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Correlation between Conformational Equilibria of Free Host and Guest Binding Affinity in Non-preorganized Receptors

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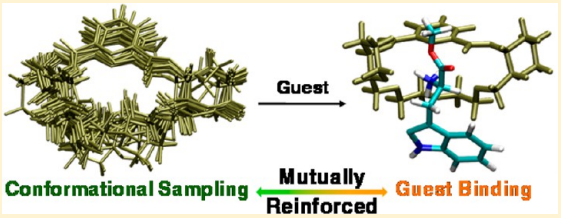
Supporting Information

ABSTRACT: Positive cooperativity between host conformational equilibria and guest binding has been widely reported in protein receptors. However, reported examples of this kind of cooperativity in synthetic hosts are scarce and largely serendipitous, among other things because it is hard to envision systems which display this kind of cooperativity. In order to shed some light on the correlation between conformational equilibria of free host and guest binding, selected structural modifications have been performed over a family of nonpreorganized hosts in order to induce conformational changes and to analyze their effect on the binding affinity. The conformational effect was evaluated by a theoretical conformational search and correlated with the ability of the receptors. All data suggest that those receptors that display the best association constants are able to sample folded conformations analogous to the conformational requirements for the binding of the guests. On the contrary, for those receptors where folded conformers are scarce, then the association constant and enantioselectivity clearly drop.



INTRODUCTION

Conformational landscape induced by the chemical structure is one of the main factors governing the design and synthesis of efficient receptors.[1] Traditionally, good binding affinities have been envisioned by conformational control through highly organized and/or rigid structural features, in order to restrict the conformational freedom toward the optimal geometry for binding.[2] Recently, though, it has been postulated that conformational equilibria in a flexible receptor can also enhance the binding affinity due to positive cooperativity between the conformational landscape of the receptor and the noncovalent interactions between host and guest.[3,4] Indeed, intrareceptor noncovalent interactions involved in the conformational equilibria of free host may induce the same conformational restrictions on parts of the receptor than guest binding. It has been proved that conformational rearrangements identical to those required by guest binding contribute to relieve part of the adverse binding entropy and therefore to favor complex stability.[5] Consequently, binding is not only mediated by direct host−guest interactions but also by intrareceptor interactions, both of which are mutually reinforced. Such positive cooperative mechanism is fairly frequent in proteins, but there are just a few precedents reported in synthetic receptors,[6−9] among other reasons because accomplishment of this kind of cooperativity in synthetic systems represents a substantial challenge in terms of design. Consequently, dissection of molecular mechanisms by which conformational rearrangements of the host reinforce molecular recognition is highly relevant, and thus the development of simple models to study this kind of cooperativity is imperative in order to facilitate a smart control and further useful application of this exciting strategy to enhance guest binding.[10]

In this regard, we have recently reported that small synthetic receptor **1*cis*** (Figure 1)[11] displays such a positively cooperative mechanism, which was proved by isothermal titration calorimetry (ITC) and by a linear-free energy relationship (LFER) between the thermodynamic potential and the activation energy of association.[9] Therefore, receptor **1*cis*** may constitute an excellent model system to gain insight on the correlation between the performance of the receptor and the conformational effect of certain structural features. Receptor **1*cis*** has a folded bound state, and a similar folded conformation is also found in free **1*cis*** (Figure 2a). Preorganization, though, can be excluded because the system is quickly switching between two degenerate folded conformations, continuously unfolding and refolding.[9] Herein, we report the modulation of such conformational landscape through structural modifications made on receptor **1*cis***. Conformational equilibria of all receptors were analyzed through a theoretical conformational search and correlated to the binding affinity and to the enantiodiscrimination.

RESULTS AND DISCUSSION

The conformational equilibria were tuned through three variables: the stereochemistry of the tetrahydropyran unit, the

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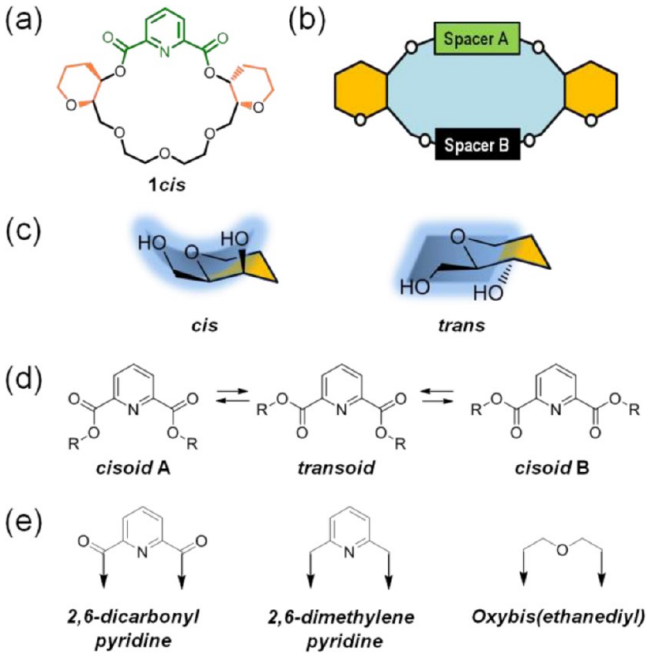

Figure 1. (a) Receptor **1*cis***. (b) Design for the whole family of receptors synthesized. (c) Effect of the stereochemistry of the tetrahydropyran unit: at least one conformer of the *cis* isomer is curved whereas *trans* isomer is completely flat. (d) Conformational equilibria for 2,6-pyridine diester: there are two *cisoid* conformers and two equivalent *transoid* conformers, all having similar stability. (e) Spacers employed.

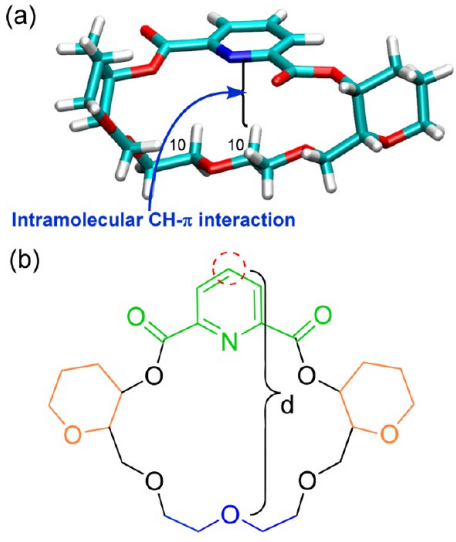

Figure 2. (a) Crystal structure of receptor **1*cis***.[11] (b) Distance taken as the geometrical parameter to determine the folded geometry of the receptors.

nature and position of the spacers. On one hand, it has been reported that *trans* stereochemistry of the tetrahydropyran unit yields close to flat conformations, whereas *cis* stereochemistry induces curvature.[12] On the other hand, the 2,6-dicarbonylpyridine spacer is involved in well-known *cisoid*−*transoid* conformational equilibria due to dipole−dipole interactions between both carbonyl moieties and the pyridine nitrogen, which are reportedly able to cause relevant shape changes in receptors.[13] As the folded receptor displays a *transoid* conformation on the 2,6-dicarbonyl pyridine spacer, it is also relevant to explore the effect of structural modifications over the pyridine spacer, particularly on the carbonyl moieties. Finally, there are two linking points for the spacers with completely different dynamical properties (spacers A and B in Figure 1b), with the secondary alcohol less flexible, as it is directly bonded to the tetrahydropyran ring. Accordingly, the family of receptors shown in Scheme 1 was synthesized and analyzed.

Synthesis of all receptors was carried out from the same starting material for each stereochemical series through a divergent synthetic strategy (Scheme 2). To carry out the synthesis of compounds **1*cis***, **2*cis***, and **3*cis*** (Scheme 2), the diol **10*cis*** was selectively protected involving 1,3-benzylidene ketalization followed by DIBAL-H reduction to give the benzyl ether **11*cis***. The O-alkylation of the primary alcohol of **11*cis*** with diethylene glycol ditosylate followed by cleavage of the benzyl protecting group under hydrogenation conditions provided the diol **15*cis*** in good yield. The diol **15*cis*** was used as a common precursor for the synthesis of receptors **1*cis***, **2*cis***, and **3*cis***. The diester **1*cis*** was prepared by reacting 2,6-pyridinedicarbonyl dichloride with the diol **15*cis***. The O-alkylation of the secondary alcohol of diol **15*cis*** with 2,6-bis(bromomethyl)pyridine provided the receptor **2*cis***. When this reaction was carried out using as alkylating reagent diethylene glycol ditosylate we obtained the receptor **3*cis***.

To perform the synthesis of the receptors **6*cis*** and **9*cis***, a selective protection of primary alcohol of the diol **10*cis*** with benzyl bromide provided the benzyl ether **12*cis***. Then, the same sequence of reactions described above to obtain receptors **2*cis*** and **1*cis*** from alcohol **11*cis*** was applied to alcohol **12*cis*** to give receptors **6*cis*** and **9*cis***, respectively. In order to obtain receptors **4*cis***, **5*cis***, and **8*cis***, it was necessary change the nature of the protective group. Thus, the diol **10*cis*** was protected, as the bis-silyl ethers, followed by selective deprotection of the silyl ether of the primary alcohol to afford compound **17*cis***, which was used to obtain the diol **18*cis*** by O-alkylation with 2,6-bis(bromomethyl)pyridine and further deprotection of the silyl protective groups. Using the same reactions to obtain receptors **1*cis*** and **2*cis*** from diol **15*cis***, in the diol **18*cis*** afforded receptors **4*cis*** and **5*cis***, respectively. To carry out the synthesis of receptor **8*cis*** a silyl protective group less prone to migrate was used. Thus, the diol **10*cis*** was monoprotected as the triisopropylsilyl ether **19*cis***, which was used to obtain receptor **8*cis*** using the same sequence of reactions described to obtain receptor **4*cis***. The synthesis of all receptors with stereochemical ***trans*** were performed with identical synthetic strategy but using as starting material the diol **10*trans*** (Scheme 1S in the Supporting Information). Unfortunately, all attempts to make both receptors **7** were unfruitful due to the formation of multiple oligomeric products.

