methanol 7:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.51 (s, 1H), 7.73 (t, ^3J = 7.7 Hz, 2H), 7.37 (d, ^3J = 7.6 Hz, 2H), 7.26 (bs, 2H), 7.17 (d, ^3J = 7.4 Hz, 2H), 7.13 (d, ^3J = 7.3 Hz, 2H), 7.12 (t, ^3J = 7.2 Hz, 2H), 7.05 (d, ^3J = 7.3 Hz, 2H), 7.03 (s, 1H), 6.99 (s, 1H), 6.86 (t, ^3J = 7.0 Hz, 2H), 6.84 (d, ^3J = 6.2 Hz, 1H), 6.78 (d, ^3J = 6.2 Hz, 1H), 6.63 (bs, 2H), 6.44 (bs, 2H), 4.99−4.89 (m, 4H), 4.52 (d, ^2J = 16.7 Hz, 2H), 4.48 (d, ^2J = 16.7 Hz, 2H), 4.42−4.40 (m, 2H), 4.26 (q, ^3J = 7.1 Hz, 2H), 4.25 (q, ^3J = 7.1 Hz, 4H), 4.15 (q, ^3J = 7.1 Hz, 2H), 4.08−4.04 (m, 2H), 3.93−3.80 (m, 4H), 3.71 (d, ^3J(H,P) = 11.2 Hz, 3H), 3.27 (d, ^2J = 12.5 Hz, 2H), 3.24 (d, ^2J = 12.5 Hz, 2H), 2.99−2.95 (m, 4H), 1.33−1.23 (m, 18H); ESI-MS *m*/*z* 1441.5 (100, $[M + Na]^+$), 1419.7 (20, $[M + H]^+$). Anal. Calcd for $C_{75}H_{83}O_{20}N_6P$ (1419.5): C, 63.46; H, 5.89; N, 5.92. Found: C, 63.58; H, 5.98; N, 5.96.

Compound 11a. A mixture of **10a** (0.05 g, 0.037 mmol) and NaI (0.06 g, 0.373 mmol) in dry acetone (5 mL) was stirred and heated at 60 °C in a Schlenk tube for 4 days. The solution was concentrated to dryness, the residue was dissolved in CH_2Cl_2 (5 mL), washed with water (5 mL), dried over $MgSO_4$, and the solvent was removed at reduced pressure to give a residue which was purified by precipitation with cold Et_2O, yielding the product **11a** as a yellowish solid: yield: 73%; TLC eluent dichloromethane/methanol 11:1; mp > 160 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, ^3J = 7.0 Hz, 2H), 7.67 (bs, 2H), 7.26−7.13 (m, 14H), 7.07 (s, 4H), 6.90 (t, ^3J = 7.2 Hz, 2H), 5.09 (bs, 4H), 4.80 (d, ^2J = 13.4 Hz, 2H), 4.74 (d, ^2J = 13.4 Hz, 2H), 4.47 (bs, 4H), 4.20 (q, ^3J = 6.9 Hz, 4H), 4.13−4.07 (m, 6H), 3.79−3.77 (m, 2H), 3.52−3.49 (m, 4H), 3.30−3.27 (m, 4H), 2.80 (dd, ^3J = 5.8 Hz, ^2J = 13.6 Hz, 2H), 2.71−2.69 (m, 2H), 1.25 (d, ^3J = 7.0 Hz, 6H), 1.18 (t, ^3J = 7.2 Hz, 6H), 1.12 (d, ^3J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 170.6, 169.0, 157.4, 156.8, 137.0, 135.7, 135.6, 133.6, 133.3, 129.6, 129.4, 128.6, 127.4, 126.7, 126.2, 123.4, 71.7, 70.9, 66.6, 60.9, 60.3, 51.1, 49.7, 36.2, 31.5, 17.9, 14.2, 14.1; ESI-MS *m*/*z* 1349.7 (100, $[M + Na]^+$). Anal. Calcd for $C_{70}H_{79}O_{20}N_4P$ (1327.4): C, 63.34; H, 6.00; N, 4.22. Found: C, 63.29; H, 5.99; N, 4.15.

