Glucopyranoside Recognition by Polypyridine-Macrocyclic Receptors Possessing a Wide Cavity with a Flexible Linkage

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New polypyridine-macrocyclic receptors for glucopyranosides were designed and synthesized. The artificial receptors possess a terpyridine skeleton as a hydrogen-bonding site and a flexible polyoxyethylene chain as a bridge for the macrocyclic structure, in which the cavity of the receptors is large enough to incorporate pyranosides. The receptors showed high affinities for *n*-octyl *β*-(D)-glucopyranoside, and selective binding of the receptors was observed between epimeric pyranosides. The results obtained in this paper demonstrated versatility of the terpyridine skeleton as a hydrogen-bonding site for saccharides.

Introduction

Saccharide sugars play important role in biological information transfer events, especially in the intercellular recognition.[1] Thus, artificial receptors that recognize and bind to specific saccharides are receiving increased attention from the viewpoints not only of biomimetic chemistry but also of pharmaceutical science.[2] Among the various artificial receptors, however, only a few of those have been effective for the recognition of saccharides using hydrogen bonds.[3] This is possibly because of the three-dimensional complexity of saccharide structures and the difficult distinction between the families of closely related stereoisomers.[4]

As part of our program aimed at the development of artificial hydrogen-bonding receptors for each of the key saccharides, we have already reported polypyridine-macrocyclic receptors for *β*-ribofuranosides[5,6] and for *β*-deoxyribofuranosides,[7] representative pentoses. To extend this approach to more challenging projects, we targeted artificial hexose saccharide receptors, especially glucose, which is the most important monosaccharide in all biological systems.[8] Here we describe the synthesis and strong complexation of rationally designed, new polypyridine-macrocyclic receptors for *β*-glucopyranosides.

Results and Discussion

Preliminary Experiments for Molecular Design of Glucopyranoside Receptors. In the stable conformation of *β*-glucopyranosides, the three secondary OH groups (2-C, 3-C, and 4-C) are all equatorial, so pseudo-coplanarity of the hydrogen-bonding site for receptors will be necessary. Thus, we first judged whether the hydrogen-bonding site of the ribofuranoside receptor **1** could be used or not for the recognition of glucopyranosides because of its possible coplanar arrangement. The previous paper, however, demonstrated that the affinity of the ribofuranoside receptor **1** for glucose was too weak to obtain any information for the binding as shown by extraction experiments,[5] so that an acyclic receptor **2** was used in order to evaluate the recognition ability of the hydrogen-bonding site for *n*-octyl *β*-(D)-glucopyranoside (**7**) in $CDCl_3$ (Scheme 1). The 1:1 stoichiometries for the complexation of **2** with methyl *β*-(D)-ribofuranoside (**6**) and **7** were confirmed by the continuous variation (Job) plots.[9] Benesi−Hildebrand analysis[10] of the shifts in δ_{NH} for **2** (under conditions of constant [**2**] with varying [**6** and **7**]) by use of ^{1}H NMR revealed that the receptor **2** displayed K_a values of 1.0×10^2 M^{-1} ($-\Delta G_{298} = 11.4$ kJ/mol) and 1.7×10^2 M^{-1} ($-\Delta G_{298} = 12.7$ kJ/mol) for **6** and **7**, respectively (Table 1). The acyclic receptor **2** does bind

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Scheme 1

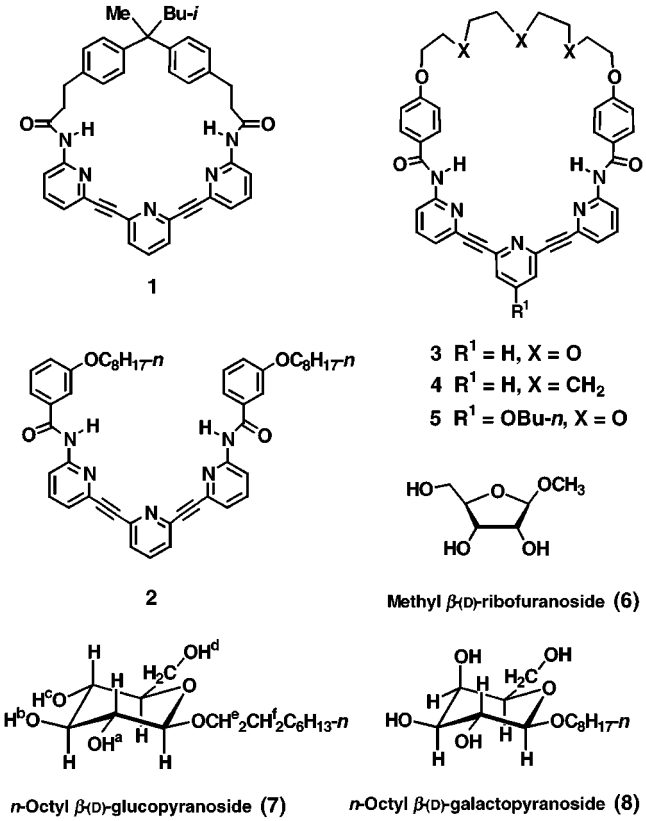

Table 1. Association Constants and Free Energy Changes Determined for the Binding of Monosaccharides 6−8 to the Receptors 2−5 in $CDCl_3$ at 25 °C

receptor	monosaccharide	K_a (M^{-1})	$-\Delta G_{298}$ (kJ/mol)
2	**6**	$(1.0 \pm 0.1) \times 10^2$	11.4
	7	$(1.7 \pm 0.1) \times 10^2$	12.7
	8	$(1.5 \pm 0.1) \times 10^2$	12.4
3	**6**	$(5.2 \pm 0.2) \times 10^3$	21.2
	7	$(5.6 \pm 0.2) \times 10^3$	21.4
	8	$(1.4 \pm 0.1) \times 10^3$	17.9
4	**7**	$(4.7 \pm 0.2) \times 10^3$	20.9
5	**7**	$(7.3 \pm 0.3) \times 10^3$	22.0

glucopyranosides and showed small selectivity for the glucopyranosides in contrast to the ribofuranoside receptor **1**.

