Remarkably Strong, Uncharged Hydrogen-Bonding Interactions of Polypyridine-Macrocyclic Receptors for Deoxyribofuranosides

Masahiko Inouye,* Kunihide Takahashi, and Hiroyuki Nakazumi

Contribution from PRESTO, Japan Science and Technology Corporation (JST), Department of Applied Materials Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Received October 6, 1998

Abstract: Novel macrocyclic saccharide receptors that possess a pyridine−pyridone−pyridine arrangement as a hydrogen-bonding motif are presented. The artificial receptors exhibited a remarkably strong binding affinity for deoxyribofuranoside derivatives in $CDCl_3$ ($K_a = 19\,000\ M^{-1}$; $-\Delta G_{298} = 24.4$ kJ/mol), one of the highest values of artificial receptors having only uncharged hydrogen-bonding sites for monosaccharide derivatives. Selective extraction of deoxyribose by the receptors was also observed; the extractabilities, or affinities to the receptors of various pentoses and hexoses, decreased in the following order: deoxyribose > lyxose ≅ ribose > arabinose ≅ fructose ≅ xylose > glucose > mannose > galactose.

Introduction

Unlike other intermolecular interactions such as electrostatic or hydrophobic, the hydrogen bonding interaction is critically vectorial in solution; thus, the hydrogen bonding plays a leading role in most biological information-transfer events.[1] Thus, constructing synthetic models employing hydrogen bonding is a rapidly growing field in current supramolecular chemistry because it may not only serve as a basic concept to understand biological functions but also lead to the development of new pharmaceutical methodologies, new types of biorelevant materials, etc.[2−4] Among the many artificial models, however, only a few of those have been effective even to some extent for the recognition of saccharides using hydrogen bonds.[3−7] This is possibly because of the three-dimensional complexity of saccharide structures and of the weak intermolecular hydrogen-bonding abilities of the hydroxyl residues.[3,7] We have developed polypyridine-macrocyclic structures possessing convergent functional groups with hydrogen bond donor/acceptor properties as efficient synthetic receptors for β-ribofuranosides.[8] Another important pentose is deoxyribose, a component monosaccharide of DNA. In the deoxyribofuranoside form, however, in addition to the essentially weak hydrogen bonding ability, only two hydroxyl residues are expected to take part in the intermolecular interactions. Here we show remarkably strong uncharged hydrogen-bonding interactions of novel polypyridine-macrocyclic receptors for β-deoxyribofuranoside.

Results and Discussion

As a starting point for the design of deoxyribofuranoside receptors, we examined the adaptability of the ribofuranoside receptor **2**[8] for the recognition of deoxyribofuranoside. To evaluate the recognition abilities of the receptors for ribofuranoside and deoxyribofuranoside in aprotic solvents such as $CHCl_3$, 3-*n*-octyl derivatives of uridine (**1a**) and thymidine (**1b**) were chosen, respectively (Chart 1). The *n*-octyl substituents make the furanosides soluble in such solvents and prevent the nucleobase residues of **1** from interacting with the hydrogen-bonding motif of the receptors, so that a net interaction between the hydroxyl groups of **1** and the receptors will be assessed.

* To whom correspondence should be addressed.

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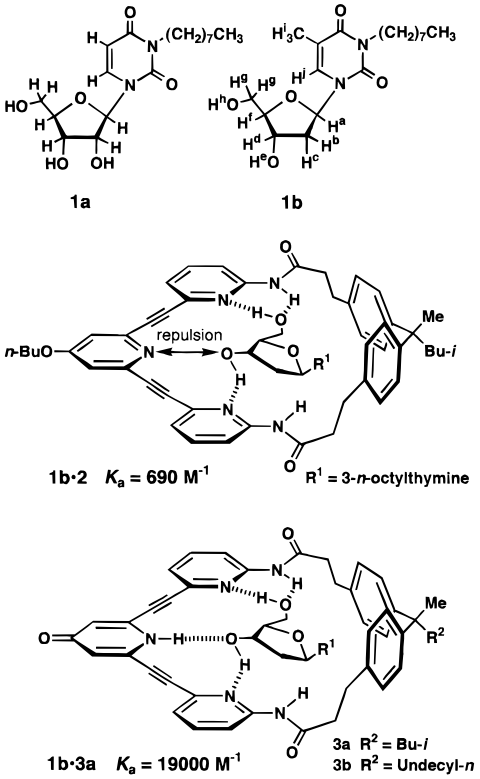
10.1021/ja983539u CCC: $18.00
Published on Web 01/05/1999