Compound 11b. Compound **11b** was prepared with the same procedure reported for compound **11a**. The product was purified by flash column chromatography (dichloromethane/methanol 9:1): yield 35%; TLC eluent dichloromethane/methanol 7:1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 2H), 8.13 (bs, 1H), 7.74 (bs, 1H), 7.64 (d, ^3J = 7.2 Hz, 2H), 7.33 (d, ^3J = 7.4 Hz, 2H), 7.23−7.03 (m, 16H), 6.98 (t, ^3J = 7.2 Hz, 2H), 6.86 (t, ^3J = 7.2 Hz, 2H), 5.07 (bs, 4H), 4.79 (d, ^2J = 12.8 Hz, 2H), 4.75 (d, ^2J = 15.3 Hz, 2H), 4.47 (bs, 4H), 4.21−4.08 (m, 10H), 3.92−3.90 (m, 2H), 3.61−3.59 (m, 4H), 3.35−2.20 (m, 4H), 2.86−2.84 (m, 4H), 1.25 (t, ^3J = 7.2 Hz, 12H), 1.18 (d, ^3J = 6.7 Hz, 6H); ESI-MS *m*/*z* 1403 (80, $[M - H]^-$). Anal. Calcd for $C_{74}H_{81}O_{20}N_6P$ (1405.4): C, 63.24; H, 5.81; N, 5.98. Found: C, 63.50; H, 5.88; N, 5.71.

Compound 12. A solution in methanol of compound **11a** was titrated with a solution of Bu_4NOH (0.001 M) in methanol to obtain, after evaporation of the solvent, the anionic receptor **12** in quantitative yield as a solid: mp 133−134 °C; $[\alpha]^{20}_D$ = +1.3 (*c* = 0.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, ^3J = 6.8 Hz, 2H), 7.29 (d, ^3J = 5.3 Hz, 2H), 7.23 (t, ^3J = 4.8 Hz, 4H), 7.19−7.13 (m, 6H), 6.94 (t, ^3J = 5.6 Hz, 2H), 6.61 (bs, 2H), 6.53 (bs, 2H), 6.52 (bs, 2H), 5.04−5.00 (m, 4H), 4.89 (d, ^2J = 13.4 Hz, 4H), 4.48 (bs, 4H), 4.36−4.34 (m, 2H), 4.25 (q, ^3J = 7.1 Hz, 4H), 4.15 (q, ^3J = 7.1 Hz, 4H), 4.06−4.03 (m, 2H), 3.86−3.83 (m, 4H), 3.28−3.23 (m, 8H), 3.25 (d, ^2J = 13.4 Hz, 2H), 3.24 (d, ^2J = 14.3 Hz, 2H), 3.00 (dd, ^3J = 5.7 Hz, ^2J = 13.4 Hz, 2H), 2.94−2.92 (m, 2H), 1.65−1.62 (m, 8H), 1.45−1.39 (m, 8H), 1.33−1.25 (m, 18H), 0.98 (t, ^3J = 10.8 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 171.5, 170.0, 157.2, 137.0, 136.1, 136.0, 129.9, 128.9, 127.3, 126.9, 124.0, 71.9, 71.2, 65.6, 59.8, 59.7, 59.6, 51.8, 49.7, 36.7, 31.8, 30.1, 24.6, 20.2, 18.1, 14.1, 14.0; ESI-MS *m*/*z* 1326 (80, $[M - NBu_4]^-$). Anal. Calcd for $C_{86}H_{114}O_{20}N_5P$ (1568.8): C, 65.84; H, 7.32; N, 4.46. Found: C, 65.79; H, 7.90; N, 4.37.

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Supporting Information Available: General experimental methods and 1D and 2D ^{1}H NMR spectra of pseudopeptides and receptors are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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