Molecular Design. To consider the above results, CPK molecular model examinations were carried out. The terminals of the hydrogen-bonding site of **1** were tightly connected with the short diphenylmethane bridge, so that the cavity of **1** is rather small than that expected. The cavity of **1** is just fitted for incorporating the furanose structure, but too small to recognize the pyranose one by taking advantage of the full potential of the hydrogen-bonding site that may result in the low binding affinity of **1** for glucose (Figure 1). On the other hand, the acyclic, tension-free receptor **2** can easily interact with both **6** and **7** in agreement with the observed K_a values, and the relatively low affinities of **2** compared to those of **1** will be attributed to the free rotation about the pyridine−pyridine axis in **2**. In the terpyridine skeleton, the most predominant conformation of **2** is anticipated for the anti form, in which each pyridine nitrogen atom is located on opposite sides of the ethynediyl bonds in order to cancel the dipoles. Indeed, ab initio calculation revealed that the anti form is more stable than the desired syn form by ca. 10 kJ/mol.[6] The loss in the energy resulting from the rotation about the pyridine−pyridine axis in **2** in order to interact with saccharides may be responsible to the low affinities of **2**. To inhibit the free rotation and to incorporate the pyranose structure, macrocyclic but more relaxed structures are necessary. Thus, we designed new polypyridine-macrocyclic receptors **3**−**5** possessing a large cavity by replacement of the diphenylmethane bridge of **1** by polyoxyethylene and polyethylene chains (Scheme 1).

Synthesis. The polypyridine-macrocyclic receptors **3**−**5** were synthesized from the key intermediates, diamidoterpyridine derivatives **10**, and tetraethylene glycol di-*p*-tosylate or 1,11-undecanediol di-*p*-tosylate by base-mediated macrocyclization in the final step. The acyclic receptor **2** and MOM-protected diamidoterpyridine derivatives **9** (the precursors of **10**) were prepared from 2-ethynylpyridine derivatives **17** and **18** with 2,6-dibromopyridines, respectively, by Sonogashira reaction.[11] The ethynylpyridines **17** and **18** were also synthesized by Sonogashira reaction from **13** and **14**, respectively, followed by deprotection of the acetylene terminal. The amide-substituted bromopyridines **13** and **14** were derived from the corresponding benzoic acids **11** and **12**, respectively (Scheme 2).

Recognition Mode in Solution. The interactions of the receptor **3** in $CDCl_3$ with *n*-octyl β-(D)-glucopyranoside (**7**) were investigated by ^1H NMR. Treatment of a $CDCl_3$ solution of **3** (2.5 mM) with 1 equiv of **7** resulted in several characteristic changes in the spectrum (Figure 2).[12] Large downfield shifts were observed for the 2-C, 3-C, and 4-C OH protons of **7** (H^a: 2.95, H^b: 2.25, and H^c: 2.75 ppm), while the primary 6-C OH proton (H^d: 0.45 ppm) was shifted rather small. The amide-NH proton of **3** was also shifted downfield (0.90 ppm); on the other hand, $OCH^e{}_2CH^f{}_2$ protons of the alkyl glycoside moiety of **7** were largely shifted upfield (H^e: 0.30 and H^f: 0.30 ppm). The downfield shifts reflect the formation of a multipoint hydrogen-bonded complex as expected (but a weak participation only for 6-C OH), and the upfield ones may be attributed to the influence of the diamagnetic anisotropy of the benzene ring of **3** that is perpendicular to the terpyridine site. On the basis of the above observations, a possible recognition mode for the complex (**3**·**7**) is shown in Figure 3.

Quantitative Binding Studies. Benesi−Hildebrand analysis[10] between **3** and **7** gave the association constant (K_a) of 5.6×10^3 M^{-1} ($-\Delta G_{298} = 21.4$ kJ/mol). Noteworthy is the fact that the increased binding affinity compared to that for the acyclic **2** ($-\Delta\Delta G_{298} = 8.7$ kJ/mol) gave rough agreement with the energy compensation resulting from the inhibition for the free-rotation about the pyridine−pyridine axis in **2** (vide supra). Although recently, Davis and Wareham reported a tricyclic polyamide receptor that shows a remarkably strong affinity for β-glucopyranoside ($-\Delta G_{298} = 30.7$ kJ/mol in $CHCl_3$),[8] the value obtained for **3** to **7** is notable in view of the demonstration for the versatility of the terpyridine skeleton.

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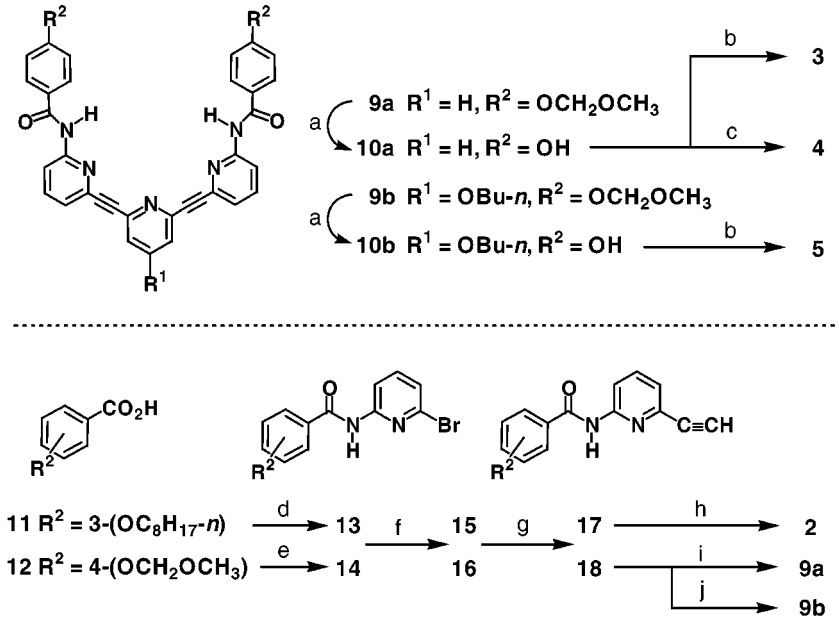
(12) The all OH protons of **6**−**8** were successfully assigned on the basis of $^1H-^1H$ COSY spectra. Carefully dried and acid-free $CDCl_3$ was used in order to assess all CH−OH correlations.