The association constants (K_a) of the hosts with the methyl ester of amino acid ammonium picrates (G^+Pic^-) in $CHCl_3$ at 298 K were determined on the basis of the differential UV spectrometry at three wavelengths (380, 385, and 390 nm) by the typical nonlinear least-squares method (1:1 simulation).[14] The measured K_a, the enantioselectivity (K_D/K_L), and the Gibbs free energy of association (ΔG_a) are summarized in Table 1 except for receptors **3**, **7**, and **8**, both *cis* and *trans*, as they display unsatisfactory association constants (K_a < 100 M^{-1}). On one hand, Table 1 shows the high influence of the stereochemistry. Undoubtedly, there is a general superior ability of receptors *cis* respect to receptors *trans*. This fact is particularly notable for receptors **1** and **4**. Thus the association

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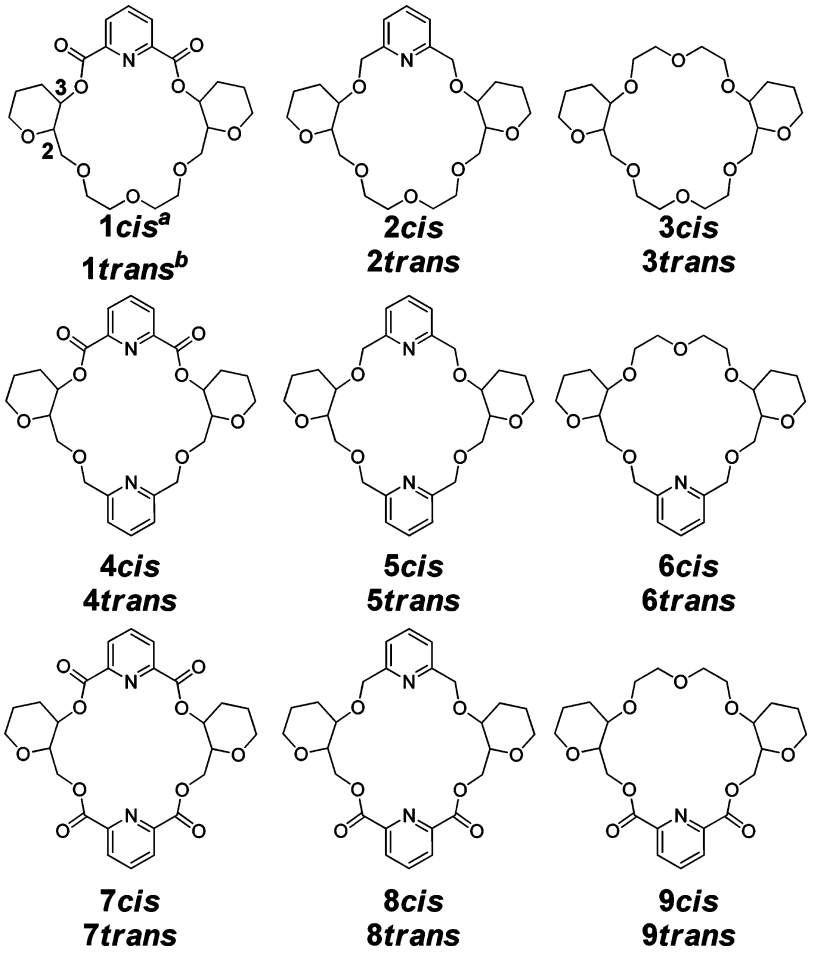
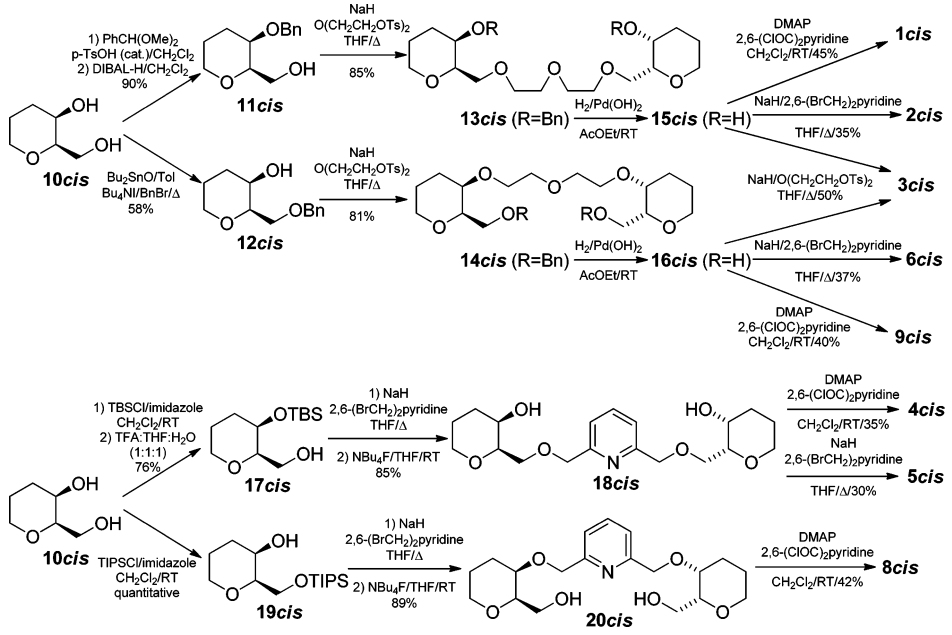
Scheme 1. Chemical Structure of the Family of Receptors Studied[a]



[a]Key: (a) **2*R*, 3*R***; (b) **2*R*, 3*S***.

Scheme 2. Synthesis of *All-Cis* Receptors



constant of **1*trans*** with D-Trp-OMe$^+$ drops almost 6 times compared to that of **1*cis***, and the enantiodiscrimination decreases more than three times, and a similar behavior is observed for receptors **4*cis*** and **4*trans***. On the other hand, the

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Table 1. Association Constants (K_a), Enantioselectivity (K_D/K_L), Gibbs Free Energy of Association (ΔG_a in kJ mol^{-1}), and $\Delta\Delta G_a$ Calculated from ΔG_a for Complexation of the Hosts with Chiral Organic Ammonium Picrates in $CHCl_3$ at 298 K

host	guest[a]	K_a[b,c] (M^{-1})	K_D/K_L	$-\Delta G_a$	$\Delta\Delta G_a$	host	guest[a]	K_a[b,c] (M^{-1})	K_D/K_L	$-\Delta G_a$	$\Delta\Delta G_a$
1*cis*	D-Ala-OMe$^+$	25990[d]	1.80	25.19	1.46	**1*trans***	D-Ala-OMe$^+$	7350	1.00	22.06	0.00
1*cis*	L-Ala-OMe$^+$	14410[d]		23.73		**1*trans***	L-Ala-OMe$^+$	7370		22.06	
1*cis*	D-Trp-OMe$^+$	76190[d]	10.39	27.85	5.80	**1*trans***	D-Trp-OMe$^+$	12770	3.12	23.43	2.82
1*cis*	L-Trp-OMe$^+$	7330[d]		22.05		**1*trans***	L-Trp-OMe$^+$	4090		20.61	
2*cis*	D-Ala-OMe$^+$	210	0.48	13.25	−1.83	**2*trans***	D-Ala-OMe$^+$	410	1.37	14.91	0.78
2*cis*	L-Ala-OMe$^+$	440		15.08		**2*trans***	L-Ala-OMe$^+$	300		14.13	
2*cis*	D-Trp-OMe$^+$	540	1.69	15.59	1.30	**2*trans***	D-Trp-OMe$^+$	360	0.58	14.58	−1.35
2*cis*	L-Trp-OMe$^+$	320		14.29		**2*trans***	L-Trp-OMe$^+$	620		15.93	
4*cis*	D-Ala-OMe$^+$	13510	1.41	23.57	0.85	**4*trans***	D-Ala-OMe$^+$	3460	0.99	20.19	−0.02
4*cis*	L-Ala-OMe$^+$	9590		22.72		**4*trans***	L-Ala-OMe$^+$	3480		20.21	
4*cis*	D-Trp-OMe$^+$	30360	7.69	25.57	5.05	**4*trans***	D-Trp-OMe$^+$	6740	2.32	21.84	2.08
4*cis*	L-Trp-OMe$^+$	3950		20.52		**4*trans***	L-Trp-OMe$^+$	2910		19.76	
5*cis*	D-Ala-OMe$^+$	720	1.26	16.30	0.58	**5*trans***	D-Ala-OMe$^+$	*e*			
5*cis*	L-Ala-OMe$^+$	570		15.72		**5*trans***	L-Ala-OMe$^+$				
5*cis*	D-Trp-OMe$^+$	440	0.61	15.08	−1.22	**5*trans***	D-Trp-OMe$^+$				
5*cis*	L-Trp-OMe$^+$	720		16.30		**5*trans***	L-Trp-OMe$^+$				
6*cis*	D-Ala-OMe$^+$	1620	1.54	18.31	1.07	**6*trans***	D-Ala-OMe$^+$				
6*cis*	L-Ala-OMe$^+$	1050		17.24		**6*trans***	L-Ala-OMe$^+$				
6*cis*	D-Trp-OMe$^+$	1550	1.44	18.20	0.89	**6*trans***	D-Trp-OMe$^+$				
6*cis*	L-Trp-OMe$^+$	1080		17.31		**6*trans***	L-Trp-OMe$^+$				

[a]Picrate salts were used. [b]The association constants were determined on the basis of differential UV/vis spectroscopy at three wavelengths (380, 385, and 390 nm) by the typical nonlinear least-squares method (1:1 simulation). [c]These values are the average of at least three independent measurements. [d]Values obtained from ref 11. [e]Association constant lower than 100 M^{-1}.

nature of the spacers seems to be another fundamental factor for the ability of the receptor. Accordingly, it is noticeable that enantioselectivities are low except for **1*cis*** and **4*cis***, which have remarkably high ones. In fact, host **1*cis*** presents 2 orders of magnitude higher association constants and better enantioselectivity than host **2*cis***. As Table 1 shows, the association constant of **1*cis*** with D-Trp-OMe$^+$ is 76190 M^{-1}, whereas for **2*cis*** it is 540 M^{-1} and the enantioselectivity (K_D/K_L) for the same substrate is 10.39 and 1.69, respectively. Receptor **4*cis*** is also much better than **5*cis*** displaying an association constant with D-Trp-OMe$^+$ almost 70 times higher and much better enantiodiscrimination. It should be emphasized that the only difference between host **1*cis*** and **2*cis*** and between **4*cis*** and **5*cis*** is the presence of the carbonyl groups next to the pyridine. However, the chemical nature of the spacer is not enough to generate a good binding and chiral discrimination ability in the receptor. Indeed, receptors **1*cis*** and **4*cis*** are isomers of **9*cis*** and **8*cis***, respectively, with the only difference being the way in which spacers are linked to the tetrahydropyran rings and yet the effect of that subtle difference is dramatic: receptors **9*cis*** and **8*cis*** show very low association constant and enantiodiscrimination. In conclusion, Table 1 shows there are two essential structural features for a receptor to be good: *cis* stereochemistry in the tetrahydropyran unit and 2,6-pyridine dicarbonyl as spacer A.