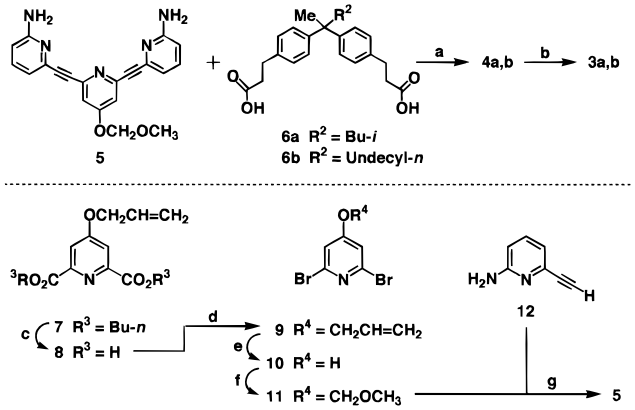
Chart 1



The ribofuranoside receptor **2** revealed K_a values of 10 000 M^{-1} ($-\Delta G_{298}$ = 22.8 kJ/mol) and 690 M^{-1} ($-\Delta G_{298}$ = 16.2 kJ/mol) in $CDCl_3$ for **1a** and **1b** at 25 °C, respectively.[9] The low association constant between **2** and the deoxyribofuranoside derivative **1b** may be due not only to the decreased number of hydrogen-bonding interactions compared to that for the ribofuranoside derivative **1a** but also to the electrostatic repulsion between the lone electron pairs of the 3-OH groups of **1b** and the receptor nitrogen.

We thought that this difficulty could be overcome by replacing the central pyridine ring of the receptor by a pyridone ring; the pyridone-NH protons will change the repulsion into an attractive hydrogen bond.[4,10] For this purpose, the receptors **3** are obvious candidates, in which a novel hydrogen-bonding donor(amide)−acceptor(pyridine)−donor(pyridone)−acceptor(pyridine)−donor(amide) arrangement is convergently incorporated in the macrocyclic structures. The new polypyridine-macrocyclic receptors **3** were synthesized from protected diaminoterpyridine derivative **5** and dicarboxylic acid derivatives **6**[8] by Mukaiyama's macrocyclization[11] followed by deprotection of the methoxymethyl groups. The diaminoterpyridine derivative **5** was prepared from known pyridine derivatives **7**[12] and **12**.[8] *n*-Undecyl groups in **3b** were introduced for solubility problems in extraction experiments instead of *i*-Bu groups in **3a** (Scheme 1). The spectroscopic properties such as Fourier transform infrared, ^{1}H and ^{13}C NMR, and fast atom bombardment mass spectroscopy of **3** were in agreement with the assigned structures. CPK model examinations and preliminary computer

Scheme 1. Synthetic Scheme for **3**[a]



[a] Reagents: (a) 2-Chloro-1-methylpyridinium iodide, Et_3N, CH_3CN; (b) CSA·H_2O, THF, *i*-PrOH; (c) NaOH, EtOH; (d) 1-hydroxy-2-pyridinethion, DCC, DMAP, $BrCCl_3$; (e) $RhCl(PPh_3)_3$, DABCO, CH_3CN, H_2O, EtOH; (f) CH_3OCH_2Cl, NaH, THF; (g) $PdCl_2(PPh_3)_2$, CuI, Et_2NH.

modelings revealed the suitable multipoint hydrogen-bonding arrangement between the two hydroxyl groups of **1b** and the pyridine−pyridone−pyridine motif of **3**. Indeed, the association constant between **1b** and **3a** displayed 19 000 M^{-1} ($-\Delta G_{298}$ = 24.4 kJ/mol), one of the highest values of synthetic receptors possessing an uncharged hydrogen bonding site not only for deoxyribofuranoside but also for other monosaccharide derivatives in $CDCl_3$.[13,14]

Useful information for the structure of the complex was obtained by their ^{1}H NMR spectra. Treatment of a $CDCl_3$ solution of **1b** (2.5 mM) with 1 equiv of **3a** resulted in several characteristic changes in the spectrum (Figure 1). Large downfield shifts were observed not only for the OH protons of **1b** (H^e: 3.6 and H^h: 3.0 ppm) but also for the amide-NH (1.0 ppm) and the pyridone-NH (2.5 ppm) protons of **3a**, while H^i and N-CH_2 protons of the nucleobase residue were shifted upfield (H^i: 0.3 and N-CH_2: 0.2 ppm). The former downfield shifts reflect the formation of a multipoint hydrogen-bonded complex as expected, and the latter may be attributed to the fact that the nucleobase residue of **1b** was placed on the diphenylmethane bridge that is perpendicular to the hydrogen-bonding site. Furthermore, the receptor signals of the flexible ethylene protons (-CH_2CH_2-) showed substantial splits after the recognition of **1b**, suggesting the formation of a chiral complex between the chiral **1b** and the achiral **3a**. On the basis of the above observations, a possible recognition mode for the complex (**1b·3a**) is shown in Chart 1.

The extraction of native monosaccharides into $CHCl_3$ containing **3b** showed further information for the binding ability of the receptors. Selective extraction of deoxyribose by the receptors was observed: the extractabilities or affinities to the receptors of various pentoses and hexoses decreased in the following order: deoxyribose > lyxose ≅ ribose > arabinose ≅ fructose ≅ xylose > glucose > mannose > galactose (Table 1). Noteworthy is the fact that extractability of deoxyribose vs ribose is reversed to that for the ribofuranoside receptor **2**.[8]

(9) The binding energy ($-\Delta G_{298}$) of **2** for methyl β-(D)-ribofuranoside in $CDCl_3$ was determined to be 21.7 kJ/mol, so that the nucleobase residues of **1** were judged to make little contribution to the binding.