1 **3**

Figure 1. CPK molecular structures of receptor **1** and **3**.

Scheme 2



(a) CSA•H_2O, THF, *i*-PrOH; (b) tetraethylene glycol di-*p*-tosylate, K_2CO_3, 18-Crown-6 ether, acetone; (c) 1,11-undecanediol di-*p*-tosylate, K_2CO_3, 18-Crown-6 ether, acetone; (d) 2-amino-6-bromopyridine, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_3CN; (e) 2-amino-6-bromopyridine, $BrCCl_3$, PPh_3, THF; (f) 2-methyl-3-butyn-2-ol, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH; (g) NaH, toluene; (h) 2,6-dibromopyridine, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH; (i) 2,6-dibromopyridine, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; (j) 4-*n*-butoxy-2,6-dibromopyridine, $(Ph_3P)_2PdCl_2$, CuI, Et_3N.

The ether oxygen in the polyoxyethylene chain of **3** may be a hydrogen-bonding acceptor for the primary 6-C OH groups of **7**. Thus, polyethylene-bridged receptor **4** was synthesized in order to shed light on this aspect. The binding constant of 4.7×10^3 M^{-1} ($-\Delta G_{298} = 20.9$ kJ/mol) was measured between **4** and **7** in $CDCl_3$, so that the oxygen in the polyoxyethylene chain of **3** was judged to make little contribution to the binding. Furthermore, increasing the electron density of the pyridine nitrogen, we anticipated a definite increase K_a due mainly to enthalpic factors. Indeed, alkoxy-substitution at the 4′ position of the central pyridine ring showed a further increment of the association constants. Thus, **5** displayed a K_a value of 7.3×10^3 M^{-1} ($-\Delta G_{298} = 22.0$ kJ/mol) for **7**, the highest value recorded for all the polypyridine-macrocyclic receptors for glucopyranosides (Table 1).

Selectivity of the Receptors. Recognition abilities of **3** for methyl β-(D)-ribofuranoside (**6**) and *n*-octyl β-(D)-galactopyranoside (**8**) were similarly evaluated in order to assess the selectivity of **3**. The glucopyranoside recep-

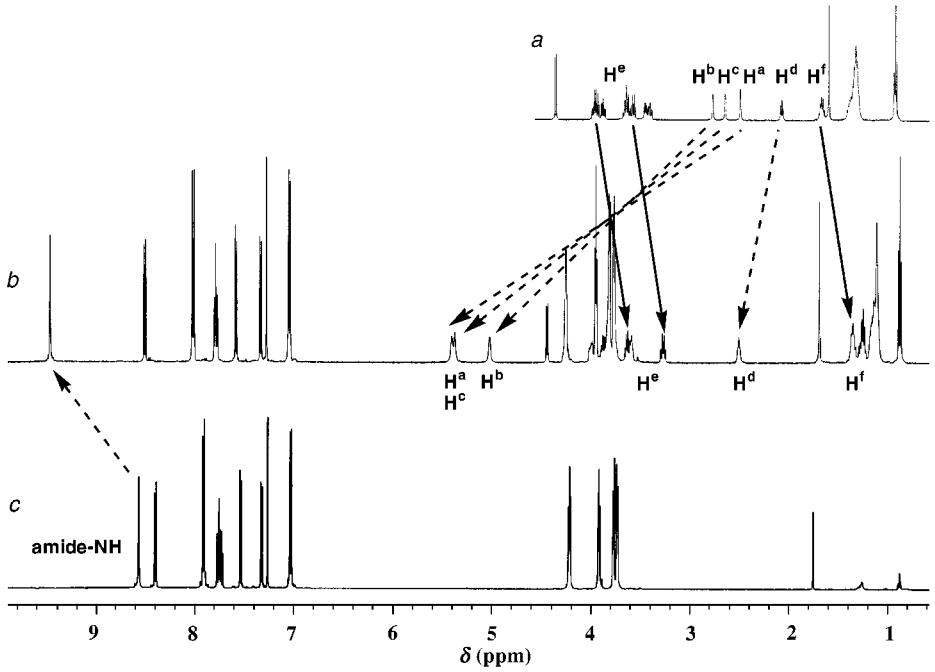


Figure 2. ^{1}H NMR spectra (500 MHz) of (a) **7** (2.5 mM), (b) **7·3**, and (c) **3** in $CDCl_3$ at 25 °C. See Scheme 1 for proton labeling.

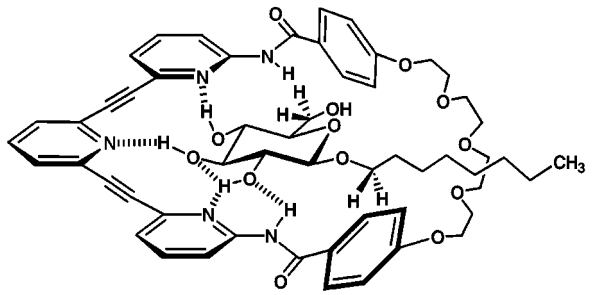


Figure 3. A possible interaction mode for the complex **3·7**.

tor **3** revealed a K_a of 5.2×10^3 M^{-1} ($-\Delta G_{298} = 21.2$ kJ/mol) for **6**. In our disappointment, **3** did not show any selectivity between **6** and **7**. We thought that the three OH groups of ribofuranoside **6** would participate in the complexation with **3**.[5] Although the glucopyranoside **7** bears four OH groups, only three of them strongly bind to **3**, the primary OH group of **7** having little influence on binding. Substantial selectivity was seen between **7** and **8**. Indeed, **3** showed a K_a of 1.4×10^3 M^{-1} ($-\Delta G_{298} =$ 17.9 kJ/mol) for the galactopyranoside **8**, a considerably weaker affinity than that for the glucopyranoside **7**. The three glucopyranoside OH groups (2-C, 3-C, and 4-C) of **7** are all equatorial different from that of the galactopyranoside OH groups (2-C and 3-C: equatorial; 4-C: axial) of **8**. Because of the pseudo-coplanarity for the hydrogen-bonding site of **3**, the three OH groups of **7** are suitable for attaining the multipoint hydrogen-bonding; on the other hand, the direction of three OH groups of **8** is not enough to take advantage of the full potential of the hydrogen-bonding site of **3**. Indeed, complexation-induced downfield and upfield shifts of **8** were rather small compared to those of **7** (Figure 4). This result means that the artificial receptors could distinguish glucopyranosides even from epimeric monosaccharide derivatives.