To gain insight into the conformational effect of such structural features, a theoretical conformational analysis was performed. Conformations were analyzed using the low-mode search (LMOD),[15] a fast and useful method to scan the whole conformational space of this kind of molecules. Obtained conformers (up to 10000 steps) were minimized using MMFF (charges provided by FF and TNGC method) in order to remove duplicates or conformers with an energy above 21 kJ mol^{-1} (5.02 kcal mol^{-1}). Significant conformational differences among the receptors are observed, but they are better discussed if a definition of folded geometry in such systems is proposed.

First, a reference system was taken. It is reasonable to consider the crystal structure of receptor **1*cis*** as the folded reference of the free receptors (Figure 2a). Second, a good parameter to follow the folding of the receptors is required. The distance between the central oxygen of the oxybis(ethanediyl) spacer B and the carbon atom in *para* position of the pyridine, or equivalent positions in each receptor, defines quite well the folding degree (Figure 2b), and therefore, it was considered as the geometrical parameter of folding. Measured on the reference system it is 5.26 Å. That value was considered the geometrical reference of folding. Finally, in order to define what a folded conformer is, a borderline was set at 6 Å which includes a top margin of almost 15% respect the folding reference value. Thus, if the distance between those selected positions is smaller than 6 Å the receptor is considered folded and it is considered unfolded if the distance is larger. According to that, there is clearly a prevalence of unfolded conformers on those receptors lacking carbonyls in spacer A or displaying *trans* stereochemistry. Indeed, among the conformers found within a 21 kJ mol^{-1} range from the global minimum (Figure 3c), 23 out of 50 conformers of receptor **1*cis*** (46%) are folded whereas they represent only four out of 35 conformers of receptor **2*cis*** (11.4%) and 33 out of 168 conformers of receptor **1*trans*** (19.6%). Moreover, while the most stable conformers of receptor **1*cis*** are folded, exactly the opposite happens to receptor **2*cis*** which lacks the carbonyls (Figure 3b). Analogous analyses can be done for receptors **4*cis***, **5*cis***, and **4*trans***. Another remarkable result extracted from the conformational search is that the carbonyls do not decrease the number of conformers by reducing flexibility as it could be expected. On the contrary, receptor **1*cis*** has more conformers (50) than receptor **2*cis*** (35) within a 21 kJ mol^{-1} range from the global minimum.

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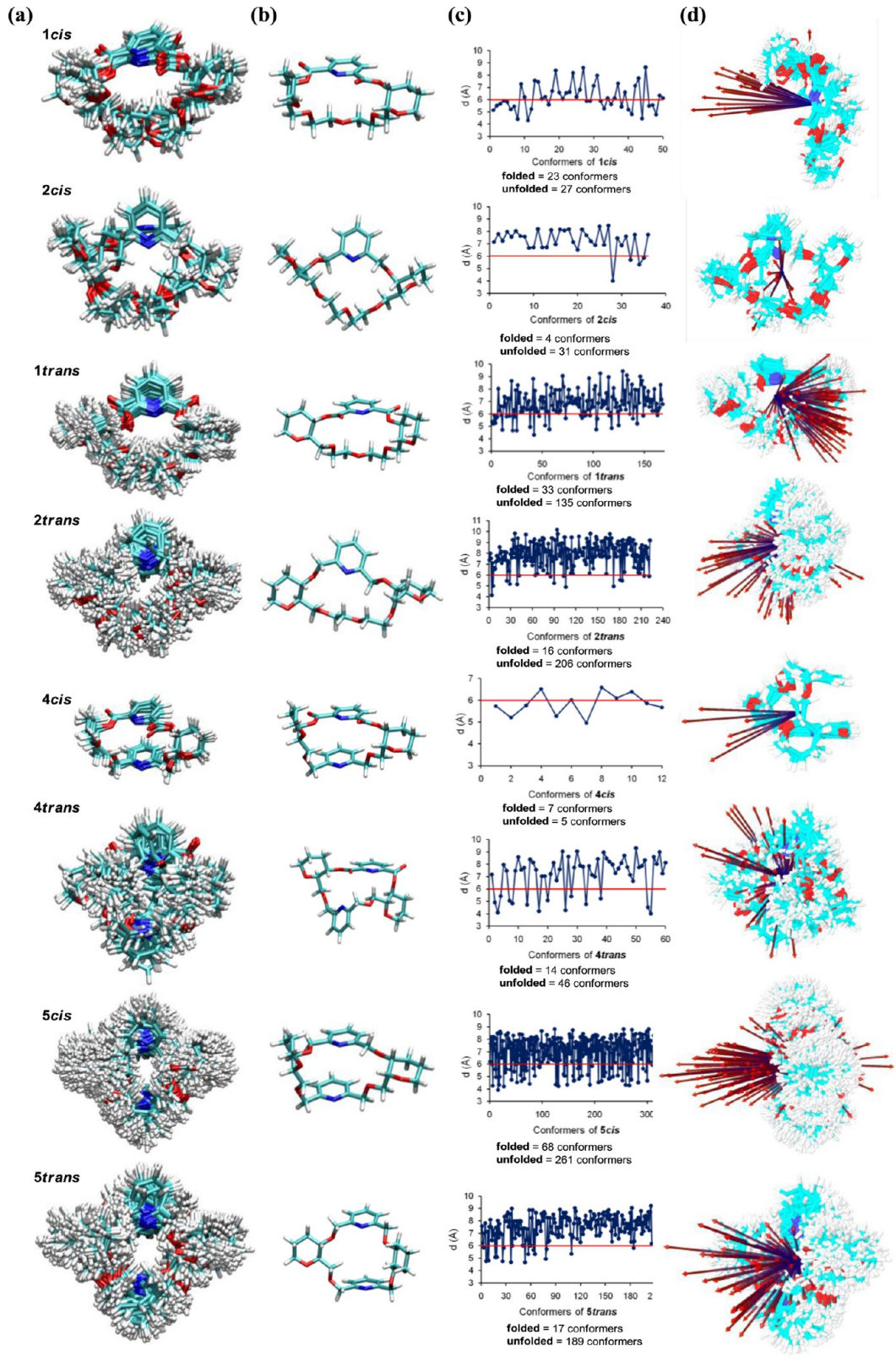

Figure 3. (a) Clustering of conformers within 16 kJ mol^{-1} from the global minimum just for visualization ease only. (b) Most stable conformer. (c) Representation of all the conformers found within 21 kJ mol^{-1} from the global minimum vs the geometrical parameter of folding *d*. The borderline was set at 6 Å (red line); thus, all of the conformers below that value are considered folded and vice versa. (d) Clustering of conformers within 16 kJ mol^{-1}, showing the molecular dipole moments. Vector directions are represented from the positive to the negative charge and their lengths are proportional to the magnitudes of the molecular dipole moments.

A simple NMR experiment can be carried out to verify the repercussions of the appropriate combination of spacer A and stereochemistry on the folding as the computational studies suggested. It consists of comparing equivalent peaks of

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receptors **1*cis*** and **2*cis*** or receptors **4*cis*** and **5*cis***, since the last member of both couples lacks the carbonyls in spacer A. The peaks corresponding to hydrogen 10 and 11 in the pyridine of spacer B are shifted upfield for receptor **4*cis*** with respect to receptor **5*cis*** (Figure 4b), indicating that the pyridine ring of

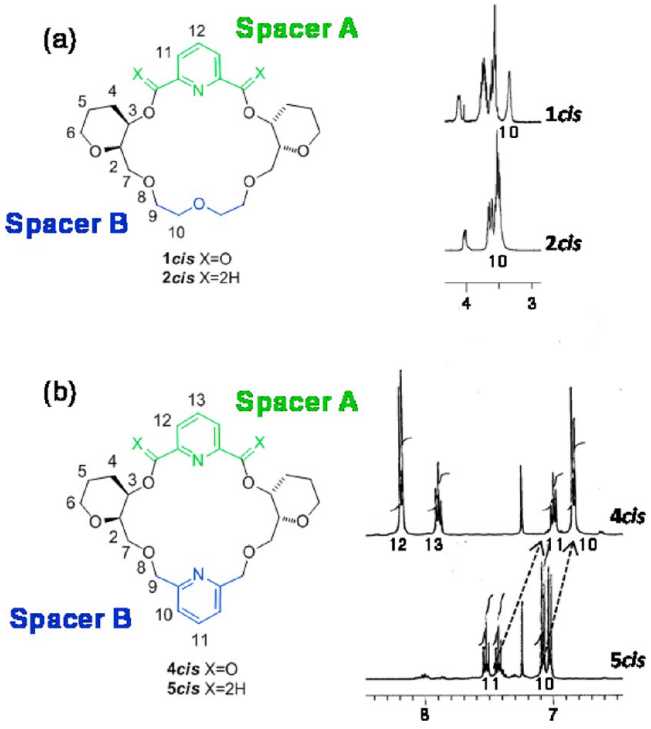

Figure 4. Experimental evidence of the increased set of folded conformers in (a) **1*cis*** and (b) **4*cis***.