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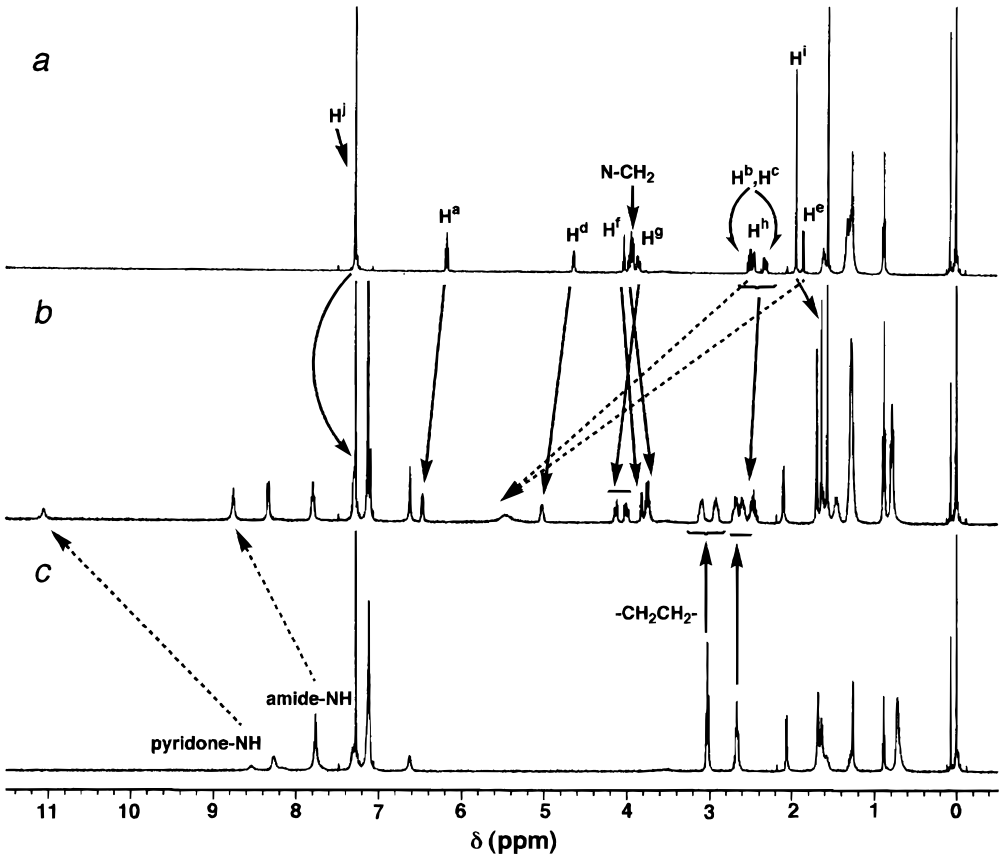

Figure 1. ^{1}H NMR spectra (500 MHz) of (a) **1b** (2.5 mM), (b) **1b**·**3a**, and (c) **3a** in $CDCl_3$ at 25 °C. See Chart 1 for proton labeling.

Table 1. Extractabilities of Various (D)-Monosaccharides with **3b** (Molar Ratios of (D)-Monosaccharides Extracted to **3b** Used)[a]

	deoxyribose	lyxose	ribose	arabinose	fructose	xylose	glucose	mannose	galactose
Monosaccharide/**3b**	1.00	0.66	0.65	0.53	0.52	0.52	0.45	0.39	0.32

[a] For details, see Experimental Section.

These results demonstrated the adjustability of the pyridine−pyridone−pyridine arrangement as a hydrogen-bonding motif for deoxyribofuranoside.

Systematic comparison of experimental $-\Delta G_{298}$ for complexation with the number of hydrogen bonds participating the complexation revealed a substantially constant increment which is 5 ± 1 kJ/mol per amide−amide type of hydrogen bond in $CHCl_3$.[3] On the other hand, hydrogen-bonding recognition of saccharides by artificial receptors remains to be investigated more satisfactorily.[7] Indeed, artificial hydrogen-bonding receptors thus far synthesized exhibited rather small binding affinities for saccharides, in which the stabilization energy of only no more than 3−4 kJ/mol per hydrogen bond was attained. Recently developed artificial receptors by Davis et al., however, bind β-glucosides in $CHCl_3$ with $-\Delta G_{298} = 30.7$ kJ/mol.[14] They postulated the complex formation of six hydrogen bonds and therefore 5 kJ/mol per the hydrogen bond. Thus, the observed $-\Delta G_{298}$ of 24.4 kJ/mol for the receptor **3a** is a remarkably but not unusually high value for the substrate having only two hydroxyl groups. The value implies the substantial participation of at least four or more hydrogen bonds. A common feature of the protein−saccharide complexes is that each of the saccharide hydroxyl groups participates in one donor and one or more acceptor interactions as elucidated by X-ray crystallography.[15] The recognition mode of the polypyridine receptors **3** may take advantage of the full potential of two hydroxyl groups of deoxyribofuranoside for hydrogen bonding resembling the protein−saccharide interactions.