Conclusion

We developed artificial glucopyranoside receptors by replacement of the diphenylmethane bridges of the ribofuranoside receptors by polyoxyethylene chains. The glucopyranoside receptors showed substantial selectivity between glucopyranoside and galactopyranoside, but never for ribofuranoside. We are currently investigating the design and synthesis of a new type of glucopyranoside receptors which can also interact with the primary 6-C OH groups of glucopyranosides. The new receptor is expected to show more high affinity and selectivity for glucopyranoside.

Experimental Section

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, unless otherwise noted. EI mass spectra were measured at 70 eV. For FAB mass experi-

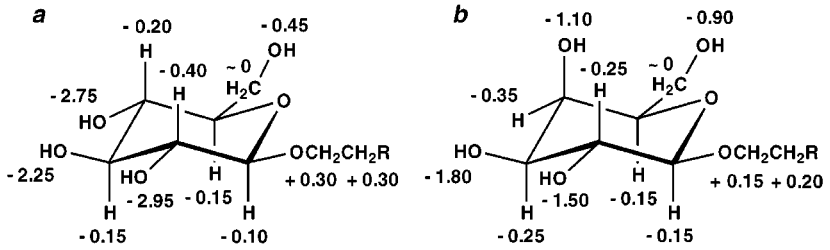


Figure 4. **3** (2.5 mM)-induced downfield (− sign) and upfield (+ sign) shifts (ppm) of all the protons for (a) **7** (2.5 mM) and (b) **8** (2.5 mM) in $CDCl_3$ at 25 °C.

ments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. The starting materials were commercially available or prepared according to literature procedures: 1,11-undecanediol di-*p*-tosylate,[13] 2-amino-6-bromopyridine,[14] and 4-*n*-butoxy-2,6-dibromopyridine.[5]

Methods for the Evaluation of Stoichiometry and Association Constants. The self-associations of **6**, **7**, and **8** were judged to be negligible at ≤12.5, 2.5, and 2.5 mM, respectively, by ^{1}H NMR dilution experiments, so that all binding assays were carried out below that concentration. Job's plot of [complex] vs mole fraction of the receptor ($f_{receptor}$) for the complexation of the receptors and **6**−**8** was obtained by ^{1}H NMR at 270 MHz in $CDCl_3$ at 25 °C under conditions where [receptor] + [**6**−**8**] is maintained at 1.25 mM.[9] The concentration of a complex in $CDCl_3$ was evaluated from $\Delta\delta_{obsd}$ for the receptor-NH, according to the equation, [complex] = [receptor]$_t$ ($\Delta\delta_{obsd}/\Delta\delta_{sat.}$) (t = total; obsd = observed; sat. = saturated).

Determination of association constants (K_a) was carried out by ^{1}H NMR (270 MHz) under Benesi−Hildebrand conditions at 25 °C in $CDCl_3$.[10] The receptor concentration for **2** was 0.125 mM, while that of **3**−**5** was 0.05 mM. The concentration of monosaccharide derivatives **6**−**8** was 1.25−2.5 and 0.5−1.1 mM for **2** and **3**−**5**, respectively. The chemical shifts of the receptor-NH protons were monitored as a function of **6**−**8** concentration. In every case, the double reciprocal plots according to the equation, $1/\Delta\delta_{obsd} = 1/\Delta\delta_{sat.} + 1/\Delta\delta_{sat.}K_a$[receptor]$_t$ gave good linearity with a correlation coefficient $r \geq 0.99$. For every K_a, at least a 16−88% complexation was covered.

3-*n*-Octoxybenzoic Acid (11). A toluene (10 mL) suspension of 3-hydroxybenzoic acid (1.38 g, 10 mmol), *n*-BuOH (7.41 g, 100 mmol), and concd H_2SO_4 (0.1 mL) was refluxed with a Dean−Stark apparatus for 12 h. After removal of the solvent, the residue was subjected to column chromatography (silica gel; eluent, hexane/AcOEt 7:1) to give *n*-butyl 3-hydroxybenzoate: yield 99% (1.92 g); mp 40−41 °C; IR (KBr) 3429, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 3 H), 1.46 (sext, J = 7.1 Hz, 2 H), 1.75 (quint, J = 7.1 Hz, 2 H), 4.33 (t, J = 7.1 Hz, 2 H), 5.70 (s, 1 H), 7.07 (d, J = 7.8 Hz, 1 H), 7.31(t, J = 7.8 Hz, 1 H), 7.59−7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.75, 19.25, 30.68, 65.14, 116.28, 120.11, 121.90, 129.69, 131.78, 155.73, 166.74; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 195 (MH^+, 100%). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.90; H, 7.30. An acetone (60 mL) solution of *n*-butyl 3-hydroxybenzoate (1.89 g, 9.73 mmol), 1-iodooctane (7.20 g, 30 mmol), and K_2CO_3 (8.30 g, 60 mmol) was refluxed for 12 h and evaporated. The residue was dissolved in water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, hexane/CH_2Cl_2 5:1) to give *n*-butyl 3-*n*-octoxybenzoate: yield 93% (2.80 g); oil; IR (KBr) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.6 Hz, 3 H), 1.29−1.49 (m, 12 H), 1.75−1.83 (m, 4 H), 4.00 (t, J = 6.6 Hz, 2 H), 4.32 (t, J = 6.6 Hz, 2 H), 7.08 (d, J = 7.6 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.55 (s, 1 H), 7.61 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.73, 14.08, 19.25, 22.64, 26.01, 29.17, 29.22, 29.33, 30.75, 31.78, 64.82, 68.13, 114.73, 119.55, 121.66, 129.23, 131.71, 159.06, 166.53; FABMS (in 2-nitrophenyl octyl ether) *m/e* (rel intensity) 307 (MH^+, 95%). To an EtOH (5 mL) solution of *n*-butyl 3-*n*-octoxybenzoate (2.75 g, 8.97 mmol) was added an EtOH (15 mL) solution of KOH (3.02 g, 53.8 mmol) at room temperature. The reaction mixture became turbid, and the cloudy solution was allowed to stand for 10 h at this temperature. After removal of the solvent, the residue was poured into water and acidified to pH 1 with concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried in vacuo to give **11**: yield 94% (2.12 g); mp 75−76 °C; IR (KBr) 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.29−1.51 (m, 10 H), 1.80 (quint, J = 6.8 Hz, 2 H), 4.01 (t, J = 6.8 Hz, 2 H), 7.15 (d, J = 7.9 Hz, 1 H), 7.37 (t, J = 7.9 Hz, 1 H), 7.62 (s, 1 H), 7.70 (d, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.67, 26.01, 29.15, 29.23, 29.33, 31.80, 68.25, 114.99, 120.93, 122.45, 129.47, 130.43, 159.16, 172.14; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 250 (M^+, 17%). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.23; H, 9.09.