the spacer A is close to the pyridine ring of the spacer B, therefore suggesting a greater role of folded conformers in receptor **4*cis***. Analogously, the peak corresponding to hydrogen 10 in receptor **1*cis*** (Figure 4a) is clearly shifted upfield with respect to the analogous peak of receptor **2*cis***, implying that the pyridine of spacer A is on average closer to the oxybis(ethanediyl) spacer (spacer B) in receptor **1*cis***, therefore suggesting a more relevant role of folded conformers. Indeed, the X-ray structure of receptor **1*cis*** (Figure 2a)[11] unequivocally shows a folded structure with the 2,6-pyridine dicarbonyl spacer (spacer A) in the *transoid* conformation, which might suggest some influence of a dipole−dipole interaction between the carbonyls and the pyridine. An intramolecular CH−π interaction between hydrogen 10 and the pyridine is also observed, which is probably assisting the folding.[16] It is noteworthy that crystal packing is usually driven by an improvement of the noncovalent bonding that restricts dynamic behavior.[3]

In addition, a careful geometrical analysis of the **1*cis***·D-Trp-OMePic complex structure in $CDCl_3$ by NMR[14] shows a folded structure also for the complex. Intramolecular ROEs were observed (Figure 5a) between protons in position 10 and 10′ with protons 11 and 11′ of the pyridine and cross peak ROE between pyridine proton 11′ and axial proton 5′. In combination with the coupling constants of all peaks, a 3D structure of the complex could be obtained (Figure 5b).[17] The structure of receptor **1*cis*** upon binding in $CDCl_3$ is quite similar to some of the conformers found in the conformational search of free receptor **1*cis***.

All of the conformational studies above-mentioned suggest that there is an evident correlation between folded conformations and an enhanced ability of the receptor. Indeed, the computational study also shed light on the reason for such correlation: Most of the folded conformers of **1*cis*** and **4*cis*** have their molecular dipole moment pointing toward the recognition cavity, while the unfolded conformers, which are preponderant in the rest of receptors like **2*cis***, do not show such an orientation (Figure 3d). It is well-known that the existence of permanent dipoles within the host is important to explain the ability of cation receptors. Indeed, Hay et al. have already pondered the effect of the orientation of the dipole moments of every single building block in multidentated hosts.[18] In our case, receptors **1*cis*** and **4*cis*** display a considerable set of folded conformations which, at the same time, have a convergent orientation of molecular dipole moments, particularly well arranged for guest binding, and therefore, those receptors are understandably the best ones.

■ CONCLUSION

In summary, we have examined the conformational effect of certain structural features on the binding affinity and chiral discrimination of a synthetic receptor. All of the data indicate a high relevance of specific moieties that induce the same conformational restrictions than guest binding. In particular, a combination of *cis* stereochemistry and 2,6-dicarbonylpyridine as spacer A increase the set of folded conformers analogous to the complex geometry. It was found that folded conformers display their molecular dipole toward the recognition cavity which favors guest binding. As mentioned, it can be stated that the best receptors sample conformations in the free state that impose similar local restrictions than guest binding. This causes a mutual reinforcement of conformational sampling and binding, or in other words, a reinforced molecular recognition, which has been already confirmed by other means in receptor **1*cis*** and analogous receptors.[8,9] Conformational sampling by the free receptor is known to play a vital role in the catalytic activity of enzymes,[19] allosteric signaling,[20] and ligand binding in proteins.[21] Therefore, it is markedly relevant to understand the correlation between the conformational landscape induced by structural modifications and the function that finally emerges, although this is an extremely challenging task. Model systems based on synthetic receptors such as those presented herein are useful for shedding light on the mechanisms by which the dynamics play a role in the reinforced molecular recognition and catalysis, which is highly relevant in a number of important fields, including enzymatic catalysis and drug development.

■ EXPERIMENTAL SECTION

Materials and General Methods. ^{1}H NMR spectra were recorded at 500, 400, or 300 MHz, ^{13}C NMR spectra were recorded at 75 or 100 MHz, and chemical shifts are reported in ppm and referenced to the solvent peak. The temperature was calibrated with methanol and ethylene glycol standards. Melting points were taken on a capillary melting point apparatus and are uncorrected. Optical rotations were obtained on a polarimeter at 589 nm at 25 °C using a 10 cm path length and a 1.0 mL volume. Concentration (c) is reported in g per 100 mL of the solvent specified. Infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}). Low- and high-resolution mass spectra were recorded with dual-focusing sector field analyzer mass spectrometers by using fast atom bombardment (FAB) mode or with TOF analyzer mass spectrometers by using electrospray ionization (ESI) mode, as specified in each case. Column chromatography was

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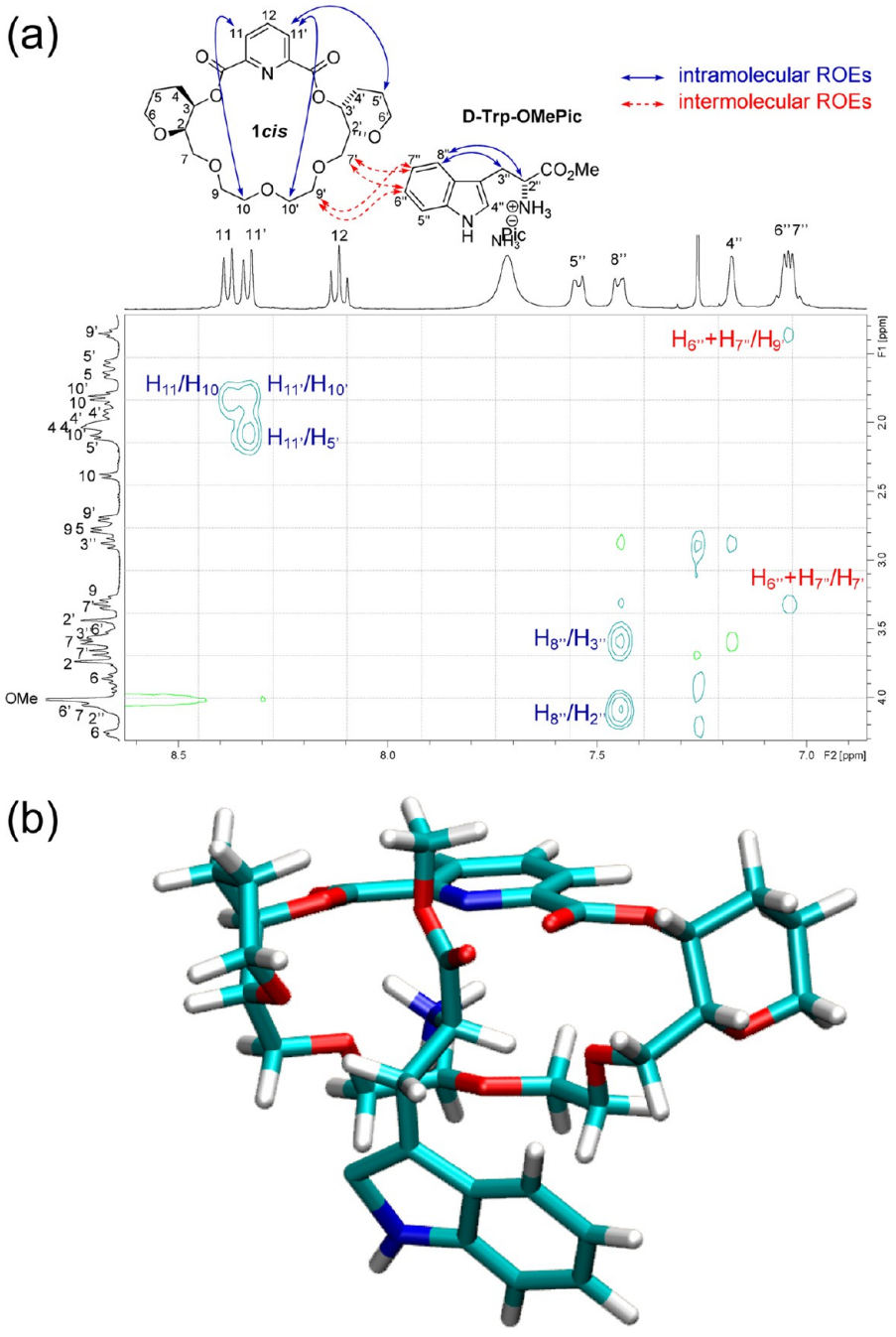

Figure 5. (a) 2D ROESY section showing crucial intra- and intermolecular ROEs for complex **1*cis***·D-Trp-OMePic in $CDCl_3$ at 223 K. (b) 3D structure of complex **1*cis***·D-Trp-OMePic in $CDCl_3$.

performed on silica gel, 60 Å and 0.2−0.5 mm. Compounds were visualized by use of UV light, 2.5% phosphomolybdic acid in ethanol or vanillin with acetic and sulfuric acid in ethanol with heating. All solvents were purified by standard techniques.[22] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions. Compounds **10*cis***,[12,23] **10*trans***,[23] **11*trans***,[24] **17*cis***,[12] and **17*trans***[25] were prepared as previously described.