Conclusions

The novel hydrogen-bonding site, pyridine−pyridone−pyridine structure on the macrocycle was found to be effective for the recognition of deoxyribose. The binding affinity of the artificial receptors for β-deoxyribofuranoside was very high. We are currently investigating the design and synthesis of a nucleobase recognition site as well as connecting it to the saccharide receptors, which are expected to bind native nucleosides and deoxynucleosides.

Experimental Section

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively, unless otherwise noted. EI mass spectra were measured at 70 eV. For FAB mass experiments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. The starting materials were all commercially available, and **6a**,[8] **7**,[12] and **12**[8] were prepared according to literature procedures.

Methods for the Evaluation of Stoichiometry and Association Constants. Job's plot of [complex] vs mole fraction of the receptor ($f_{receptor}$) for the complexation of the receptor and **1** was obtained by ^{1}H NMR in $CDCl_3$ at 25 °C under conditions where [receptor] + [**1**] is maintained at 1.0 mM.[16] The concentration of a complex in $CDCl_3$

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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). The 1:1 stoichiometry was confirmed by the plots that contained a maximum at a mole ratio of 0.5 in each case. Association constants (K_a) were determined by Benesi−Hildebrand analysis of the ^{1}H NMR shifts in δ_{NH} for **2** (0.15 mM) and **3a** (0.05 mM) in the presence of a 10−20-fold molar excess of the furanoside derivatives **1** at 25 °C in $CDCl_3$.[17] All binding assays were carried out below the concentration so that the self-association of each substrates is negligible. In every case, the double reciprocal plots according to the equation, $1/\Delta\delta_{obsd} = 1/\Delta\delta_{sat} + 1/\Delta\delta_{sat}K_a[\mathbf{1}]_t$ gave good linearity with a correlation coefficient $r \geq 0.99$.

Extraction Experiments. The suspension of a large excess of each monosaccharide (solid) and **3b** (0.01 mmol) in $CHCl_3$ (1 mL) was stirred at 25 °C for 24 h. The suspension was filtered, and the filtrate (0.85 mL) was added into D_2O (0.85 mL). The mixed phases were stirred at 25 °C for 2 h, and the D_2O phase was separated by centrifuge. To the D_2O (0.6 mL) solution was added a D_2O (0.06 mL) solution of TSP (sodium 3-(trimethylsilyl)propionate(2,2,3,3-d_4), 0.1 mmol). The D_2O solutions were analyzed by means of ^{1}H NMR spectroscopy. The amount of monosaccharide re-extracted was evaluated by comparison of a ^{1}H NMR integration ratio of the total monosaccharide CH proton resonances to that of TSP (9H) added as the integration standard. Some monosaccharides are slightly soluble in $CHCl_3$. In such cases, the extractability of each monosaccharide by **3b** was corrected for by subtracting the value obtained in a blank.

3-*n*-Octyluridine (1a). To an EtOH−H_2O (10 + 2.5 mL) mixed solution of uridine (611 mg, 2.5 mmol) and KOH (140 mg, 2.5 mmol) was added *n*-octyl bromide (531 mg, 2.8 mmol) dropwise at room temperature. The reaction mixture was refluxed for 42 h. After removal of the solvent, the residue was dissolved in $CHCl_3$ and washed with water to remove the unreacted starting materials. The $CHCl_3$ phase was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 10:1) to give **1a**: yield = 58% (512 mg); mp 88−90 °C; IR (KBr) 3416, 2918, 1697, 1651, 1619, 1465, 1269, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.19−1.40 (m, 10 H), 1.55−1.68 (m, 2 H), 2.31 (dd, J = 5.5, 3.7 Hz, 1 H), 3.00 (d, J = 3.7 Hz, 1 H), 3.79−4.04 (m, 5 H), 4.25 (q, J = 3.1 Hz, 1 H), 4.35−4.47 (m, 2 H), 5.64 (d, J = 4.9 Hz, 1 H), 5.77 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.65, 26.98, 27.56, 29.22, 29.28, 31.81, 41.37, 62.13, 70.99, 75.27, 85.90, 93.73, 101.91, 138.66, 151.84, 162.64; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 357 (MH^+, 60%). Anal. Calcd for $C_{17}H_{28}O_6N_2$: C, 57.29; H, 7.92; N, 7.86. Found: C, 56.95; H, 8.01; N, 7.51.