4-(Methoxymethoxy)benzoic Acid (12). *n*-Butyl 4-hydroxybenzoate was synthesized from 4-hydroxybenzoic acid (13.8 g, 0.1 mol) in a manner similar to that described for *n*-butyl 3-hydroxybenzoate. *n*-Butyl 4-hydroxybenzoate: yield 99% (19.3 g); mp 70−71 °C; IR (KBr) 3386, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3 H), 1.47 (sext, J = 7.3 Hz, 2 H), 1.74 (quint, J = 7.3 Hz, 2 H), 4.31 (t, J = 7.3 Hz, 2 H), 6.19 (s, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.96 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.71, 19.22, 30.67, 65.04, 115.33, 122.04, 131.91, 160.71, 167.59; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 195 (MH^+, 100%). Anal. Calcd for $C_{11}H_{17}O_3$: C, 68.02; H, 7.26. Found: C, 67.67; H, 7.26. To a THF (25 mL) suspension of NaH (2.4 g, 60 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a THF (40 mL) solution of *n*-butyl 4-hydroxybenzoate (9.1 g, 46.8 mmol) dropwise at 0 °C. After stirring at that temperature for 1 h, to the solution was added $ClCH_2OCH_3$ (4.8 g, 60 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h and evaporated. The residue was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, hexane/CH_2Cl_2 1:10) to give *n*-butyl 4-(methoxymethoxy)benzoate: yield 92% (10.3 g); oil; IR (KBr) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.47 (sext, J = 7.4 Hz, 2 H), 1.74 (quint, J = 7.4 Hz, 1 H), 3.48 (s, 3 H), 4.30 (t, J = 7.4 Hz, 3 H), 5.23 (s, 2 H), 7.05 (d, J = 8.6 Hz, 2 H), 7.99 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.71, 19.21, 30.74, 56.12, 64.50, 93.98, 115.50, 123.89, 131.39, 160.78, 166.26; MS *m/e* (rel intensity) 238 (M^+, 100%). To an EtOH (30 mL) solution of *n*-butyl 4-(methoxymethoxy)benzoate (16.6 g, 69.7 mmol) was added an EtOH (100 mL) solution of KOH (23.6 g, 420 mmol) at room temperature. The reaction mixture became turbid, and the cloudy solution was allowed to stand for 3 h at this temperature. After removal of the solvent, the residue was poured into water, neutralized to pH 5 with 10% aqueous hydrochloric acid solution, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, AcOEt/$CHCl_3$ 1:1) to give **12**: yield 87% (11.1 g); mp 126−127 °C; IR (KBr) 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3 H), 5.25 (s, 2 H), 7.09 (d, J = 8.8 Hz, 2 H), 8.07 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 56.28, 94.01, 115.68, 122.63, 132.27, 161.64, 171.99; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 183 (MH^+, 100%). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 62.31; H, 5.84.

***N*-2-(6-Bromopyridyl)-3-*n*-octoxybenzamide (13).** A CH_3CN (20 mL) solution of **11** (1.50 g, 6 mmol), 2-amino-6-bromopyridine[14] (865 mg, 5 mmol), and 2-chloro-1-methylpyridinium iodide (3.83 g, 15 mmol) was stirred at 80 °C. Then to a reaction mixture was added Et_3N (1.2 mL), and the mixture was stirred at that temperature for 10 h. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, hexane/$CHCl_3$ 1:1) to give **13**: yield 60% (1.22 g); mp 46−47 °C; IR (KBr) 3305, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.30−1.49 (m, 10 H), 1.81 (quint, J = 6.9 Hz, 2 H), 4.02 (t, J = 6.9 Hz, 2 H), 7.11 (d, J = 7.8 Hz, 1 H), 7.26 (d, J = 7.8 Hz, 1 H), 7.37−7.44 (m, 3 H), 7.62 (t, J = 7.8 Hz, 1 H), 8.36 (d, J = 7.8 Hz, 1 H), 8.54 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.64, 25.96, 29.12, 29.20, 29.30, 31.77, 68.28, 112.44, 112.85, 118.79, 119.32, 123.66, 129.83, 134.94, 139.26, 140.69, 151.52, 159.57, 165.44; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 405 (MH^+, 100%), 407 (MH^+ + 2, 83%). Anal. Calcd for $C_{20}H_{25}O_2N_2Br$: C, 59.26; H, 6.22; N, 6.91. Found: C, 59.39; H, 6.28; N, 6.55.