Synthesis of 11*cis*. To a stirred solution of diol **10*cis*** (2.0 g, 15.1 mmol) in dry CH_2Cl_2 (50 mL) were sequentially added a catalytic amount of CSA (175 mg, 0.8 mmol) and benzaldehydedimethyl acetal (3.4 mL, 22.7 mmol) at room temperature. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion to the benzylidene derivative. Then Et_3N was added until pH ≈ 7, and the mixture was stirred for 5 min, evaporated under reduced pressure, and purified by silica gel flash-chromatography. To a stirred solution of the benzylidene derivative in dry CH_2Cl_2 (150 mL) at 0 °C was added dropwise DIBAL-H (76 mL, 1 M in hexane, 76 mmol). The reaction mixture was stirred for 30 min, quenched with water (3 mL), and allowed to warm to room temperature. The mixture was stirred for 30 min, dried over $MgSO_4$, and filtered through a pad of Celite. The solvent was evaporated, and the residue was purified by silica gel flash chromatography, yielding **11*cis*** (3.03 g, 90% overall yield) as an oil: $[\alpha]^{25}_D = -58.9$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.35−1.49 (m, 2H), 1.96−2.15 (m, 2H), 2.34 (bs, 1H), 3.40−3.45 (m, 1H), 3.49 (s, 1H), 3.55 (dd, *J* = 4.2, 11.5 Hz, 1H), 3.84 (dd, *J* = 7.1, 11.5 Hz, 1H), 4.03 (m, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.7 (t), 25.8 (t), 63.5 (t), 68.0 (t), 70.6 (t), 71.9 (d), 79.5 (d), 127.7 (d), 127.9 (d), 128.4 (d), 138.2 (s), 170.1 (s); IR (film, NaCl plates)

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(cm^{-1}) 3431, 2932, 2945, 2852, 1455, 1209, 1099; LRMS (FAB) *m/ z* (relative intensity) 245 $[M + Na]^+$ (16), 223 $[M + H]^+$ (43), 91 (100); HRMS (FAB) *m/ z* calcd for $C_{13}H_{18}O_3Na$ $[M^+ + Na]$ 245.1154, found 245.1150.

Synthesis of 13*cis*. To a stirred solution of the alcohol **11*cis*** (2.0 g, 9.0 mmol) and diethylene glycol ditosylate (1.87 g, 4.5 mmol) in dry THF (59 mL) under nitrogen was added NaH was added (396 mg, 9.9 mmol, 60% oil dispersion) at room temperature. The mixture was stirred at reflux for 7 h. Then, the reaction mixture was cooled to room temperature and diluted with Et_2O. The mixture was washed with an aqueous saturated NH_4Cl solution and then dried, filtered, concentrated, and purified by silica gel flash chromatography, yielding the benzyl ether **13*cis*** (1.97 g, 85% yield) as an oil: $[\alpha]^{25}_D = -51.0$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.34 (d, *J* = 13.4 Hz, 2H), 1.44 (m, 2H), 1.97 (m, 2H), 2.08 (d, *J* = 13.9 Hz, 2H), 3.43−3.62 (m, 18H), 3.98 (m, 2H), 4.39 (d, *J* = 12.1 Hz, 2H), 4.62 (d, *J* = 12.1 Hz, 2H), 7.21−7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.6 (t), 25.9 (t), 67.9 (t), 70.3 (t), 70.6 (t), 70.8 (t), 71.3 (d), 71.5 (t), 78.4 (d), 127.4 (d), 127.8 (d), 128.2 (d), 138.5 (s); IR (film, NaCl plates) (cm^{-1}) 2943, 2858, 1455, 1213, 1100; LRMS (FAB) *m/z* (relative intensity) 553 $[M + K]^+$ (7), 537 $[M + Na]^+$ (76), 515 $[M + H]^+$ (40), 91 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{43}O_7$ $[M + H]^+$ 515.3009, found 515.3009.

Synthesis of 13*trans*. The same procedure as the one followed for the synthesis of **13*cis*** was applied to **11*trans*** (2.0 g, 9.0 mmol) to afford **13*trans*** (2.01 g, 87% yield) as an oil: $[\alpha]^{25}_D = -55.6$ (c 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.33−1.49 (m, 2H), 1.56−1.67 (m, 4H), 2.24 (m, 2H), 3.27−3.40 (m, 6H), 3.63 (m, 10H), 3.76 (m, 2H), 3.92 (d, *J* = 11.3 Hz, 2H), 4.46 (d, *J* = 11.6 Hz, 2H), 4.60 (d, *J* = 11.6 Hz, 2H), 7.25−7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.4 (t), 67.8 (t), 70.4 (t), 70.8 (t), 70.9 (t), 71.2 (t), 73.4 (d), 80.4 (d), 127.6 (d), 127.7 (d), 128.3 (d), 138.5 (s); IR (film, NaCl plates) (cm^{-1}) 2937, 2862, 1718, 1456, 1272, 1098; LRMS (FAB) *m/z* (relative intensity) 537 $[M + Na]^+$ (28), 515 $[M + H]^+$ (15), 136 (17), 91 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{43}O_7$ $[M + H]^+$ 515.3009, found 515.3021.

Synthesis of 15*cis*. A mixture of the benzyl ether **13*cis*** (1.9 g, 3.7 mmol) and $Pd(OH)_2$ (100 mg) in EtOAc (37 mL) was placed under H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography affording **15*cis*** (1.23 g, quantitative) as an oil: $[\alpha]^{25}_D = -1.2$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.32 (d, *J* = 12.2 Hz, 2H), 1.58 (m, 2H), 1.89−2.06 (m, 4H), 3.32 (s, 2H), 3.42 (dd, *J* = 5.1, 5.1 Hz, 4H), 3.55−3.69 (m, 12H), 3.84 (m, 2H), 3.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.2 (t), 30.2 (t), 65.5 (d), 68.6 (t), 70.4 (t), 70.8 (t), 72.3 (t), 77.9 (d); IR (film, NaCl plates) (cm^{-1}) 3440, 2925, 2860, 1444, 1215, 1091; LRMS (FAB) *m/z* (relative intensity) 357 $[M + Na]^+$ (39), 335 $[M + H]^+$ (61), 55 (100); HRMS (FAB) *m/z* calcd for $C_{16}H_{31}O_7$ $[M + H]^+$ 335.2070, found 335.2054.

Synthesis of 15*trans*. The same procedure as the one followed for the synthesis of **15*cis*** was applied to **13*trans*** (1.95 g, 3.8 mmol) to obtain **15*trans*** (1.27 g, quantitative yield) as an oil: $[\alpha]^{25}_D = -2.3$ (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.43 (dddd, *J* = 12.4, 12.4, 12.4, 4.9 Hz, 2H), 1.60−1.75 (m, 4H), 2.09 (m, 2H), 3.15 (ddd, *J* = 3.8, 3.8, 8.9 Hz, 2H), 3.33 (ddd, *J* = 3.4, 11.3, 11.3 Hz, 2H), 3.56−3.73 (m, 12H), 3.83 (dd, *J* = 3.5, 11.4 Hz, 2H), 3.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 25.4 (t), 31.6 (t), 66.9 (d), 68.0 (t), 70.5 (t), 70.6 (t), 71.8 (t), 81.0 (d)); IR (film, NaCl plates) (cm^{-1}) 3419, 2927, 2858, 1455, 1282, 1092; LRMS (FAB) *m/ z* (relative intensity) 357 $[M + Na]^+$ (38), 335 $[M + H]^+$ (71), 137 (69), 97 (35); HRMS (FAB) *m/z* calcd for $C_{16}H_{30}O_7Na$ $[M + Na]^+$ 357.1889, found 357.1891.

Synthesis of 1*cis*. To a solution of the diol **15*cis*** (115 mg, 0.34 mmol) in dry CH_2Cl_2 (7 mL) under nitrogen were added 2,6-pyridinedicarbonyl dichloride (70 mg, 0.34 mmol) and DMAP (85 mg, 0.69 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C, and the reaction was allowed to warm to room temperature. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel, to yield the receptor **1*cis*** (72 mg, 45% yield) as an oil: $[\alpha]^{25}_D = -18.6$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.50 (d, *J* = 13.1 Hz, 2H), 1.89 (m, 2H), 2.04 (m, 2H), 2.22 (d, *J* = 13.6 Hz, 2H), 3.28−3.32 (m, 4H), 3.51−3.74 (m, 12H), 4.05 (d, *J* = 11.9 Hz, 2H), 5.27 (s, 2H), 7.97 (dd, *J* = 7.5, 7.5 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 21.0 (t), 27.4 (t), 67.6 (t), 69.3 (d), 70.3 (t), 76.6 (d), 127.4 (d), 137.9 (d), 148.8 (s), 164.2 (s); IR (film, NaCl plates) (cm^{-1}) 2950, 2858, 1719, 1451, 1349, 1246, 1145, 1092; LRMS (FAB) *m/z* (relative intensity) 488 $[M + Na]^+$ (48), 307 (24), 137 (69), 69 (24); HRMS (FAB) *m/z* calcd for $C_{23}H_{31}NO_9Na$ $[M + Na]^+$ 488.1897, found 488.1896.

Synthesis of 1*trans*. The same procedure than the one followed for the synthesis of **1*cis*** was applied to the diol **15*trans*** (200 mg, 0.6 mmol) to obtain **1*trans*** (128 mg, 46% yield) as a solid: mp 110−112 °C; $[\alpha]^{25}_D = +51.5$ (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.68−1.84 (m, 6H), 2.35 (m, 2H), 3.34 (m, 4H), 3.45 (ddd, *J* = 2.3, 11.7, 11.7 Hz, 2H), 3.57 (dd, *J* = 5.3, 5.3 Hz, 4H), 3.61−3.68 (m, 6H), 4.02 (m, 2H), 5.06 (m, 2H), 7.98 (dd, *J* = 7.5, 7.5 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.3 (t), 68.1 (t), 70.6 (t), 71.7 (d), 72.0 (t), 78.1 (d), 127.6 (d), 138.0 (d), 148.7 (s), 163.8 (s); IR (film, NaCl plates) (cm^{-1}) 2949, 2866, 1721, 1454, 1242, 1147, 1099; LRMS (FAB) *m/z* (relative intensity) 504 $[M + K]^+$ (6), 488 $[M + Na]^+$ (10), 466 $[M + H]^+$ (18), 219 (3), 168 (4); HRMS (FAB) *m/z* calcd for $C_{23}H_{32}NO_9$ $[M + H]^+$ 466.2077, found 466.2080.