3-*n*-Octylthymidine (1b). To an EtOH−H_2O (20 + 1 mL) mixed solution of thymidine (1.21 g, 5.0 mmol) and KOH (281 mg, 5.0 mmol) was added *n*-octyl bromide (1.06 g, 5.5 mmol) dropwise at room temperature. The reaction mixture was refluxed for 20 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and washed with water to remove the unreacted starting materials. The CH_2Cl_2 phase was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 20:1) to give **1b**: yield = 55% (953 mg); mp 89−90 °C; IR (KBr) 3513, 2926, 1689, 1668, 1636, 1471, 1291, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.17−1.42 (m, 10 H), 1.52−1.69 (m, 2 H), 1.93 (s, 3 H), 2.15−2.65 (m, 4 H), 3.79−4.00 (m, 4 H), 4.02 (q, J = 3.7 Hz, 1 H), 4.61 (dt, J = 3.7, 7.3 Hz, 1 H), 6.18 (t, J = 6.7 Hz, 1 H), 7.31 (d, J = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.29, 14.04, 22.59, 26.96, 27.54, 29.16, 29.22, 31.75, 40.12, 41.55, 62.35, 71.45, 86.93, 110.32, 134.62, 150.97, 163.49; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 355 (MH^+, 84%). Anal. Calcd for $C_{18}H_{30}O_5N_2$: C, 61.00; H, 8.53; N, 7.90. Found: C, 60.59; H, 8.56; N, 7.75.

4-Allyloxypyridine-2,6-dicarboxylic acid (8). To an EtOH (74 mL) solution of **7**[12] (12.5 g, 37.2 mmol) was added an EtOH (222 mL) solution of NaOH (5.96 g, 148.9 mmol) at room temperature. The reaction mixture became turbid, and the cloudy solution was allowed to stand for 12 h at this temperature. After removal of the solvent, the residue was poured into water and washed with CH_2Cl_2 to remove the unreacted starting materials. The water phase was acidified to pH 1 with concentrated hydrochloric acid, and the resulting precipitate was filtered and washed with water. The precipitate was dried in vacuo to give **8**: yield = 94% (7.79 g); mp 160−161 °C; IR (KBr) 3508, 3104, 1927, 1731, 1599, 1336, 1199, 1032 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.84 (d, J = 4.9 Hz, 2 H), 5.29−5.45 (m, 2 H), 5.98−6.12 (m, 1 H), 7.72 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 69.21, 113.99, 118.54, 132.42, 149.91, 165.44, 166.47; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 224 (MH^+, 100%). Anal. Calcd for $C_{10}H_9O_5N_1$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.33; H, 4.28; N, 5.89.

4-Allyloxy-2,6-dibromopyridine (9). A $BrCCl_3$ (160 mL) suspension of **8** (4.93 g, 22.1 mmol), 1-hydroxy-2-pyridinethion (6.17 g, 48.6 mmol), dicyclohexylcarbodiimide (10.0 g, 48.6 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (5.93 g, 48.6 mmol) was stirred at 110 °C for 2 h. After removal of the solvent, the residue was poured into CH_2Cl_2, and the suspension was filtered. The filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2: hexane = 1:1) to give **9**: yield = 35% (2.27 g); oil; IR (KBr) 3085, 2931, 1572, 1535, 1417, 1373, 1283, 1156, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.57−4.59 (m, 2 H), 5.35−5.46 (m, 2 H), 5.91−6.03 (m, 1 H), 6.99 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 69.59, 114.04, 119.40, 130.90, 141.15, 166.60; MS *m*/*e* (relative intensity) 293 (M^+ + 2, 56%). Anal. Calcd for $C_8H_7ONBr_2$: C, 32.80; H, 2.41; N, 4.78. Found: C, 32.78; H, 2.54; N, 4.69.

2,6-Dibromo-4-pyridone (10). A mixture of **9** (994 mg, 3.4 mmol), $(PPh_3)_3RhCl$ (188 mg, 0.2 mmol), and DABCO (30.5 mg, 0.27 mmol) in CH_3CN-H_2O−EtOH (7 + 7 + 7 mL) was heated at 70 °C for 6 h. After removal of the solvent, the residue was poured into CH_2Cl_2, and the resulting precipitate was filtered. The precipitate was washed with CH_2Cl_2 to give **10**. Then the filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:AcOEt = 10:1) to afford additional **10**: yield = 90% (772 mg); mp 209−212 °C; IR (KBr) 3021, 1588, 1562, 1543, 1415, 1285, 1209, 1151 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.03 (s, 2 H), 11.78 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.06, 140.43, 167.19; MS *m*/*e* (relative intensity) 253 (M^+ + 2, 100%). Anal. Calcd for $C_5H_3ONBr_2$: C, 23.75; H, 1.20; N, 5.54. Found: C, 23.93; H, 1.17; N, 5.33.

2,6-Dibromo-4-(methoxymethoxy)pyridine (11). To a THF (12 mL) suspension of NaH (281 mg, 7.0 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a THF (3 mL) solution of **10** (1.48 g, 5.9 mmol) dropwise at 0 °C. After the mixture was stirred at that temperature for 30 min, to the solution was added chloromethyl methyl ether (566 mg, 7.0 mmol) dropwise at the same temperature. The reaction mixture was stirred at room temperature for an additional 24 h. The reaction mixture was filtered, and the filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:hexane = 1:1) to give **11**: yield = 90% (1.57 g); mp 64−65 °C; IR (KBr) 2919, 1574, 1538, 1433, 1373, 1263, 1155, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3 H), 5.21 (s, 2 H), 7.13 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 56.85, 94.43, 115.09, 141.13, 165.33; MS *m*/*e* (relative intensity) 297 (M^+ + 2, 62%). Anal. Calcd for $C_7H_7O_2NBr_2$: C, 28.31; H, 2.38; N, 4.72. Found: C, 28.26; H, 2.41; N, 4.43.