***N*-2-(6-Bromopyridyl)-4-(methoxymethoxy)benzamide (14).** To a THF (80 mL) solution of **12** (13.8 g, 80 mmol), 2-amino-6-bromopyridine[14] (7.28 g, 40 mmol), and PPh_3 (10.7

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g, 40.8 mmol) was added $BrCCl_3$ (7.88 mL) at room temperature. The reaction mixture was refluxed for 1.5 h and filtered. The filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **14**: yield 52% (6.99 g); mp 151−153 °C; IR (KBr) 3317, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50 (s, 3 H), 5.25 (s, 2 H), 7.13 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.87 (d, J = 8.7 Hz, 2 H), 8.35 (d, J = 7.6 Hz, 1 H), 8.46 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.28, 94.11, 112.39, 116.12, 123.48, 126.77, 129.09, 139.22, 140.66, 151.69, 160.65, 164.89; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 337 (MH^+, 100%), 339 ($MH^+ + 2$, 100%). Anal. Calcd for $C_{14}H_{13}O_3N_2Br$: C, 49.87; H, 3.89; N, 8.31. Found: C, 49.33; H, 3.78; N, 7.86.

***N*-2-[6-(3-Hydroxy-3-methyl-1-butynyl)pyridyl]-3-*n*-octoxybenzamide (15).** To an Et_2NH (22 mL) solution of **13** (2.28 g, 5.6 mmol), $(Ph_3P)_2PdCl_2$ (79 mg, 0.11 mmol), and CuI (11 mg, 0.056 mmol) was added 2-methyl-3-butyn-2-ol (522 mg, 6.2 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 5.5 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2) to give **15**: yield 97% (1.27 g); mp 101−102 °C; IR (KBr) 3336, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.30−1.49 (m, 10 H), 1.66 (s, 6 H), 1.81 (quint, J = 6.9 Hz, 2 H), 2.53 (br s, 1 H), 4.02 (t, J = 6.9 Hz, 2 H), 7.10 (d, J = 8.1 Hz, 1 H), 7.21 (d, J = 8.1 Hz, 1 H), 7.38 (t, J = 8.1 Hz, 1 H), 7.44−7.46 (m, 2 H), 7.72 (t, J = 8.1 Hz, 1 H), 8.38 (d, J = 8.1 Hz, 1 H), 8.70 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.62, 25.96, 29.13, 29.20, 29.30, 31.22, 31.77, 65.27, 68.21, 80.62, 94.16, 113.02, 113.81, 119.02, 119.11, 123.24, 129.67, 135.15, 138.75, 140.60, 151.55, 159.50, 165.64; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 409 (MH^+, 100%). Anal. Calcd for $C_{25}H_{32}O_3N_2$: C, 73.50; H, 7.89; N, 6.86. Found: C, 73.02; H, 7.89; N, 6.56.

***N*-2-[6-(3-Hydroxy-3-methyl-1-butynyl)pyridyl]-4-(methoxymethoxy)benzamide (16).** To an Et_2NH (100 mL) solution of **14** (6.74 g, 20 mmol), $(Ph_3P)_2PdCl_2$ (281 mg, 0.4 mmol), and CuI (39 mg, 0.2 mmol) was added 2-methyl-3-butyn-2-ol (1.58 g, 22 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2/AcOEt 10:1) to give **16**: yield 96% (6.5 g); mp 116−117 °C; IR (KBr) 3365, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 6 H), 3.00 (br s, 1 H), 3.50 (s, 3 H), 5.25 (s, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.19 (d, J = 7.9 Hz, 1 H), 7.71 (t, J = 7.9 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 2 H), 8.38 (d, J = 7.9 Hz, 1 H), 8.76 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.22, 56.22, 65.24, 80.62, 94.05, 94.08, 113.78, 115.93, 123.06, 127.00, 129.26, 138.70, 140.46, 151.70, 160.46, 165.15; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 341 (MH^+, 100%). Anal. Calcd for $C_{19}H_{20}O_4N_2$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.13; H, 5.88; N, 7.94.

***N*-2-(6-Ethynylpyridyl)-3-*n*-octoxybenzamide (17).** A toluene (30 mL) solution of **15** (2.68 g, 6.58 mmol) and NaH (27 mg, 0.658 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was stirred at 120 °C for 40 min and evaporated. The residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2/hexane 1:1) to give **17**: yield 88% (2.05 g); mp 54−56 °C; IR (KBr) 3435, 3265, 3219, 2108, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.29−1.51 (m, 10 H), 1.81 (quint, J = 6.9 Hz, 2 H), 3.18 (s, 1 H), 4.02 (t, J = 6.9 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.36−7.44 (m, 3 H), 7.75 (t, J = 8.0 Hz, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.58 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.60, 25.93, 29.10, 29.18, 29.27, 31.75, 68.23, 77.20, 82.08, 112.71, 114.29, 118.78, 119.27, 123.53, 129.79, 135.17, 138.74, 140.07, 151.47, 159.52, 165.54; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 351 (MH^+, 100%). Anal. Calcd for $C_{22}H_{26}O_2N_2$: C, 75.40; H, 7.47; N, 7.99. Found: C, 75.56; H, 7.75; N, 7.63.

***N*-2-(6-Ethynylpyridyl)-4-(methoxymethoxy)benzamide (18).** A toluene (12 mL) solution of **16** (998 mg, 2.93 mmol) and NaH (12 mg, 0.293 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was stirred at 120 °C for 40 min and evaporated. The residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **18**: yield 73% (605 mg); mp 149−150 °C; IR (KBr) 3332, 3236, 2106, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (s, 1 H), 3.52 (s, 3 H), 5.25 (s, 2 H), 7.13 (d, J = 8.8 Hz, 2 H), 7.27 (d, J = 7.9 Hz, 1 H), 7.74 (t, J = 7.9 Hz, 1 H), 7.87 (d, J = 8.8 Hz, 2 H), 8.41 (d, J = 7.9 Hz, 1 H), 8.52 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.25, 77.15, 82.15, 94.10, 114.29, 116.08, 123.40, 127.00, 129.04, 138.72, 140.04, 151.64, 160.52, 165.03; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 283 (MH^+, 100%). Anal. Calcd for $C_{16}H_{14}O_3N_2$: C, 68.08; H, 5.00; N, 9.92. Found: C, 67.45; H, 4.79; N, 9.65.