Synthesis of 2*cis*. To a solution of diol **15*cis*** (110 mg, 0.33 mmol) and 2,6-bis(bromomethyl) pyridine (87 mg, 0.33 mmol) in dry THF (6.6 mL) under nitrogen was added NaH (29 mg, 0.72 mmol, 60% oil dispersion) at room temperature. The reaction mixture was stirred and refluxed for 5 h. Then it was diluted with Et_2O, washed with an aqueous saturated NH_4Cl solution, dried over $MgSO_4$, and filtered, and the solvent was removed and purified by silica gel flash chromatography, yielding receptor **2*cis*** as a white solid (50 mg, 35% yield): mp 50−52 °C; $[\alpha]^{25}_D = -95.1$ (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.41 (d, *J* = 13.4 Hz, 2H), 1.54 (m, 2H), 2.07 (m, 2H), 2.17 (d, *J* = 13.8 Hz, 2H), 3.47−3.71 (m, 18H), 4.03 (m, 2H), 4.59 (d, *J* = 13.2 Hz, 2H), 4.82 (d, *J* = 13.2 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.66 (dd, *J* = 7.6, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.9 (t), 26.1 (t), 68.2 (t), 70.4 (t), 70.5 (t), 70.8 (t), 71.0 (d), 71.7 (t), 77.9 (d), 120.9 (d), 158.0 (s); IR (film, NaCl plates) (cm^{-1}) 2922, 2854, 1592, 1456, 1276, 1101; LRMS (FAB) *m/z* (relative intensity) 460 $[M + Na]^+$ (22), 438 $[M + H]^+$ (20), 137 (74), 69 (35); HRMS (FAB) *m/z* calcd for $C_{23}H_{36}NO_7$ $[M + H]^+$ 438.2496, found 438.2492.

Synthesis of 2*trans*. The same procedure as the one followed for the synthesis of **2*cis*** was applied to the diol **15*trans*** (100 mg, 0.3 mmol) to obtain **2*trans*** (93 mg, 71% yield) as an oil: $[\alpha]^{25}_D = +94.8$ (c 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.41 (dddd, *J* = 11.6, 11.6, 11.6, 11.6 Hz, 2H), 1.65 (m, 4H), 2.31 (d, *J* = 9.3 Hz, 2H), 3.24 (d, *J* = 9.3 Hz, 2H), 3.31 (m, 2H), 3.43−3.51 (m, 8H), 3.64 (m, 6H), 3.91 (d, *J* = 10.7 Hz, 2H), 4.59 (d, *J* = 12.9 Hz, 2H), 4.78 (d, *J* = 12.9 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.65 (dd, *J* = 7.7, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.3 (t), 67.8 (t), 70.2 (t), 70.5 (t), 70.8 (t), 71.7 (t), 72.8 (d), 80.5 (d), 120.6 (d), 136.9 (d), 158.0 (s); IR (film, NaCl plates) (cm^{-1}) 2928, 2859, 1593, 1456, 1276, 1095; LRMS (FAB) *m/z* (relative intensity) 460 $[M + Na]^+$ (20), 438 $[M + H]^+$ (74), 437 $[M]^+$ (8), 137 (66); HRMS (FAB) *m/z* calcd for $C_{23}H_{36}NO_7$ $[M + H]^+$ 438.2492, found 438.2511.

Synthesis of 3*cis*. To a stirred solution of the diol **15*cis*** (110 mg, 0.33 mmol) and diethylene glycol ditosylate (136 mg, 0.33 mmol) in dry THF (6.6 mL, 0.05 M), under nitrogen, was added NaH (29 mg, 0.72 mmol, 60% oil dispersion) at room temperature. The mixture was stirred at reflux for 7 h. Then, the reaction mixture was cooled to room temperature and was diluted with Et_2O. The mixture was washed with an aqueous saturated NH_4Cl solution and then dried, filtered, concentrated, and purified by silica gel flash chromatography, yielding the receptor **3*cis*** as a white solid (66 mg, 50% yield): mp 48−50 °C; $[\alpha]^{25}_D = -43.8$ (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.34 (d, *J* = 13.4 Hz, 2H), 1.48 (m, 2H), 1.93 (m, 2H), 2.06 (d, *J* =

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13.9 Hz, 2H), 3.50−3.76 (m, 26H), 3.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.7 (t), 25.9 (t), 68.1 (t), 68.3 (t), 70.3 (t), 70.6 (t), 71.0 (t), 71.9 (d), 78.0 (d); IR (film, NaCl plates) (cm^{-1}) 2922, 2859, 1461, 1214, 1099; LRMS (FAB) *m*/*z* (relative intensity) 427 $[M + Na]^+$ (38), 405 $[M + H]^+$ (44), 91 (100); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{36}O_8Na$ $[M + Na]^+$ 427.2308, found 427.2316.

Synthesis of 3*trans*. The same procedure as the one followed for the synthesis of **3*cis*** was applied to the diol **15*trans*** (120 mg, 0.36 mmol) to obtain **3*trans*** (78 mg, 54% yield) as an oil: $[\alpha]^{25}_D$ = +54.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.36 (m, 2H), 1.67 (m, 4H), 2.24 (m, 2H), 3.24 (m, 2H), 3.38 (m, 4H), 3.60−3.78 (m, 20H), 3.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 25.3 (t), 29.4 (t), 68.0 (t), 68.7 (t), 70.5 (t), 70.8 (t), 71.0 (t), 73.7 (d), 80.5 (d); IR (film, NaCl plates) (cm^{-1}) 2929, 2863, 1457, 1276, 1097; LRMS (FAB) *m*/*z* (relative intensity) 427 $[M + Na]^+$ (17), 405 $[M + H]^+$ (39), 137 (69), 97 (41); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{36}O_8$ $[M]^+$ 404.2410, found 404.2392.

Synthesis of 12*cis*. To a solution of diol **10*cis*** (27.8 g, 210.6 mmol) in toluene (420 mL, 0.5 M) was added Bu_2SnO (68 g, 273.8 mmol) and the solution refluxed in a Dean−Stark overnight. The reaction mixture was cooled, Bu_4NI (101 g, 273.8 mmol) and benzyl bromide (32.6 mL, 273.8 mmol) were added, and the mixture was refluxed 4 h. The mixture was cooled to room temperature and filtered through Celite, the solvent was removed under vacuum, and it was purified by silica gel flash chromatography to afford **12*cis*** (27.3 g, 58% yield as an oil): $[\alpha]^{25}_D$ = +54.0 (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.35−1.40 (m, 1H), 1.62−1.66 (m, 1H), 1.91−2.02 (m, 2H), 2.77 (s, 1H), 3.46−3.52 (m, 2H), 3.64 (d, *J* = 4.9 Hz, 2H), 3.83 (s, 1H), 4.03 (ddd, *J* = 1.8, 3.0, 11.3 Hz, 1H), 4.56 (s, 2H), 7.25−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.0 (t), 30.2 (t), 66.0 (d), 68.6 (t), 71.4 (t), 73.7 (t), 78.2 (d), 127.7 (d), 127.8 (d), 128.3 (d), 137.6 (s); IR (film, NaCl plates) (cm^{-1}) 2929, 2863, 1457, 1276, 1097; LRMS (FAB) *m*/*z* (relative intensity) 223.1 $[M + Na]^+$ (40), 245.1 $[M + H]^+$ (10); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{19}O_3$ $[M + H]^+$ 223.1334, found: 223.1338.

Synthesis of 12*trans*. The same procedure as the one followed for the synthesis of **12*cis*** was applied to the diol **10*trans*** (5.0 g, 38.0 mmol) to obtain **12*trans*** (8.1 g, 96% yield) as an oil: $[\alpha]^{25}_D$ = −80.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.41 (m, 1H), 1.67 (m, 2H), 2.11 (m, 1H), 2.77 (s, 1H), 2.85 (d, *J* = 3.0 Hz, 1H), 3.27 (m, 1H), 3.35 (m, 1H), 3.56 (m, 1H), 3.67 (dd, *J* = 5.5, 9.8 Hz, 1H), 3.72 (dd, *J* = 5.0, 9.8 Hz, 1H), 3.92 (m, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 7.25−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 25.5 (t), 32.5 (t), 68.1 (t), 69.5 (d), 72.2 (t), 74.1 (t), 80.2 (d), 128.2 (d), 128.9 (d), 138.1 (s); LRMS (FAB) *m*/*z* (relative intensity) 223.1 $[M + H]^+$ (11), 136.0 (91), 91.1 (44); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{19}O_3$ $[M + H]^+$ 223.1334, found 223.1344.

Synthesis of 14*cis*. The same procedure as the one followed for the synthesis of **13*cis*** was applied to alcohol **12*cis*** (2.0 g, 9.0 mmol) to obtain **14*cis*** (1.88 g, 81% yield) as an oil: $[\alpha]^{25}_D$ = −51.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.31−1.46 (m, 4H), 2.03−2.09 (m, 4H), 3.41−3.67 (m, 18H), 3.98 (m, 2H), 4.49 (dd, *J* = 3.0, 12.1 Hz, 2H), 4.60 (dd, *J* = 3.0, 12.1 Hz, 2H), 7.25−7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.7 (t), 26.2 (t), 68.0 (t), 68.6 (t), 70.4 (t), 70.7 (t), 72.9 (d), 73.4 (t), 78.4 (d), 127.5 (d), 127.7 (d), 128.3 (d), 138.3 (s); IR (film, NaCl plates) (cm^{-1}) 2928, 2858, 1720, 1274, 1095; LRMS (FAB) *m*/*z* (relative intensity) 537.3 $[M + Na]^+$ (27), 515.3 $[M + H]^+$ (13); HRMS (FAB) *m*/*z* calcd for $C_{30}H_{43}O_7$ $[M + H]^+$ 515.3009, found 515.3009.