2,6-Bis[(6-aminopyrid-2-yl)ethynyl]-4-(methoxymethoxy)pyridine (5). An Et_2NH (27 mL) solution of **11** (2.64 g, 8.9 mmol), **12**[8] (3.16 g, 26.7 mmol), $(PPh_3)_2PdCl_2$ (125 mg, 0.178 mmol), and CuI (17 mg, 0.089 mmol) was stirred at 50 °C for 12 h. The resulting precipitate was filtered and washed with $CHCl_3$ to give **5**: yield = 84% (2.77 g); mp 216−219 °C; IR (KBr) 3306, 3180, 2218, 1626, 1584, 1553, 1466, 1146, 1024 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.41 (s, 3 H), 5.39 (s, 2 H), 6.21 (br s, 4 H), 6.52 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 6.7 Hz, 2 H), 7.29 (s, 2 H), 7.43 (t, J = 7.9 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 57.25, 86.16, 89.84, 94.86, 110.44, 115.93, 117.26, 138.41, 139.98, 144.67, 160.82, 164.27; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 372 (MH^+, 97%). Anal. Calcd for $C_{21}H_{17}O_2N_5$: C, 67.91; H, 4.61; N, 18.86. Found: C, 68.40; H, 4.44; N, 18.39.

4,4′-(Tridec-2-ylidene)bis(dihydrocinnamic acid) (6b). This compound was synthesized from the corresponding bisphenol derivative in a manner similar to that described for **6a**.[8] To a mixture of phenol (9.91 g, 50.0 mmol) and 2-tridecanone (14.1 g, 150 mmol) was bubbled dry HCl gas at 60 °C for 1 week. The reaction mixture was subjected to column chromatography (silica gel; eluent, CH_2Cl_2:AcOEt = 10:1)