Acyclic Receptor 2. To an Et_2NH (20 mL) solution of 2,6-dibromopyridine (614 mg, 2.6 mmol), $(Ph_3P)_2PdCl_2$ (73 mg, 0.104 mmol), and CuI (10 mg, 0.052 mmol) was added an Et_2-NH (30 mL) solution of **17** (2.0 g, 5.7 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After removal of the solvent, the residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated, chromatographed (silica gel; eluent, CH_2Cl_2), and washed with AcOEt to give **2**: yield 65% (1.32 g); mp 169−171 °C; IR (KBr) 3437, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 6 H), 1.30−1.50 (m, 20 H), 1.82 (quint, J = 6.8 Hz, 4 H), 4.03 (t, J = 6.8 Hz, 4 H), 7.11 (d, J = 7.5 Hz, 2 H), 7.37−7.46 (m, 8 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.73−7.82 (m, 3 H), 8.45 (d, J = 7.5 Hz, 2 H), 8.61 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.64, 25.97, 29.14, 29.21, 29.30, 31.78, 68.28, 87.27, 87.62, 112.80, 114.51, 118.80, 119.33, 124.15, 127.33, 129.83, 135.24, 136.67, 138.83, 140.26, 142.97, 151.64, 159.58, 165.63; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 776 (MH^+, 100%). Anal. Calcd for $C_{31}H_{53}O_2N_2$: C, 75.84; H, 6.88; N, 9.03. Found: C, 75.70; H, 6.94; N, 8.88.

***N*,*N*′-[4-(Methoxymethoxy)benzoyl]-2,6-bis[(6-aminopyrid-2-yl)ethynyl]pyridine (9a).** An Et_3N (11 mL) solution of 2,6-dibromopyridine (221 mg, 0.913 mmol), **18** (569 mg, 2.01 mmol), $(Ph_3P)_2PdCl_2$ (26 mg, 0.0365 mmol), and CuI (4 mg, 0.01825 mmol) was stirred at 60 °C for 4 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2) and washed with AcOEt to give **9a**: yield 78% (454 mg); mp 194−196 °C; IR (KBr) 3435, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50 (s, 6 H), 5.25 (s, 4 H), 7.14 (d, J = 8.8 Hz, 4 H), 7.42 (d, J = 7.6 Hz, 2 H), 7.61 (d, J = 7.6 Hz, 2 H), 7.73−7.81 (m, 3 H), 7.89 (d, J = 8.8 Hz, 4 H), 8.44 (d, J = 7.6 Hz, 2 H), 8.56 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 56.25, 87.20, 87.66, 94.10, 114.48, 116.08, 123.98, 127.04, 127.28, 129.08, 136.65, 138.77, 140.17, 142.95, 151.78, 160.54, 165.08; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 640 (MH^+, 100%). Anal. Calcd for $C_{37}H_{29}O_3N_5$: C, 69.47; H, 4.57; N, 10.94. Found: C, 69.35; H, 4.38; N, 10.64.

***N*,*N*′-[4-(Methoxymethoxy)benzoyl]-2,6-bis[(6-aminopyrid-2-yl)ethynyl]-4-*n*-butoxypyridine (9b).** This compound was synthesized from 4-*n*-butoxy-2,6-dibromopyridine[5] (463 mg, 1.5 mmol) and **18** (960 mg, 3.35 mmol) in a manner similar to that described for **9a**. **9b**: yield 50% (530 mg); mp 163−165 °C; IR (KBr) 3361, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3 H), 1.50 (sext, J = 7.3 Hz, 2 H), 1.81 (quint, J = 7.3 Hz, 2 H), 3.51 (s, 6 H), 4.05 (t, J = 7.3 Hz, 2 H), 5.25 (s, 4 H), 7.12−7.16 (m, 6 H), 7.42 (d, J = 7.9 Hz, 2 H), 7.78 (t, J = 7.9 Hz, 2 H), 7.89 (d, J = 8.8 Hz, 4 H), 8.43 (d, J = 7.9 Hz, 2 H), 8.56 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.72, 19.05, 30.70, 56.27, 68.39, 87.02, 87.46, 94.13, 114.35, 114.43, 116.10, 124.01, 127.07, 129.09, 138.77, 140.25, 143.87, 151.77, 160.55, 165.10, 165.33; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 712 (MH^+, 100%). Anal. Calcd for $C_{41}H_{37}O_7N_5$: C, 69.19; H, 5.24; N, 9.84. Found: C, 68.44; H, 5.05; N, 9.19.

***N*,*N*′-(4-Hydroxybenzoyl)-2,6-bis[(6-aminopyrid-2-yl)-ethynyl]pyridine (10a).** An *i*-PrOH−THF (15 + 15 mL) solution of **9a** (461 mg, 0.65 mmol) and (+)-(*S*)-camphor-10-sulfonic acid monohydrate (1.14 g, 4.55 mmol) was stirred at 80 °C for 4 h. Solid $NaHCO_3$ was added to the reaction mixture until no more CO_2 evolved. After removal of the solvent, the residue was continuously extracted with THF by a Soxhlet extractor for 1.5 days. The THF extract was evaporated, and the residue was washed with CH_2Cl_2 and MeOH to give **10a**: yield 75% (269 mg); mp 268−271 °C; IR (KBr) 3385, 1678 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.84 (d, J =

7.3 Hz, 2 H), 7.75 (d, J = 8.1 Hz, 2 H), 7.91−8.01 (m, 7 H), 8.28 (d, J = 8.1 Hz, 2 H), 10.21 (s, 2 H), 10.80 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 86.76, 87.73, 114.98, 115.58, 123.42, 124.22, 127.71, 130.34, 138.14, 138.93, 139.31, 142.21, 153.02, 161.11, 165.70; FABMS (in 3-nitrobenzyl alcohol with DMSO) *m/e* (rel intensity) 552 (MH^+, 100%). Anal. Calcd for $C_{33}H_{21}O_4N_5 \cdot H_2O$: C, 69.59; H, 4.07; N, 12.30. Found: C, 69.22; H, 3.54; N, 11.72.