Synthesis of 14*trans*. The same methodology used to obtain **14*cis*** was applied to alcohol **12*trans*** (2.0 g, 9.0 mmol) to obtain **14*trans*** (1.92 g, 83% yield) as an oil: $[\alpha]^{25}_D$ = +23.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.25−1.43 (m, 2H), 1.65−1.69 (m, 4H), 2.03−2.07 (m, 2H), 3.25−3.48 (m, 12H), 3.64−3.73 (m, 6H), 3.92−3.96 (m, 2H), 4.54 (dd, *J* = 2.3, 12.3 Hz, 2H), 4.61 (dd, *J* = 2.3, 12.3 Hz, 2H), 7.22−7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.4 (t), 67.8 (t), 68.3 (t), 69.9 (t), 70.7 (t), 73.5 (t), 74.3 (d), 80.4 (d), 127.4 (d), 127.8 (d), 128.2 (d), 138.4 (s); IR (film, NaCl plates) (cm^{-1}) 2936, 2861, 1721, 1454, 1278, 1099; LRMS (FAB) *m*/*z* (relative intensity) 515.1 $[M + H]^+$ (6); HRMS (FAB) *m*/*z* calcd for $C_{30}H_{43}O_7$ $[M + H]^+$ 515.3009, found 515.2997.

Synthesis of 6*cis*. A mixture of the benzyl ether **14*cis*** (200 mg, 0.39 mmol) and $Pd(OH)_2$ (15 mg) in EtOAc (37 mL) was placed under H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was filtered through a pad of Celite. The solvent was removed under vacuum, and the crude of the diol **16*cis*** was used in the next step without further purification. Then a solution of the diol **16*cis*** was treated under the same conditions as described to obtain receptor **2*cis*** affording receptor **6*cis*** as a colorless oil (63 mg, 37% yield): $[\alpha]^{25}_D$ = −13.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.24−1.52 (m, 4H), 1.83−2.04 (m, 4H), 3.27−3.69 (m, 18H), 3.97−4.01 (m, 2H), 4.57 (d, *J* = 13.1 Hz, 2H), 4.75 (d, *J* = 13.1 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.69 (dd, *J* = 7.7, 7.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.7 (t), 26.0 (t), 68.1 (t), 68.3 (t), 69.7 (t), 70.2 (t), 72.3 (d), 74.3 (t), 78.1 (d), 121.3 (d), 137.2 (d), 157.5 (s); IR (film, NaCl plates) (cm^{-1}) 2924, 2856, 1724, 1593, 1458, 1213, 1098; LRMS (FAB) *m*/*z* (relative intensity) 460.06 $[M + Na]^+$ (15), 438.1 $[M + H]^+$ (17); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{36}NO_7$ $[M + H]^+$ 438.2496, found 438.2500.

Synthesis of 6*trans*. The same methodology used to obtain **6*cis*** was applied to benzyl ether **14*trans*** (180 mg, 0.35 mmol) to obtain **6*trans*** (66 mg, 43% yield as an oil): $[\alpha]^{25}_D$ = +15.1 (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.25−1.32 (m, 2H), 1.60 (m, 4H), 2.11−2.15 (m, 2H), 3.19−3.71 (m, 18H), 3.85−3.91 (m, 2H), 4.54 (d, *J* = 13.6 Hz, 2H), 4.66 (d, *J* = 13.6 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.1 (t), 29.2 (t), 67.9 (t), 68.2 (t), 68.6 (t), 69.6 (t), 70.7 (t), 73.9 (d), 74.2 (t), 80.1 (d), 121.1 (d), 136.9 (d), 157.8 (s); IR (film, NaCl plates) (cm^{-1}) 2933, 2861, 1592, 1459, 1095; LRMS (FAB) *m*/*z* (relative intensity) 438.3 $[M + H]^+$ (6); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{36}NO_7$ $[M + H]^+$ 438.2492, found 438.2540.

Synthesis of 9*cis*. A solution of the benzyl ether **14*cis*** (190 mg, 0.37 mmol) was treated under the same conditions as described to obtain receptor **1*cis*** to afford receptor **9*cis*** (69 mg, 40% yield) as a colorless oil: $[\alpha]^{25}_D$ = −18.6 (c 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.36−1.58 (m, 4H), 1.92−2.10 (m, 4H), 3.48−4.03 (m, 2H), 4.34 (dd, *J* = 10.0, 10.0 Hz, 2H), 4.77 (dd, *J* = 4.6, 9.9 Hz, 2H), 7.99 (dd, *J* = 7.7, 7.7 Hz, 1H), 8.29 (d, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.8 (t), 25.8 (t), 62.8 (t), 68.1 (t), 68.4 (t), 69.7 (t), 70.8 (d), 75.4 (d), 128.0 (d), 138.0 (d), 148.3 (s), 165.0 (s); IR (film, NaCl plates) (cm^{-1}) 2924, 2853, 1723, 1641, 1343, 1142, 1095; LRMS (FAB) *m*/*z* (relative intensity) 504.09 $[M + K]^+$ (6), 488.15 $[M + Na]^+$ (7), 466.2 $[M + H]^+$ (9); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{32}NO_9$ $[M + H]^+$ 466.2077, found 466.2068.

Synthesis of 9*trans*. The same methodology used to obtain **9*cis*** was applied to the benzyl ether **14*trans*** (180 mg, 0.35 mmol) to obtain **9*trans*** (70 mg, 43% yield) as a solid: $[\alpha]^{25}_D$ = +12.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.32−1.42 (m, 2H), 1.64−1.68 (m, 4H), 2.25−2.29 (m, 2H), 3.34−3.43 (m, 4H), 3.49−3.56 (m, 2H), 3.59−3.71 (m, 6H), 3.77−3.82 (m, 2H), 3.92 (m, 1H), 3.95 (m, 1H), 4.58 (dd, *J* = 2.7, 11.7 Hz, 2H), 4.84 (dd, *J* = 2.7, 11.7 Hz, 2H), 7.97 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.25 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$, 298 K) δ = 25.1 (t), 29.2 (t), 64.8 (t), 68.0 (t), 68.2 (t), 70.0 (t), 73.8 (d), 79.2 (d), 104.2 (s), 116.4 (s), 127.6 (d), 137.8 (d); IR (film, NaCl plates) (cm^{-1}) 1725, 1601, 1322, 1144, 1100; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{31}NO_9Na$ $[M + Na]^+$ 488.1897, found 488.1902.

Synthesis of 18*cis*. Alcohol **17*cis*** (1.2 g, 4.87 mmol) was dissolved in dry THF (45 mL, 0.1 M). 2,6-Bis(bromomethyl)pyridine (430 mg, 1.62 mmol) was added along with a catalytic amount of NBu_4I. The reaction mixture was stirred and cooled to 0 °C. NaH (60%, 215 mg, 5.35 mmol) was then added.The mixture was allowed to sit at room temperature overnight. Water was added and the mixture extracted with AcOEt (3 × 30 mL). The organic phases were collected and dried over $MgSO_4$, the solvent was removed under vacuum, and the crude was used in the next step without further purification. To a solution of the mentioned crude in dry THF (8 mL,

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0.2 M) was added NBu_4F (1 M in THF, 2.1 mL, 2.1 mmol). After 5 h, water was added (10 mL) and the mixture extracted with AcOEt (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, the solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography to afford **18*cis*** (506 mg, 85% overall yield) as an oil: $[\alpha]^{25}_D$ = +1.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.36−1.46 (m, 2H), 1.54−1.64 (m, 4H), 1.90−1.97 (m, 2H), 3.27−3.30 (m, 2H), 3.48−3.52 (m, 2H), 3.63−3.68 (m, 4H), 3.85 (s, 2H), 3.97 (dd, *J* = 3.4, 8.4 Hz 2H), 4.59 (d, *J* = 13.6 Hz, 1H), 4.64 (d, *J* = 13.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.64 (dd, *J* = 7.6, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 24.1 (t), 30.1 (t), 65.2 (d), 68.5 (t), 71.6 (t) 73.6 (t), 78.0 (d), 120.5 (d), 137.5 (d), 157.4 (s); IR (film, NaCl plates) (cm^{-1}) 3372, 2941, 2874, 1461, 1881; LRMS (FAB) *m*/*z* (relative intensity) 368 $[M + H]^+$ (5.3), 242 (100), 184 (8.4), 142 (12.9); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{30}NO_6$ $[M + H]^+$ 368.2073, found 368.2068.

Synthesis of 18*trans*. The same methodology used to obtain **18*cis*** was applied to alcohol **17*trans*** (2.0 g, 8.1 mmol) to obtain **18*trans*** (0.9 g, 60% overall yield) as an oil: $[\alpha]^{25}_D$ = −11.2 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.47 (dddd, *J* = 5.1, 11.7, 11.7, 11.7 Hz, 2H), 1.63−1.69 (m, 4H), 2.07−2.13 (m, 2H), 3.17−3.21 (m, 2H), 3.36 (ddd, *J* = 3.5, 10.1, 10.1 Hz, 2H), 3.72−3.82 (m, 4H), 3.89−3.94 (m, 2H), 4.02 (dd, *J* = 3.1, 10.1, 10.1 Hz, 2H), 4.67 (d, *J* = 13.2 Hz, 4H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.68 (dd, *J* = 7.7, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.6 (t), 31.5 (t), 66.0 (d), 68.3 (t), 71.2 (t), 72.3 (t), 81.7 (d), 121.7 (d), 138.1 (d), 151.7 (s); IR (film, NaCl plates) (cm^{-1}) 3428, 2939, 2860, 1643, 1039; LRMS (FAB) *m*/*z* (relative intensity) 390 $[M + Na]^+$ (80.3), 368 $[M + H]^+$ (100), 242 (35.5), 186 (12.7), 133 (6.8); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{30}NO_6$ $[M + H]^+$ 368.2073, found 368.2056.