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to give 4,4′-(tridec-2-ylidene)diphenol: yield = 60% (11.1 g); oil; IR (KBr) 3285, 2933, 2854, 1612, 1512, 1464, 1375, 1240, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (t, J = 6.7 Hz, 3 H), 0.98−1.37 (m, 18 H), 1.55 (s, 3 H), 1.95−2.01 (m, 2 H), 4.94 (br s, 2 H), 6.71 (d, J = 8.6 Hz, 4 H), 7.04 (d, J = 8.6 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.18, 22.73, 24.76, 27.92, 29.38, 29.61, 29.65, 29.68, 30.44, 31.95, 42.14, 44.94, 114.62, 128.48, 142.51, 153.19; MS *m*/*e* (relative intensity) 213 ($M^+ - C_{11}H_{23}$, 100%). To a pyridine (70 mL) solution of 4,4′-(tridec-2-ylidene)diphenol (11.1 g, 30.1 mmol) was added trifluoromethanesulfonic anhydride (19.6 g, 69.2 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and then allowed to warm to room temperature and stirred at this temperature for 3 h. After removal of the solvent, the residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 10% aqueous hydrochloric acid solution twice, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography (silica gel; eluent, hexane:CH_2Cl_2 = 10:1) to give 4,4′-(tridec-2-ylidene)diphenyl ditriflate: yield = 90% (17.1 g); oil; IR (KBr) 2929, 2856, 1596, 1500, 1426, 1250, 1213, 1142, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 0.96−1.37 (m, 18 H), 1.63 (s, 3 H), 2.02−2.08 (m, 2 H), 7.18 (d, J = 9.2 Hz, 4 H), 7.23 (d, J = 9.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.73, 24.59, 27.73, 29.38, 29.46, 29.63, 30.21, 31.95, 41.84, 46.22, 116.43, 120.94, 129.14, 147.70, 149.52; MS *m*/*e* (relative intensity) 477 ($M^+ - C_{11}H_{23}$, 100%). To a DMF (80 mL) solution of 4,4′-(tridec-2-ylidene)diphenyl ditriflate (16.5 g, 26.2 mmol), $(PPh_3)_2$-$PdCl_2$ (367 mg, 0.5 mmol), LiCl (6.66 g, 157.2 mmol), and Et_3N (21.2 g, 209.6 mmol) was added methyl acrylate (5.08 g, 59.0 mmol) at room temperature. The reaction mixture was stirred at 75 °C 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 and chromatographed (silica gel; eluent, hexane:AcOEt = 10:1) to give dimethyl 4,4′-(tridec-2-ylidene)bis(cinnamate): yield = 76% (10.0 g); oil; IR (KBr) 3446, 2933, 2853, 1723, 1635, 1436, 1314, 1273, 1170, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 0.98−1.36 (m, 18 H), 1.62 (s, 3 H), 2.04−2.10 (m, 2 H), 3.79 (s, 6 H), 6.40 (d, J = 15.9 Hz, 2 H), 7.19 (d, J = 8.5 Hz, 4 H), 7.42 (d, J = 8.5 Hz, 4 H), 7.67 (d, J = 15.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.65, 24.57, 27.24, 29.30, 29.44, 29.57, 30.27, 31.87, 41.45, 46.53, 51.60, 117.22, 127.81, 127.85, 131.93, 144.49, 151.99, 167.45; MS *m*/*e* (relative intensity) 349 ($M^+ - C_{11}H_{23}$, 100%). An AcOEt (10 mL) solution of dimethyl 4,4′-(tridec-2-ylidene)-bis(cinnamate) (10.0 g, 19.8 mmol) and 5% Pd/C (1.0 g) was stirred at room temperature for 24 h under hydrogen (at an initial pressure of 40 atm) in an autoclave. The reaction mixture was filtered through Celite, and the filtrate was evaporated to give dimethyl 4,4′-(tridec-2-ylidene)-bis(dihydrocinnamate): yield = 93% (9.32 g); oil; IR (KBr) 3467, 2928, 2857, 1741, 1511, 1438, 1253, 1196, 1165 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 0.98−1.37 (m, 18 H), 1.58 (s, 3 H), 1.99−2.05 (m, 2 H), 2.61 (t, J = 7.3 Hz, 4 H), 2.91 (t, J = 7.3 Hz, 4 H), 3.67 (s, 6 H), 7.08 (s, 8 H); ^{13}C NMR ($CDCl_3$) δ 14.16, 22.73, 24.73, 27.62, 29.38, 29.57, 29.65, 29.69, 30.45, 31.95, 35.65, 41.92, 45.64, 51.62, 127.44, 127.75, 137.51, 147.92; MS *m*/*e* (relative intensity) 353 ($M^+ - C_{11}H_{23}$, 100%). To an EtOH (18 mL) solution of dimethyl 4,4′-(tridec-2-ylidene)bis(dihydrocinnamate) (9.32 g, 18.3 mmol) was added an EtOH (110 mL) solution of KOH (6.17 g, 110.0 mmol) at room temperature. The reaction mixture became turbid, and the cloudy solution was allowed to stand for 12 h at this temperature. After removal of the solvent, the residue was poured into water and washed with $CHCl_3$ to remove the unreacted starting materials. The water phase was neutralized to pH 5 with 10% aqueous hydrochloric acid solution and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to give **6b**: yield = 99% (8.70 g); oil; IR (KBr) 2932, 2855, 1712, 1511, 1414, 1300, 1215, 1106 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 0.99−1.36 (m, 18 H), 1.59 (s, 3 H), 1.99−2.08 (m, 2 H), 2.66 (t, J = 7.3 Hz, 4 H), 2.92 (t, J = 7.3 Hz, 4 H), 7.09 (s, 8 H); ^{13}C NMR ($CDCl_3$) δ 14.16, 22.73, 24.75, 27.62, 29.40, 29.57, 29.69, 30.09, 30.44, 31.95, 35.57, 41.92, 45.68, 127,51, 127.77, 137.17, 148.04, 179.42; MS *m*/*e* (relative intensity) 325 ($M^+ - C_{11}H_{23}$, 100%). Anal. Calcd for $C_{31}H_{44}O_4$: C, 77.46; H, 9.23; N, 13.31. Found: C, 77.05; H, 9.41; N, 12.85.

Receptor 4a. To a CH_3CN (600 mL) solution of **5** (1.76 g, 4.73 mmol), **6a**[8] (1.81 g, 4.73 mmol), and Et_3N (7.66 g, 75.7 mmol) was added a CH_3CN (100 mL) solution of 2-chloro-1-methylpyridinium iodide (4.83 g, 18.9 mmol) dropwise at 70 °C. The reaction mixture was stirred at this temperature for 24 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, CH_2Cl_2:AcOEt = 8:1) to give **4a**: yield = 7% (244 mg); mp 239−242 °C; IR (KBr) 2953, 2361, 1702, 1573, 1546, 1452, 1365, 1226, 1155, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, J = 6.6 Hz, 6 H), 1.54−1.76 (m, 4 H), 2.07 (d, J = 5.0 Hz, 2 H), 2.66 (d, J = 7.9 Hz, 4 H), 2.99 (d, J = 7.9 Hz, 4 H), 3.51 (s, 3 H), 5.27 (s, 2 H), 7.15 (s, 2 H), 7.10 (d, J = 8.5 Hz, 4 H), 7.13 (d, J = 8.5 Hz, 4 H), 7.23 (d, J = 6.6 Hz, 2 H), 7.70 (t, J = 7.6 Hz, 2 H), 8.05 (br s, 2 H), 8.17 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.67, 25.26, 27.58, 30.78, 40.50, 45.95, 49.52, 56.73, 87.26, 87.81, 94.12, 114.08, 114.16, 122.44, 127.78, 127.81, 137.50, 138.70, 139.91, 143.97, 148.77, 151.48, 163.79, 171.33; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 718 (MH^+, 100%). Anal. Calcd for $C_{45}H_{43}O_4N_5$: C, 75.29; H, 6.04; N, 9.76. Found: C, 75.84; H, 6.21; N, 9.30.