***N,N′*-(4-Hydroxybenzoyl)-2,6-bis[(6-aminopyrid-2-yl)-ethynyl]-4-*n*-butoxypyridine (10b).** This compound was synthesized from **9b** (340 mg, 0.48 mmol) in a manner similar to that described for **10a**. **10b**: yield 70% (208 mg); mp 241−244 °C; IR (KBr) 3398, 1687 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7.1 Hz, 3 H), 1.45 (sext, J = 7.1 Hz, 2 H), 1.73 (quint, J = 7.1 Hz, 2 H), 4.18 (t, J = 7.1 Hz, 2 H), 6.84 (d, J = 8.5 Hz, 4 H), 7.33 (s, 2 H), 7.48 (d, J = 7.3 Hz, 2 H), 7.90−7.97 (m, 6 H), 8.27 (d, J = 8.5 Hz, 2 H), 10.19 (s, 2 H), 10.76 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 13.67, 18.57, 30.27, 68.38, 86.95, 87.20, 114.32, 114.98, 115.50, 123.35, 124.22, 130.31, 138.87, 139.36, 143.33, 152.97, 161.11, 165.31, 165.67; FABMS (in 3-nitrobenzyl alcohol with DMSO) *m/e* (rel intensity) 624 (MH^+, 100%). Anal. Calcd for $C_{37}H_{29}O_5N_5 \cdot H_2O$: C, 69.26; H, 4.87; N, 10.91. Found: C, 68.60; H, 4.57; N, 10.44.

Receptor 3. An acetone (100 mL) solution of **10a** (198 mg, 0.36 mmol), tetraethylene glycol di-*p*-tosylate (185 mg, 0.36 mmol), 18-crown-6 ether (77 mg, 0.29 mmol), and K_2CO_3 (552 mg, 3.6 mmol) was refluxed for 3 days and evaporated. The residue was poured into $CHCl_3$, and the resulting precipitate was filtered. The filtrate was evaporated, and the residue was poured into water, neutralized to pH 5 with 10% aqueous hydrochloric acid solution, and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, MeOH/CH_2Cl_2 1:100) to give **3**: yield 25% (65 mg); mp 315−317 °C; IR (KBr) 3413, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.72−3.78 (m, 8 H), 3.92 (t, J = 4.8 Hz, 4 H), 4.22 (t, J = 4.8 Hz, 4 H), 7.03 (d, J = 8.7 Hz, 4 H), 7.33 (d, J = 7.5 Hz, 2 H), 7.54 (d, J = 7.5 Hz, 2 H), 7.71−7.78 (m, 3 H), 7.91 (d, J = 8.7 Hz, 4 H), 8.40 (d, J = 8.4 Hz, 2 H), 8.58 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 67.66, 69.42, 70.85, 71.01, 87.19, 87.75, 114.08, 114.62, 122.98, 126.28, 126.45, 129.13, 136.45, 138.55, 140.21, 143.12, 151.91, 162.09, 165.09; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 710 (MH^+, 100%). Anal. Calcd for $C_{41}H_{35}O_7N_5$: C, 69.38; H, 4.97; N, 9.87. Found: C, 68.83; H, 4.83; N, 9.52.

Receptor 4. This compound was synthesized from **10a** (276 mg, 0.5 mmol) and 1,11-undecanediol di-*p*-tosylate[13] (249 mg, 0.5 mmol) in a manner similar to that described for **3**. **4**: yield 29% (102 mg); mp 280−282 °C; IR (KBr) 3417, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34−1.49 (m, 14 H), 1.83 (quint, J = 6.7 Hz, 4 H), 4.00 (t, J = 6.7 Hz, 4 H), 7.00 (d, J = 8.8 Hz, 4 H), 7.33 (d, J = 7.4 Hz, 2 H), 7.54 (d, J = 7.4 Hz, 2 H), 7.72−7.78 (m, 3 H), 7.89 (d, J = 8.8 Hz, 4 H), 8.41 (d, J = 8.3 Hz, 2 H), 8.55 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.66, 28.77, 28.95, 29.48, 68.13, 87.12, 87.70, 114.15, 114.57, 123.20, 125.84, 126.79, 129.11, 136.43, 138.56, 140.23, 143.11, 151.93, 162.56, 165.21; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 704 (MH^+, 100%). Anal. Calcd for $C_{44}H_{41}O_4N_5 \cdot H_2O$: C, 73.21; H, 6.00; N, 9.70. Found: C, 73.59; H, 5.72; N, 9.37.

Receptor 5. This compound was synthesized from **10b** (124 mg, 0.2 mmol) and tetraethylene glycol di-*p*-tosylate (100 mg, 0.2 mmol) in a manner similar to that described for **3**. **5**: yield 25% (39 mg); mp 284−286 °C; IR (KBr) 3392, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3 H), 1.52 (sext, J = 7.3 Hz, 2 H), 1.83 (quint, J = 7.3 Hz, 2 H), 3.73−3.78 (m, 8 H), 3.92 (t, J = 4.9 Hz, 4 H), 4.08 (t, J = 7.3 Hz, 2 H), 4.22 (t, J = 4.9 Hz, 4 H), 7.02−7.07 (m, 6 H), 7.31 (d, J = 7.9 Hz, 2 H), 7.75 (t, J = 7.9 Hz, 2 H), 7.91 (d, J = 8.5 Hz, 4 H), 8.39 (d, J = 8.3 Hz, 2 H), 8.58 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.75, 19.06, 30.78, 67.64, 68.26, 69.41, 70.83, 70.99, 87.19, 87.37, 113.43, 114.02, 114.61, 122.91, 126.26, 129.13, 138.52, 140.22, 143.99, 151.88, 162.07, 165.10, 165.28; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 782 (MH^+, 100%). Anal. Calcd for $C_{45}H_{43}O_8N_5 \cdot H_2O$: C, 67.57; H, 5.67; N, 8.76. Found: C, 67.91; H, 5.39; N, 8.55.

Supporting Information Available: Copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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