Synthesis of 4*cis*. Starting from the diol **18*cis*** (200 mg, 0.54 mmol), the same methodology used to obtain receptor **1*cis*** was employed to yield receptor **4*cis*** as a colorless oil (95 mg, 35% yield): $[\alpha]^{25}_D$ = −25.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.49−1.52 (m, 2H), 1.83−1.90 (m, 2H), 2.00−2.15 (m, 4H), 3.58−3.77 (m, 8H), 4.10−4.13 (m, 2H), 4.43 (d, *J* = 12.9 Hz, 2H), 4.52 (d, *J* = 12.9 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 7.01 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.91 (dd, *J* = 7.8, 7.8 Hz, 1 H), 8.2 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.9 (t), 27.6 (t), 68.1 (t), 68.9 (d), 69.1 (t), 74.0 (t), 76.4 (d), 120.0 (d), 127.7 (d), 136.1 (d), 137.6 (d), 148.1 (s), 156.5 (s), 163.4 (s); LRMS (FAB) *m*/*z* (relative intensity) 536.91 $[M + K]^+$ (18), 521 $[M + Na]^+$ (18), 499.04 $[M + H]^+$ (100); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{31}N_2O_8$ $[M + H]^+$ 499.2080, found 499.2104.

Synthesis of 4*trans*. The same methodology used to obtain **4*cis*** was applied to diol **18*trans*** (200 mg, 0.54 mmol) to obtain **4*trans*** (100 mg, 37% yield) as an oil: $[\alpha]^{25}_D$ = +16.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.66−1.90 (m, 6H), 2.26−2.30 (m, 2H), 3.46 (ddd, *J* = 2.2, 11.7, 11.7 Hz, 2H), 3.58−3.63 (m, 4H), 3.72−3.76 (m, 2H), 4.01−4.05 (m, 2H), 4.44 (d, *J* = 13.0 Hz, 2H), 4.56 (d, *J* = 13.0 Hz, 2H), 5.12 (m, 2H), 6.74 (m, 3H), 7.92 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.3 (t), 68.2 (t), 70.0 (t), 70.96 (d), 73.9 (t), 78.0 (d), 119.7 (d), 127.6 (d), 135.8 (d), 137.5 (d), 148.3 (s), 156.8 (s), 163.1 (s); IR (film, NaCl plates) (cm^{-1}) 2924, 2853, 1727, 1712, 1367, 1168; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{30}N_2O_8Na$ $[M + Na]^+$ 521.1900, found 521.1909.

Synthesis of 5*cis*. Diol **18*cis*** (67 mg, 0.18 mmol) was dissolved in dry THF (3.6 mL, 0.05M), and 2,6-bis(bromomethyl)pyridine (48 mg, 0.18 mmol) was added along with a catalytic amount of NBu_4I. The reaction mixture was cooled to 0 °C, and NaH (60%, 18 mg, 0.45 mmol) was added. The mixture was allowed to sit overnight at room temperature, water was added (5 mL), and the mixture was extracted with AcOEt (3 × 5 mL). The combined organic phase were dried over $MgSO_4$, and the solvent was removed under vacuum and purified by silica gel flash chromatography to afford the receptor **5*cis*** (26 mg, 30% yield) as a colorless oil: $[\alpha]^{25}_D$ = +1.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.38 (d, *J* = 13.4 Hz, 2H), 1.49−1.57 (m, 2H), 1.98−2.05 (m, 2H), 2.16 (d, *J* = 13.9 Hz, 2H), 3.49−3.62 (m, 10H), 4.02 (dd, *J* = 3.3, 8.4 Hz, 2H), 4.37 (d, *J* = 13.4 Hz, 4H), 4.66 (d, *J* = 13.4 Hz, 4H), 7.04 (d, *J* = 7.7 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.44 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.54 (dd, *J* = 7.7, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.7 (t), 25.8 (t), 68.2 (t), 69.1 (t), 70.6 (d), 71.5 (t), 73.8 (t), 77.9 (d), 120.6 (d), 120.6 (d), 136.4 (d), 136.7 (d), 157.5 (s), 157.6 (s); IR (film, NaCl plates) (cm^{-1}) 2925, 2854, 1594, 1452, 1102; LRMS (FAB) *m*/*z* (relative intensity) 493 $[M + Na]^+$ (54), 471 $[M + H]^+$ (100), 307 (7.5), 137 (37), 69 (41.3); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{35}N_2O_6$ $[M + H]^+$ 471.2495, found 471.2513.

Synthesis of 5*trans*. The same methodology used to obtain **5*cis*** was applied to diol **18*trans*** (190 mg, 0.52 mmol) to obtain **5*trans*** (73 mg, 30% yield) as an oil: $[\alpha]^{25}_D$ = −10.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ = 1.36−1.49 (m, 2H), 1.68−1.70 (m, 4H), 2.32−2.37 (m, 2H), 3.32 (ddd, *J* = 2.7, 9.3, 9.3 Hz, 2H), 3.37−3.43 (m, 2H), 3.51 (ddd, *J* = 4.5, 9.3, 9.3 Hz, 2H), 3.70 (d, *J* = 2.7 Hz, 4H), 3.98 (d, *J* = 10,6 Hz, 2H), 4.36 (d, *J* = 12.8 Hz, 2H), 4.41 (d, *J* = 12.8 Hz, 2H), 4.66 (dd, *J* = 11.0, 11.0 Hz, 4H), 6.99 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.53 (dd, *J* = 7.6, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (t), 29.1 (t), 68.2 (t), 69.2 (t), 71.2 (t), 72.4 (d), 73.9 (t), 80.1 (d), 120.5 (d), 120.7 (d), 136.7 (d), 157.5 (s), 157.6 (s); IR (film, NaCl plates) (cm^{-1}) 2932, 2868, 1634, 1076; LRMS (FAB) *m*/*z* (relative intensity) 493 $[M + Na]^+$ (11.2), 471 $[M + H]^+$ (80.16), 307 (44.2), 136 (70.5), 69 (51.9); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{35}N_2O_6$ $[M + H]^+$ 471.2495, found 471.2513.

Synthesis of 8*cis*. Diol **10*cis*** (460 mg, 3.5 mmol) was dissolved in dry CH_2Cl_2 (20 mL, 0.175 M), and imidazole (476 mg, 7 mmol) and triisopropylsilyl chloride (0.82 mL, 3.8 mmol) were added. The reaction mixture was evaporated onto silica gel and passed through a short pad of silica using a mixture of 20% hexane in ethyl acetate as eluent to yield quantitatively (1.02 g) the protected diol **19*cis***, which was subsequently dissolved in dry THF (70 mL, 0.05M). Then 2,6-bis(bromomethyl) pyridine (470 mg, 1.77 mmol) and a catalytic amount of tetrabutylammonium iodide (129 mg, 0.35 mmol) were added. Finally, NaH (280 mg, 7 mmol, 60% oil dispersion) was added and the reaction mixture allowed to stir overnight. Water was added and the mixture extracted with AcOEt (3 × 30 mL). The organic phases were collected and dried over $MgSO_4$, the solvent was removed under vacuum, and the crude was used in the next step without further purification. To a solution of the mentioned crude in dry THF (18 mL, 0.1 M) was added NBu_4F (1 M in THF, 3.9 mL, 2.1 mmol). Water was added after 5 h (10 mL) and the mixture extracted with AcOEt (3 × 5 mL). The combined organic phases were dried over $MgSO_4$,and the solvent was removed under vacuum and the mixture purified by silica gel flash chromatography affording **20*cis*** (570 mg, 89% overall yield). Then starting from the diol **20*cis*** (200 mg, 0.54 mmol), the same methodology used to obtain receptor **1*cis*** was employed to yield receptor **8*cis*** as a colorless oil (113 mg, 42% yield): $[\alpha]^{25}_D$ = +42.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.41−1.51 (m, 2H), 1.56−1.61 (m, 2H), 1.95−2.01 (m, 2H), 2.18−2.22 (m, 2H), 3.51 (ddd, *J* = 2.4, 14.0, 14.0 Hz, 2H), 3.59−3.63 (m, 2H), 3.63−3.66 (m, 2H), 4.03−4.07 (m, 2H), 4.24−4.26 (m, 4H), 4.50 (d, *J* = 13.0, 2H), 4.75 (d, *J* = 13.0 Hz, 2H), 7.29 (m, 2H), 7. 39−7.41 (m, 3H), 7.71 (dd, *J* = 7.0, 7.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 20.1 (t), 20.6 (t), 25.2 (t), 26.1 (t), 52.3 (t), 63.5 (t), 67.3 (t), 68.1 (t), 68.2 (t), 68.5 (t), 73.5 (d), 76.0 (d), 123.8 (d), 128.1 (d), 138.5 (d), 144.1 (d), 147.8 (s), 154.4 (s), 164.2 (s); IR (film, NaCl plates) (cm^{-1}) 2941, 2874, 1724, 1594, 1459, 1342, 1317, 1243, 1142, 1097; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{30}N_2O_8Na$ $[M + Na]^+$ 521.1900, found 521.1888.

Synthesis of 8*trans*. Starting from alcohol **10*trans*** (500 mg, 3.8 mmol), the same methodology used to obtain **8*cis*** was employed to yield receptor **8*trans*** (72 mg, 38% overall yield) as an oil: $[\alpha]^{25}_D$ = +57.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 1.40−1.45 (m, 2H), 1.68−1.72 (m, 4H), 2.03−2.05 (m, 2H), 3.37−3.41 (m, 2H), 3.54−3.56 (m, 2H), 3.61−3.65 (m, 2H), 3.92−4.01 (m, 2H), 4.48 (dd, *J* = 3.6, 11.6 Hz, 2H), 4.68 (d, *J* = 13.2 Hz, 2H), 4.75 (d, *J* = 13.2 Hz, 2H), 4.79 (dd, *J* = 3.6, 11.6 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ = 25.1 (t), 25.3

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(t), 32.0 (t), 66.2 (t), 67.4 (t), 67.9 (t), 76.7 (d), 79.7 (d), 128.3 (d), 138.6 (d), 147.7 (s), 147.8 (s), 163.9 (s); IR (film, NaCl plates) (cm^{-1}) 2939, 2877, 1726, 1595, 1341.9, 1243.4, 1143, 1099; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_2O_8Na$ $[M + Na]^+$ 521.1900, found 521.1888.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra, UV titration parameters, bidimensional NMR experiments, and computational details are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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