Receptor 4b. This compound was synthesized from **5** (929 mg, 2.5 mmol) and **6b** (1.20 g, 2.5 mmol) in a manner similar to that described for **4a**. **4b**: yield = 7% (145 mg); mp 190−192 °C; IR (KBr) 2923, 2853, 1704, 1573, 1548, 1452, 1365, 1226, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.09−1.35 (m, 18 H), 1.68 (s, 3 H), 2.05−2.08 (m, 2 H), 2.66 (t, J = 7.3 Hz, 4 H), 2.99 (t, J = 7.3 Hz, 4 H), 3.51 (s, 3 H), 5.27 (s, 2 H), 7.11 (s, 8 H), 7.15 (s, 2 H), 7.23 (d, J = 7.9 Hz, 2 H), 7.70 (t, J = 7.9 Hz, 2 H), 8.09 (br s, 2 H), 8.17 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.71, 24.71, 27.06, 29.36, 29.54, 29.63, 29.69, 30.50, 30.82, 31.93, 38.68, 40.50, 41.19, 45.60, 56.71, 87.32, 87.84, 94.17, 114.08, 114.20, 122.45, 127.69, 127.85, 137.47, 138.68, 139.96, 144.02, 148.61, 151.52, 163.81, 171.35; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 816 (MH^+, 100%). Anal. Calcd for $C_{52}H_{57}O_4N_5$: C, 76.54; H, 7.04; N, 8.58. Found: C, 76.17; H, 7.34; N, 8.21.

Receptor 3a. A mixture of **4a** (35 mg, 0.049 mmol) and (+)-(*S*)-camphor-10-sulfonic acid monohydrate (85 mg, 0.34 mmol) in THF−*i*-PrOH (0.22 + 0.22 mL) was stirred at room temperature for 18 h. After removal of the solvent, the residue was subjected to column chromatography (silica gel; eluent, CH_2Cl_2:AcOEt:MeOH = 20:2:1) to give **3a**: yield = 95% (31 mg); mp 209−212 °C dec; IR (KBr) 3379, 2950, 1700, 1593, 1570, 1516, 1452, 1383, 1278, 1229, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, J = 6.7 Hz, 6 H), 1.49−1.75 (m, 4 H), 2.07 (d, J = 4.9 Hz, 2 H), 2.64 (t, J = 7.6 Hz, 4 H), 2.98 (t, J = 7.6 Hz, 4 H), 6.80 (s, 2 H), 7.08 (d, J = 8.6 Hz, 4 H), 7.11 (d, J = 8.6 Hz, 4 H), 7.20 (d, J = 7.3 Hz, 2 H), 7.69 (t, J = 7.6 Hz, 2 H), 8.01 (br s, 2 H), 8.20 (d, J = 6.9 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 24.60, 25.16, 29.88, 45.20, 87.29, 87.35, 114.01, 114.15, 121.99, 126.95, 127.98, 138.45, 139.36, 139.52, 143.34, 147.85, 152.54, 165.11, 171.72; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 674 (MH^+, 100%). Anal. Calcd for $C_{43}H_{39}O_3N_5$: C, 76.65; H, 5.83; N, 10.39. Found: C, 76.48; H, 5.97; N, 10.01.

Receptor 3b. This compound was synthesized from **4b** (136 mg, 0.17 mmol) in a manner similar to that described for **3a**. **3b**: yield = 82% (106 mg); mp 161−164 °C; IR (KBr) 2926, 2854, 2670, 2369, 1702, 1569, 1527, 1452, 1384, 1279, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.07 (m, 18 H), 1.64 (s, 3H), 2.02 (m, 2 H), 2.64 (t, J = 7.3 Hz, 4 H), 2.98 (t, J = 7.3 Hz, 4 H), 6.74 (s, 2 H), 7.09 (s, 8 H), 7.19 (d, J = 7.3 Hz, 2 H), 7.67 (t, J = 7.9 Hz, 2 H), 8.09 (br s, 2 H), 8.21 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.18, 22.32, 25.88, 28.92, 29.21, 29.93, 29.98, 31.51, 44.89, 87.35, 87.39, 114.04, 114.22, 122.05, 126.85, 128.11, 138.49, 139.45, 139.55, 143.38, 147.55, 152.58, 165.16, 171.74; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (relative intensity) 772 (MH^+, 100%). Anal. Calcd for $C_{50}H_{53}O_3N_5$: C, 77.79; H, 6.92; N, 9.07. Found: C, 77.99; H, 7.37; N, 9.53.

Acknowledgment. The preliminary work in this paper was supported by Saneyoshi Scholarship Foundation and by Mitsubishi Chemical Corporation Foundation. This paper is dedicated to M.I.'s teacher, Professor Yoshihiko Ito (Kyoto University) on the occasion of his 60th birthday.

JA983539U